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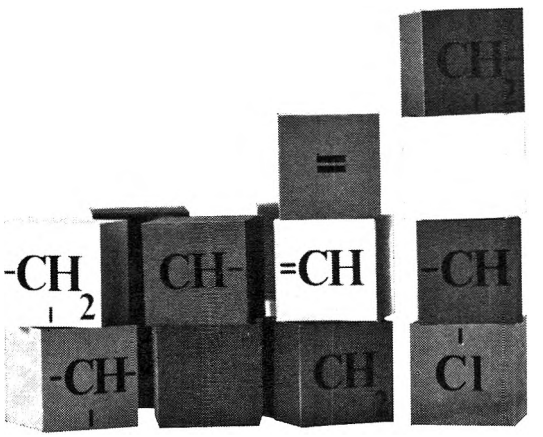

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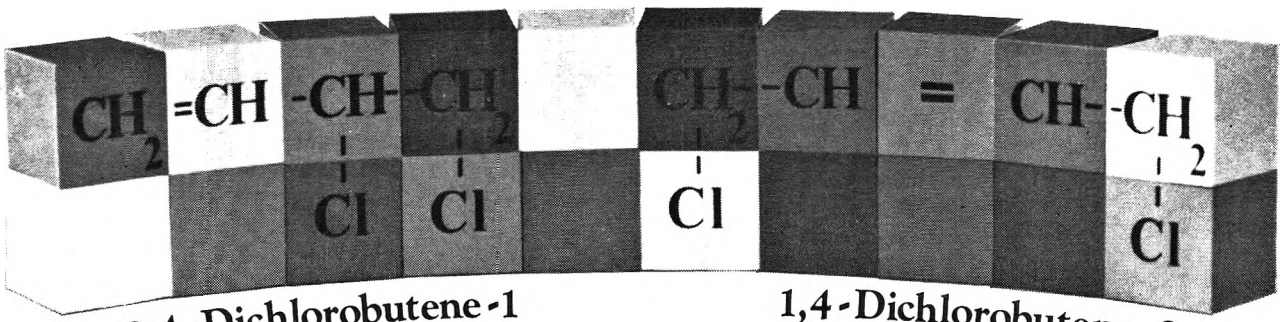

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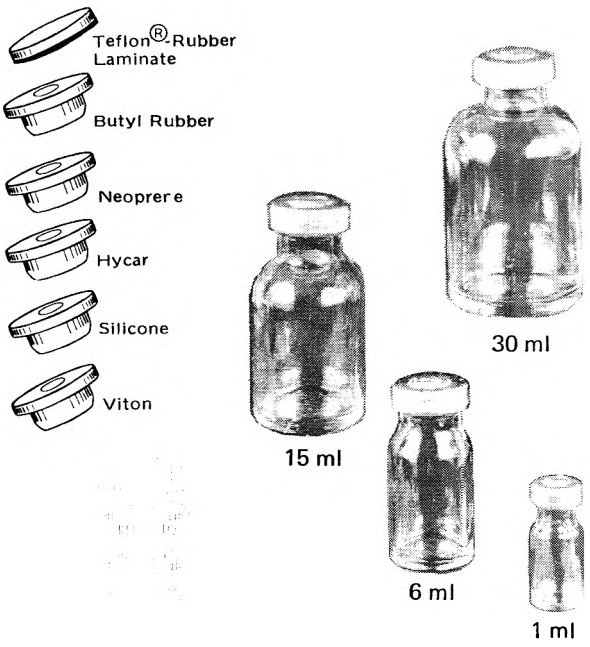

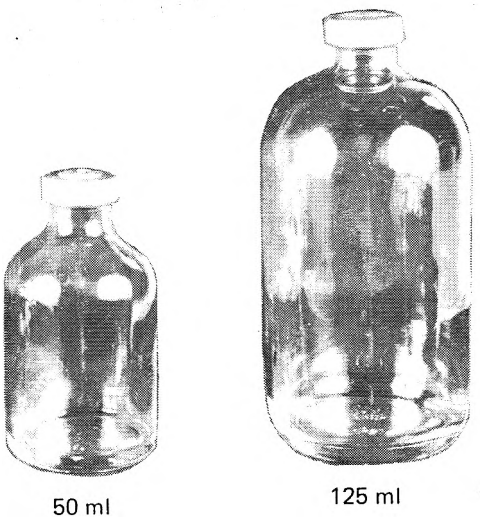

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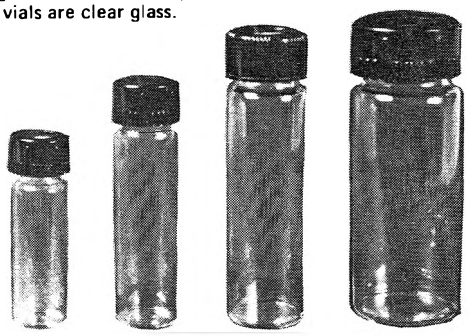

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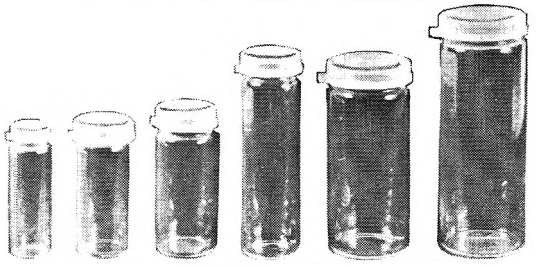

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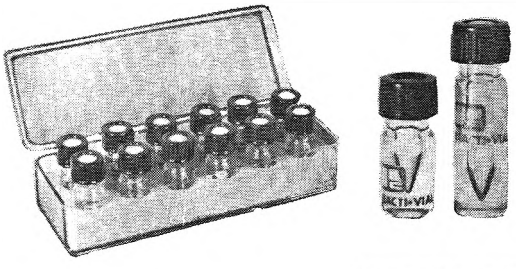

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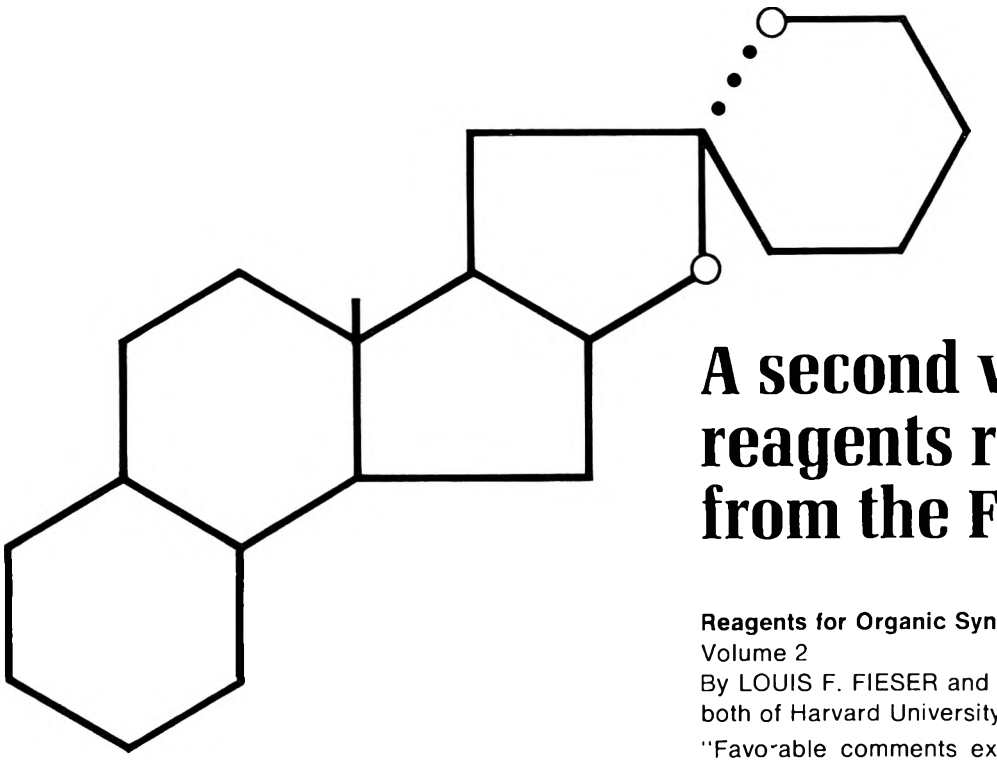

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Physical constants and spectral data should be presented in a uniform way as illustrated in the following example.

(In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet.)

"The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 10.23 g (65%) of the acetoxy ketone 12: bp 82–83° (2.9 mm); $n^{25}D$ 1.4266 [lit.[6] bp 80–82° (3 mm); $n^{25}D$ 1.4261]; d^{25}_4 0.823; $[\alpha]^{25}D$ 0.0° (c 6, CH_3OH); uv max (95% EtOH) 275 mμ (ε 21); ir (CCl_4) 1725 (C=O), 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.98 (t, 2, J = 6 Hz, CH_2OAc), 2.43 (t, 2, J = 6 Hz, CH_2CO), 2.07 (s, 3), 1.97 (s, 3), and 1.6 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 158 (5), 143 (5), 115 (6), 100 (50), 99 (11), 98 (100), 85 (10)."

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Quantitative Studies in Stereochemistry. Electrochemistry. III. The Ratio of Diastereomeric Pinacols Produced in the Electrolytic Bimolecular Reduction of 2-Acetylpyridine. Formation of Methyl-2-pyridylcarbinol as a Function of pH

JACK H. STOCKER AND ROY M. JENEVEIN

Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122

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The electropinacolization of 2-acetylpyridine produced predominantly the *meso*-pinacol in acidic media and the preference for the *meso* diastereomer increased as the media were made alkaline. These results are the inverse of those observed previously for acetophenone. It is proposed that the hydroxylic proton of the intermediate ketyl radical may intraspecies hydrogen bridge with the ring nitrogen, minimizing the interspecies bridging that is held responsible for the production of the *dl* form. Methyl-2-pyridylcarbinol is the almost exclusive product in strongly acidic media. A protonated ketyl radical is invoked as responsible for its formation.

Previous papers from this laboratory have reported on the stereochemistry observed in the electrochemical bimolecular reduction of acetophenone,[1] propiophenone,[2] and benzaldehyde.[2] All three compounds produced a slight predominance of the *dl*-glycol (pinacol) over the *meso* form in acidic media. The ratio of *dl*- to *meso*-pinacol rose sharply to 3:1 in alkaline media for the two alkyl aryl ketones, while that for benzaldehyde showed but little change. A mechanism was proposed involving *inter*species hydrogen bonding between dimerizing radicals in acid solution, and between radicals combining with radical anions in alkaline media. An effective test of this mechanism would be provided by an examination of an appropriate ketone which permitted *intra*species hydrogen bonding of the intermediate ketyl. This would minimize the interspecies bonding leading to *dl*-pinacol formation and predict predominant formation of the *meso* form from simple steric considerations. 2-Acetylpyridine was chosen as an appropriate analog that met the above requirements. Use of this model compound made necessary the establishment of the stereochemical identities of the two derived diastereomeric pinacols as well as polarographic determination of suitable controlled potentials for the reduction at various pHs.

meso- and *dl*-pinacol identities have been assigned on the basis of melting point[3] and infrared[4] and nmr spectra.[5] Each of these three possibilities presented difficulties when applied to the 2-acetylpyridine pinacols. While the two diastereomers have been previously prepared and melting points of 136–137° and 140–141° reported,[6] analogous preparation in the present study, followed by careful purification, gave identical melting points, 142°, for *both* forms, precluding an assignment on this basis. The infrared spectra of both forms showed no free OH stretch and very broad bonded OH absorption. Using the position and intensity of these two absorption bands was therefore also precluded.[4] The position of the C–O stretch did, however, correlate with certain empirical observations[4] as well as the nmr assignments described below. The crystalline forms of the pinacols also showed the expected empirical correlation with past observations on the part of the authors.[7]

Nmr spectra of both pinacols showed the hydroxylic protons to be buried in the aromatic area, and prohibited assignment on the basis of a greater preference on the part of the *dl* form for intramolecular hydrogen bonding with a corresponding downfield shift for this proton in this diastereomer.[5] Construction of Fieser-type models of the two diastereomers did, however, indicate that the most favorable conformation of the *meso*-pinacol (all corresponding groups *trans*, the pyri-

(1) J. H. Socker and R. M. Jenevein, *J. Org. Chem.*, **33**, 294 (1968).

(2) J. H. Stocker and R. M. Jenevein, *ibid.*, **33**, 2145 (1968).

(3) The diastereomer showing the higher melting point is customarily designated the *meso* form. There appear to be only two established exceptions to this rule, the acetophenone pinacols [*cf.* Cram and Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959)] and the 4,4-dimethylhydrobenzoins [*cf.* Grimshaw and Ramsey, *J. Chem. Soc.*, *C*, 653 (1966)].

(4) W. A. Mosher and N. D. Heindel, *J. Org. Chem.*, **28**, 2154 (1963).

(5) J. H. Stocker, *J. Amer. Chem. Soc.*, **88**, 2878 (1966).

(6) W. L. Bencze and M. J. Allen, *ibid.*, **81**, 4015 (1959). These authors report the higher melting compound to have been isolated from photochemical studies, while the lower melting compound was derived from the addition of methylmagnesium iodide to α-pyridil.

(7) For eight different diastereomeric pairs of pinacols, or hydrobenzoins, that have come under the authors' purview, the *dl* form has consisted in all cases of fine, silky needles, while the *meso* form was composed of either fat needles or chunky crystals.

TABLE I
ELECTROCHEMICAL REDUCTION OF 2-ACETYLPYRIDINE

Item	Electrode	Time, hr	Potential,[a] −V	Initial current, mA	Media[b,c]	Pinacol,[d] %	Ratio, *dl/meso*	Carbinol,[d] %
1	Hg	96	0.51	37	A-1	...	...	90
2	Hg	6.5	0.73	450	A-2	2.8[e]	0.77	51[e]
3	Hg	11	0.63	330	A-1	7.0[f]	0.78	68[f]
4	Hg	4	0.78	500	A-1	11.0	0.73	82
5	Hg	1	0.83	3600	A-1	0.9	0.7	94
6	Hg	6	0.99	480	Buffer-1	6.8	0.55	80
7	Hg	1.5	0.99	3000	Buffer-2	15.7	0.34	83
8	Hg	4	0.96	470	Buffer-2	67	0.28	29
9	Hg	0.33	1.22	5000	B-1	44	0.50	54
10	Hg	1.5	1.22	3800	B-1	68	0.46	32
11	Hg	1	1.20	1500	B-1	68	0.43	27
12	Cu	6	1.6	380	B-1	55	0.53	40
13	Cu	3.5	1.5	230	B-2	72	0.38	28
14	Cu	4.3	1.6	240	B-2	65[g]	0.38	22[g]
15	Hg	4	1.20	300	B-2	98	0.28	0
16	Hg	12	1.20	600	B-2	96	0.28	0
17	Hg	7.3	1.17	500	B-1	96	0.22	0
18	Hg	6	...	300	B-2	98% recovered *dl*[h]		0

[a] Measured against Ag/AgCl reference electrode. See ref 14. [b] All runs in 80% EtOH. [c] Media coded as follows: A-1, 1 *M* LiCl and 1.5 *M* AcOH; A-2, 1 *M* LiCl and 1 *M* CF_3COOH; Buffer-1, pH 6.5, 2.5 *M* AcOH and 2 *M* KOAc; Buffer-2, pH 8.5, 1 *M* NH_4OH and 2 *M* NH_4OAc; B-1, 1 *M* KOH; B-2, 2 *M* KOAc. [d] Based on starting ketone. [e] 42% ketone recovered. [f] 25% ketone recovered. [g] 8% ketone recovered. [h] Stability study at constant current, 500 mg of pure *dl*-pinacol starting material.

dine rings coplanar, and O–H–N bridging to produce two six-membered "rings") would lead to methyl groups that were strongly shielded by virtue of their position relative to the ring currents and should, accordingly, resonate at a higher field strength than those in the *dl* form. Similar conclusions would be drawn from an alternate, less satisfactory conformation involving two five-membered rings. There is no conformation for the *dl* form, involving either five- or six-membered rings, that does not involve less shielded methyl groups as well as nonbonded interactions.[8] On this basis, with the previously mentioned corroborative data, the pinacol from the organometallic route[6] was assigned *dl* and the other *meso*.

Polarographic examination indicated an $E_{1/2}$ of −0.66 V at pH 4[9] and an $E_{1/2}$ of −1.33 V at pH 14. Appropriate interpolations were used for the various media employed. Ethanol (80%) was selected as solvent to conform to earlier studies. All runs were conducted under conditions of controlled potential.

The data are tabulated in Table I.

Results and Discussion

The data in Table I permit several important conclusions.

(1) As predicted by the proposed mechanism, and in contrast to the corresponding *dl/meso* ratios observed for acetophenone, the *meso*-pinacol predominates in all cases.

(2) The carbinol (monomolecular reduction) is an important product and the almost exclusive product in strongly acidic media. This may be compared to a complete absence of carbinol from the ketones previously examined.[10]

(3) The use of appreciably larger currents (with slightly more negative potentials) increases the amount of carbinol produced at the expense of pinacol.

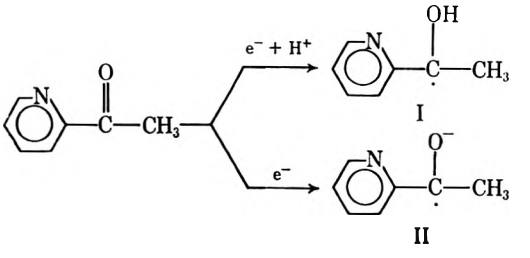
(4) The stereochemistry of the pinacol formation is related to the formation of carbinol; in general, the greater the yield of carbinol, the larger the *dl/meso* pinacol ratio.

(5) The pinacolization is pH dependent; the largest *dl/meso* ratios are observed in increasingly acidic media.

(6) The use of a copper electrode in a given medium (but at a more negative potential) gives rise to more carbinol and a larger *dl/meso* ratio than does a mercury pool electrode. This is in contrast to the absence of any changes in *dl/meso* ratios for the several electrodes investigated in the acetophenone studies.

The 2-acetylpyridine system is clearly a complex one, and, in contrast to acetophenone, may be considered a "sensitive" system. It is perhaps most effective to consider initially only those runs directly comparable to the earlier acetophenone studies, *i.e.*, use of a mercury pool electrode and relatively low initial currents (items 1–4, 6, 8, 15–17). These results show increasing amounts of *meso*-pinacol with increasing alkalinity, the ratios changing from 0.77 *dl/meso* in acid media to 0.22 *dl/meso* in strong base. The amounts of carbinol vary directly with the acidity, from approximately 90% in acidic media to 0% in strongly alkaline media. The following reasoning, modeled after that employed for the acetophenone system, may be invoked to explain these results.

Ketyl I would be formed from 2-acetylpyridine by the customary one-electron transfer in acidic media;



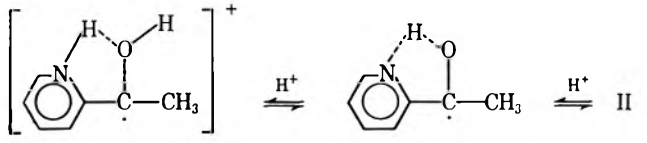
(8) An extensive nmr study of some twelve 2-pyridinealkanols, including diastereomeric pairs, will be submitted for publication shortly.

(9) É. Laveron [*Bull. Soc. Chim. Fr.*, **70**, 2326 (1961)] has reported values for pH range 2–7 in graphic form. An $E_{1/2}$ of −0.67 may be estimated from his data.

(10) Previous studies were limited to currents of less than 500 mA, and the statement carries this reservation.

the radical anion II would be anticipated in basic media.

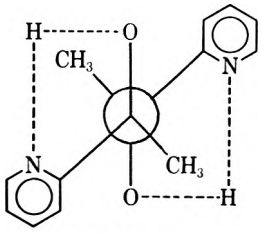
Ketyl I, either as such or in its *intra*molecularly bonded form III,[11] would be involved in a complex equilibrium, the amounts of each participating species reflecting the pH of the medium. Pinacol formation



IV III

could conceivably arise from six possible dimerizations or combinations. Ruling out the dimerization of II and of IV as involving combinations of like-charged species, and the combination of II and IV as unlikely on the grounds that they would not be expected to coexist, leads to the following more important possibilities: (A) III with IV (significant in acid media); (B) III with III (major route in both acid and base); (C) II with III (of possible significance only in strong base).

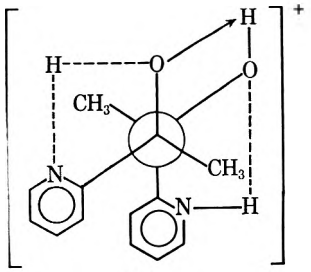
Route B, considered the major pathway, does not permit hydrogen bonding between species about to couple, and the stereochemistry would be dictated on simple steric grounds; *i.e.*, only formation of the *meso* form would permit all like groups to be in a *trans* arrangement V at the time of bond formation. The predominance of the *meso* form in all cases (Table I) is attributed to this pathway.



yields *meso*

V

Route A, the combination of radical cation and neutral radical, would permit interspecies hydrogen bonding. By analogy with the acetophenone system in which such interspecies hydrogen bonding appeared to be of major importance and to lead preferentially to the *dl* form, VI would be expected to make an important contribution.



yields *dl* (one of two forms, methyl groups *trans*)

VI

All analogous interspecies combinations leading to the *meso* form require two, rather than one, nonbonded interactions between like groups and would be less attractive. Therefore, the contribution of route A would be reflected in the form of an increased *dl/meso* ratio in acid media.[12]

The contribution of route C, the combination of radical anion with neutral radical, is more difficult to predict. To the extent that II and III combine without interspecies hydrogen bonding, simple steric control should produce predominantly the *meso*-pinacol. To the extent that II is a strong enough base to compete for the *intra*molecularly bound hydrogen in III, it could bond with that hydrogen and subsequently produce less *meso* product than simple dimerization of III. It may be further argued that the intramolecular bonding in III is sufficiently strong that it is unlikely that II is present to any appreciable extent in protic media. The observed ratios suggest that, for whichever of the above reasons, it is not necessary to invoke species II for the results under consideration.

In summary, for these runs, the largest *dl/meso* ratios would be expected from media in which the concentration of IV was highest, *i.e.*, strongly acidic media. As the concentration of IV decreased with the increasing alkalinity of the media, the *dl/meso* ratios would correspondingly decrease.

If the further reasonable assumption is made that IV is an uniquely reducible species, it also becomes the precursor of the carbinol, and the almost exclusive production of carbinol in acidic media is thereby explained. To the extent that IV is "siphoned off" to yield carbinol, it is not available to produce preferentially the *dl*-pinacol. The observed *dl/meso* ratios would be even larger if no carbinol was produced in acidic media.[13] As the media are made more basic, less IV is present, and less carbinol, as well as lowered *dl/meso* ratios, are observed. Thus IV is acting in a double capacity.

The results from the "high current" runs (items 5, 7, 9–11) and those employing a copper electrode (items 12–14) suggest that the above rationale may be oversimplified. While the copper runs also show a decrease in carbinol and *dl/meso* ratios with increasing alkalinity, the ratios are still substantially higher than those found in the analogous studies with mercury pool electrodes in which no carbinol was observed. The "high current" runs, involving somewhat more negative constant potentials (for a given pH), produced in all cases more carbinol than the lower current, lower potential runs. As much as 54% carbinol was now observed in KOH where no carbinol had been observed previously. Once again, the *dl/meso* ratios rose with increasing carbinol production. It is difficult to see, however, how IV could be invoked in strongly alkaline media as the preferred carbinol precursor.

The fact that the stereochemistry *does* change in a consistant fashion with carbinol production must mean that an intermediate in pinacol formation is also a carbinol precursor; *i.e.*, carbinol production is a two-

(11) It may be argued that III, with its favorable five-membered ring, would be the predominant species present. Experimental data for such bonding in neutral ketyl radicals, however, is not available. Whether III actually arises from the ketyl as shown or is derived from the protonated nitrogen moiety receiving the electron is not critical to the discussion.

(12) It is urged that construction of Fieser–Dreiding models be used to verify these comments, strongly condensed to conserve journal space. Reference to the earlier material for acetophenone should also prove particularly helpful.

(13) In analogous photopinacolization studies where no carbinol is observed, the higher *dl/meso* ratios of 0.75–0.98 are observed for 2-acetylpyridine in acidic media (J. H. Stocker and D. H. Kern, unpublished results).

step process. It further indicates that more than one route is involved in pinacol formation.

If it is argued that the ketyl radical III is the intermediate reduced to carbinol at higher pH's, an active role must be assigned to anion II. Then the combination of II and III (route C), in the presence of decreased amounts of III due to its loss to form carbinol, could be increasingly important and account for the higher *dl/meso* ratios. Thus, the high current, the more negative potentials on the mercury electrodes, and the appreciably more negative potentials observed with the copper electrodes would all represent the same phenomena: an increasing ease of reduction of III to carbinol, a consequent decrease in dimerization of III, and an increase in the combination of II with III. The above presupposes that the solution equilibria involved must be slow enough to be effectively disturbed by the withdrawal of some constituent; there would otherwise be no change in the stereoselectivity observed.

It may be added that the controlled potential reduction of 2-acetylpyridine should be considered attractive for the synthesis of preparative scale amounts of the carbinol and the *meso*-pinacol, the former in strongly acidic media and the latter in alkaline media at moderate current levels.

Experimental Section

The routine chemicals employed were either reagent grade or the best research grade obtainable and were further purified by conventional techniques where necessary.

The general procedure has been reported in detail.[1,2,14] All runs involved 1 g of ketone in 60 ml of solution. Modifications in the general procedure are described in Table I. *dl/meso* ratios were determined by a comparison of peak heights of the methyl groups of the two diastereomers. Yields were based on a comparison, after normalization, of the integrated area of the methyl groups with the total aromatic area. Recovered ketone was evaluated similarly.

meso-**2,3-Di(2-pyridyl)-2,3-butanediol.**—This material was isolated by simple crystallization from reaction mixtures corresponding to item 16 in Table I (2 *M* KOAc, 80% EtOH, −1.15 V, and initial current 600 mA). Two recrystallizations from hot heptane yielded chunky white crystals, mp 142–143°. Photochemical bimolecular reduction of 2-acetylpyridine was also employed.[6]

dl-**2,3-Di(2-pyridyl)-2,3-butanediol.**—A modification of the procedure reported by Bencze and Allen[6] was employed. To an ether solution of methylmagnesium iodide (from 0.25 mol of Mg and 0.25 mol of CH_3I) was added 12.1 g (0.06 mol) of α-pyridil. Following an 18-hr reflux and conventional work-up, 7.9 g of *dl*-pinacol (55%), mp 139–140°, was isolated. Two recrystallizations from hexane yielded fine needle crystals, mp 142°.

Registry No.—2-Acetylpyridine, 1122-62-9; methyl-2-pyridylcarbinol, 18728-61-5; *meso*-2,3-di(2-pyridyl)-2,3-butanediol, 20445-38-9; *dl*-2,3-di(2-pyridyl)-2,3-butanediol, 20445-39-0.

Acknowledgment.—Financial support from the U. S. Atomic Energy Commission under Contract AT-(40-1)-2833 (ORO-2833-21) is gratefully acknowledged. The nmr instrument utilized, an A-60 (Varian Corp.), was awarded to Louisiana State University in New Orleans by the National Science Foundation under Grant GP-3674.

(14) A Ag/AgCl reference electrode was used in place of the previously employed standard calomel electrode. As used with saturated KCl, it is 0.04 V more negative than the latter.

Quantitative Studies in Stereochemistry. Photochemistry. VII. Electrochemistry. IV. The Photochemical and Electrochemical Bimolecular Reduction of Aldehydes and Unsymmetrical Ketones; a Common Stereochemistry[1]

JACK H. STOCKER, ROY M. JENEVEIN, AND DAVID H. KERN

Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122

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New and previously published data in the two title areas are tabulated and the stereochemical results from the two techniques are compared. In all cases, both photochemical and electrochemical pinacolizations gave essentially the same ratios of diastereomeric *dl*- to *meso*-pinacols in acid solution with corresponding changes of ratios in basic media. Mechanisms previously proposed for the photochemical and the electrochemical routes are shown to be mutually compatible. Several examples of contrasting behavior, *i.e.*, successful pinacolization by only one of the two techniques, are reported and discussed.

A number of papers from this laboratory have reported the *dl/meso* ratios of diastereomeric pinacols formed in the photochemical[2-7] and electrochemical[8-10] bimolecular reduction of benzaldehyde and unsymmetrical ketones. As the roughly parallel studies in the two areas progressed, it became increasingly apparent that the diastereomeric ratios observed could only be explained by the two techniques sharing a common mechanism at some terminal point. This present report brings together data from all previous papers, selected to facilitate comparisons, with additional unpublished

(1) Presented in part before the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **31**, 3755 (1966). (Acetophenone in neutral and acid media)

(3) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 291 (1968). (Acetophenone in basic media; benzaldehyde)

(4) J. H. Stocker, D. H. Kern, and R. M. Jenevein, *ibid.*, **33**, 412 (1968). (*p*-Substituted acetophenones)

(5) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 1270 (1968). (Acetophenone in amine media)

(6) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 1271 (1968). (Deoxybenzoin)

(7) J. H. Stocker and D. H. Kern, submitted for publication in *J. Org. Chem.* (2-Acetylpyridine)

(8) J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, **33**, 294 (1968). (Acetophenone)

(9) J. H. Stocker and R. M. Jenevein, *ibid.*, **33**, 2145 (1968). (Benzaldehyde and propiophenone)

(10) J. H. Stocker and R. M. Jenevein, *ibid.*, **34**, 2807 (1969). (2-Acetylpyridine)

information that permits a maximum number of cross correlations. The only variable common to the two techniques that was demonstrated to have a major effect on the stereochemistry was pH; the data, accordingly, have been grouped in such a way as to reflect this. The new data appear in Table I; the summary tabulation appears in Table II.

TABLE I

PINACOLIZATION OF SUBSTITUTED ACETOPHENONES[a]

Item	Technique[b]	Time, hr	Pinacol,[c] %	Ratio of *dl*/*meso*	Modifications
			Propiophenone[d]		
1	P	2	7.4	1.34	1 drop AcOH added
2	P	18	63.9	1.24	1 drop AcOH added
3	P	30	91.1	1.23	1 drop AcOH added
4	P	18	45.2	1.45	50% aq
5	P	18	36.0	2.13	50% aq, soln 0.01 *N* in KOH
6	P	18	26.1	2.98	50% aq, soln 0.2 *N* in KOH
7	P	72	70.2	2.17	Same as 6
8	P	18	31.9	3.10	50% aq, soln 0.5 *N* in KOH
9	P	72	(98.0% *dl*, 0% *meso*)		Pure *dl*-pinacol as starting material, 50% aq, soln 0.2 *N* KOH
			p-Chloroacetophenone[e]		
10	P	24	23	2.92	Basic, see 6
11	P	48	30	2.22	Basic, see 6
12	E	3	88	1.18	Soln 1.7 *M* in AcOH, 1.0 *M* in LiCl, −1.1 V, 200 mA[f]
13	E	4	95	3.08	Soln 0.2 *M* in KOAc, −1.7 V, 410 mA[f]
			p-Methoxyacetophenone[e]		
14	P	168	26	2.25	Basic, see 6
15	E	9	96	1.24	Acidic, see 12, −1.2 V, 500 mA[f]
16	E	4	96	3.03	Basic, see 13, −1.7 V, 300 mA[f]
			p-Trifluoromethylacetophenone[e]		
17	E	1	87	1.02	Acidic, see 12, −1.2 V, 490 mA[f]
			Deoxybenzoin[g]		
18	E	1.5	44	1.33	Acidic see 12, −1.2 V, 530 mA[f]
19	E	3	98	3.20	Basic, see 13, −1.4 V, 410 mA[f]

[a] Previously unpublished. [b] P = photochemical, absolute 2-propanol solvent; E = electrochemical, Hg pool electrode, 80% ethanol solvent. [c] Based on starting ketone. [d] Isotope dilution studies utilizing propiophenone-7-^{14}C; see ref 9. [e] Nmr analysis; see ref 4. [f] Controlled potential, initial current. [g] Nmr analysis; see ref 6.

Results and Discussion[11]

A careful examination of the tabulated ratios in Table II suggests that they may be divided conveniently into three categories: (a) benzaldehyde; (b) acetylpyridine; and (c) "acetophenones," both ring and side-chain substituted. The latter category has been studied the most extensively, and the results permit

(11) Much of this discussion has appeared in previous papers,[3-10] *each dealing solely with electrochemical or photochemical studies.* Some repetition will be necessary to place the results in a larger framework. Reference to earlier papers may be made for more detailed treatment of individual cases.

TABLE II

SUMMARY TABULATION OF BIMOLECULAR REDUCTION OF ArCOR

Item	Technique[a]	*dl*/*meso* ratios[b,c] Acidic media	Basic media
	Ar = C_6H_5, R = H (Benzaldehyde)		
1	P	1.01–1.03[d]	1.15–1.20[d]
2	E	1.1[e]	1.18–1.20[e]
	Ar = C_6H_5, R = CH_3 (Acetophenone)		
3	P	1.06–1.14[f]	2.37–3.20[g]
4	E	0.93–1.41[h]	2.47–3.20[h]
	Ar = C_6H_5, R = C_2H_5 (Propiophenone)		
5	P	1.23–1.34	2.98–3.10
6	E	1.40–1.42[i]	2.67–3.05[i]
	Ar = *p*-ClC_6H_4, R = CH_3 (*p*-Chloroacetophenone)		
7	P	1.1[j]	2.9
8	E	1.2	3.1
	Ar = *p*-$CH_3OC_6H_4$, R = CH_3 (*p*-Methoxyacetophenone)		
9	P	1.3[j]	2.3
10	E	1.2	2.9
	Ar = *p*-$CF_3C_6H_4$, R = CH_3 (*p*-Trifluoromethylacetophenone)		
11	P	0.95–0.98[j]	...[k]
12	E	1.0	...[k]
	Ar = C_6H_5, R = $C_6H_5CH_2$ (Deoxybenzoin)		
13	P	1.15[l]	3.0[l]
14	E	1.3	3.2
	Ar = 2-Pyridyl, R = CH_3 (2-Acetylpyridine)		
15	P	0.78–0.98[m]	0.62–0.65[m]
16	E	0.73–0.78[n]	0.22–0.28[n]

[a] P = photochemical, E = electrochemical. [b] Results from a single run are expressed to the nearest tenth; all other ratios involve 2–12 runs and have been expressed as ranges. [c] Photochemical ratios reported for acid media involve only absolute 2-propanol solvent; in basic media both absolute and 50% aqueous 2-propanol results are included. All electrochemical ratios reported were determined in 80% ethanol and are limited to those runs involving a maximum current of 500 mA or less. [d] From ref 3. [e] From ref 9. [f] From ref 2. [g] From ref 3. [h] From ref 8. [i] From ref 9. [j] From ref 4. [k] Ketone is consumed; no pinacol produced. [l] From ref 6. [m] From ref 7. [n] From ref 10.

somewhat more satisfactory conclusions. After the following general comments, the several categories will be treated individually.

General.—It is generally accepted that the ketyl radical I is produced both photochemically and electrochemically as follows:

$$\underset{h\nu \text{ excited triplet}}{Ar{-}\overset{O}{\overset{\|}{C}}{-}R} + R'H \longrightarrow \underset{I}{Ar{-}\overset{OH}{\overset{|}{C}}{-}R} + R'\cdot$$

$$Ar{-}\overset{O}{\overset{\|}{C}}{-}R + e + H^+ \longrightarrow I$$

Further, it appears well established that the radical anion II is produced electrochemically under "basic" or aprotic conditions.

$$Ar{-}\overset{O}{\overset{\|}{C}}{-}R + e \longrightarrow \underset{II}{Ar{-}\overset{O^-}{\overset{|}{C}}{-}R}$$

Successful photopinacolizations in basic media lead us to suggest that the following equilibrium is involved,

$$I + OB^- \rightleftharpoons II + BOH$$

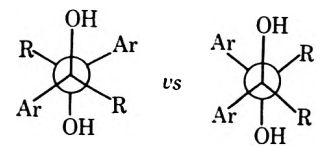
(B = H, alkyl)

both photochemically and electrochemically, the relative amounts of I and II reflecting the amount and strength of added base. Accordingly, *three* possible combinations leading to pinacol have to be considered.

(a) I + I
(b) I + II → *dl*- and *meso*-pinacols
(c) II + II

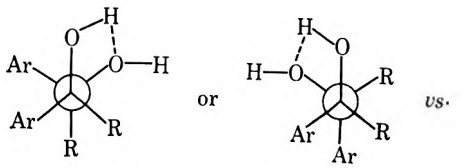
Combination a would be expected to predominate in acid media; combination c would be rejected on the basis of electrostatic repulsion between like-charged species; and combination b would then be expected to make a major contribution in alkaline media. *The following discussion refers interchangeably to both the photochemical and electrochemical techniques.*

Acetophenones.—Perhaps the two most obvious factors that might be expected to exercise stereochemical control of bond formation between species about to combine are the simple steric and the hydrogen bonding. The former would lead to the prediction of a predominance of the *meso* form from A, the *only* possible conformation at the time of bond formation that has *no*

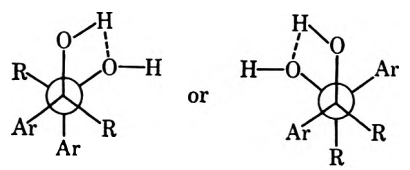


(yields *meso*) A (yields *dl*) B

nonbonded interactions between like groups. *All* other possibilities leading to either diastereomer have one or two such interactions, for example, B. Interspecies hydrogen bonding, however, would appear to favor the *dl* form; a comparison of C or D, each with two nonbonded interactions, with E or F, each with only one, illustrates this.

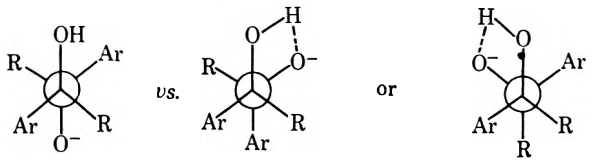


(yields *meso*) C (yields *meso*) D



(yields *dl*) E (yields *dl*) F

The above considerations, in light of the observed slight predominance of the *dl* form for acetophenones in neutral and acidic media, lead to the conclusion that hydrogen bonding is not only important but plays a decisive role. This viewpoint is further strengthened by an examination of the results in alkaline media. Here we have the possibility of hydrogen bridging *via* the anionic oxygen of the radical anion; and the earlier comparison of E or F, producing *dl*, with A, producing *meso*, now becomes a contrasting of H or I with G.



(yields *meso*) G (yields *dl*) H (yields *dl*) I

The greater strength of hydrogen bonding should be reflected in an increased preference for H or I relative to G. This increased preference would be reflected in a sharply increased *dl*/*meso* ratio.[12]

In choosing between E (aryl–aryl interactions) and F (alkyl–alkyl interactions), it is pertinent to note that there is a definite increase in the *dl*/*meso* ratios in acid solution as the alkyl group goes from methyl to benzyl or ethyl. This increase would support the assignment of a greater "effective bulk" to methyl than to phenyl and would lead to the series ethyl ≅ benzyl > methyl > phenyl. Expressed in another way, if the aryl group interactions were the more controlling (*i.e.*, E), the *dl*/*meso* ratios should *decrease* as the alkyl group grew more bulky.[13]

This evaluation receives additional support from certain nmr data. Measurement of the separation of the hydroxylic proton resonance frequencies of the two diastereomers of each pinacol in dilute solution should reflect the relative degree of *intra*molecular hydrogen bonding. The greater the separation in any one pair of diastereomers, the more effectively internally bound the *dl* form (the more deshielded form in all cases) must be. The pertinent figures ($\Delta\ \tau$) are 0.32 for the acetophenone pinacols, 0.46 for the propiophenone pinacols, and 0.61 for the deoxybenzoin pinacols. These figures indicate an increasing amount of intramolecular hydrogen bonding in the *dl* form, relative to the *meso*, with increasing alkyl "size" and strongly suggest control by E (and, by implication, H) of the resultant stereochemistry.

Benzaldehyde.—The diastereomer ratios reported for benzaldehyde show only a very slight stereoselectivity in either acid or base. While it is possible to consider the results as arising from competition between steric control and hydrogen bonding, with hydrogen and phenyl groups interacting, it seems considerably more reasonable to assume simply that hydrogen interactions at the time of coupling may be permitted and the less favorable conformations rejected, for the acetophenones play a greater role. It is further possible that the benzaldehyde ketyl radical and radical anion are simply more reactive than their acetophenone counterparts and hence less discriminating.[14]

These interpretations would lead to the prediction that all aromatic aldehydes would be expected to

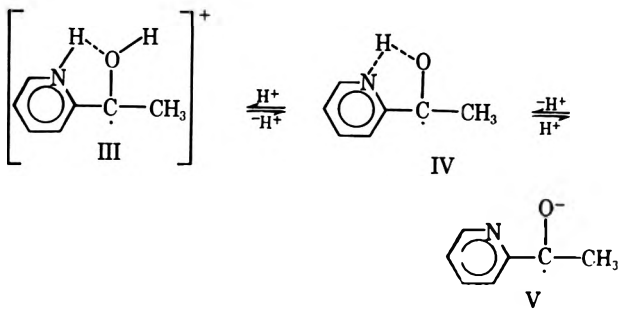
(12) For some comments about the relative fraction of the reaction proceeding through (a) radical dimerization and (b) radical coupling with radical anion, see ref 3, footnote 10.

(13) Preliminary data from cyclohexyl phenyl ketone (electrochemical only) and *ortho*-substituted acetophenones support this viewpoint. The former shows a *dl*/*meso* ratio greater than 1.5:1 in acid media and the latter show sharply *reduced* (compared with acetophenone) ratios in alkaline media.

(14) Some stability data from esr studies support this possibility; *i.e.*, N. Steinberger and G. K. Fraenkel, *J. Chem. Phys.*, **40**, 723 (1964).

display negligible stereoselectivity.[15] What is more germane to this report is, however, that, irrespective of the correctness of this prediction, whatever conclusions are drawn should apply equally satisfactorily to the stereochemistry of both the photochemical and the electrochemical bimolecular reductions.

2-Acetylpyridine.—The results for 2-acetylpyridine require some additional comment. The important intermediates to be considered would be the following.



III IV V

Rejecting any important contribution from the dimerization of charged species III and IV, and assuming that the concentration of V, a rather strong base, will be very small in any protic media, there is left only the dimerization of IV and the coupling of III and IV.

The dimerization of IV would not involve *inter*species hydrogen bonding and would be subject to simple steric control. It should yield predominantly the *meso* form by analogy with the acetophenone systems and would constitute the major pathway. The coupling of III and IV, with possible *inter*species hydrogen bridging, should favor formtion of the *dl* form. To the extent that this coupling makes a contribution in increasingly acid solution, the *dl*/*meso* ratios of pinacols should less favor the *meso* form. Accordingly, for both the electrochemical and photochemical techniques, we would find predominantly the *meso* form, with the highest *dl*/*meso* ratios observed in strong acid and the lowest in strong base.[16,17]

Contrasts between the Two Techniques.—It must be kept in mind that *only* the *final* step in the photopinacolization and electropinacolization reactions is under consideration. The two techniques have very different mechanisms prior to this step, and *only those compounds successfully pinacolized by both techniques can be compared.* Any alternate pathways available to any intermediate and unique to that particular technique would make hypothetical predictions of the expected stereochemistry meaningless. Some specific examples of "unsuccessful" pinacolizations by only one of the two techniques have been observed in this laboratory and are tabulated in Table III. The unsuccessful photopinacolizations of benzaldehyde and 2-acetylpyridine in strong base (>0.1 *N* KOH) are due to an as yet undetermined uv-accelerated alternate reaction. Phenyl cyclohexyl ketone, in turn, photopinacolizes so slowly that alternative cleavage reactions are more rapid and take precedence.[18] Electrochemically, 2-acetylpyridine proceeds so overwhelmingly to the carbinol in strongly acidic media that its pinacolization should be classed as a failure.

Electrochemical failure of the trifluoro ketone to pinacolize is due to complete C–F fission at a potential lower than that required for pinacolization.[19]

TABLE III
CONTRASTS IN PHOTO- AND ELECTROPINACOLIZATION

	Photochemical	Electrochemical
Benzaldehyde	Unsuccessful in strong base	Successful in strong base
α,α,α-Trifluoroacetophenone	Successful in acid	Unsuccessful in acid
2-Acetylpyridine	(a) unsuccessful in strong base (b) successful in strong acid	(a) successful in strong base (b) unsuccessful in strong acid
Phenyl cyclohexyl ketone	Unsuccessful	Successful

Experimental Section

The general procedures and the specialized apparatus employed in the isotope dilution studies have been previously described (electrochemical,[8] photochemical[2]). Alterations in the general procedures to permit nmr analysis have also been reported.[4,9,10] Sources of materials for previously unreported studies may be cross referenced in Table II, *e.g.*, the propiophenone-7-^{14}C and its related pinacols utilized in the photochemical studies are described in the indicated reference to the electrochemical analogs.

Registry No.—Propiophenone, 93-55-0; *p*-chloroacetophenone, 99-91-2; *p*-methoxyacetophenone, 100-06-1; *p*-trifluoromethylacetophenone, 709-63-7; deoxybenzoin, 451-40-1.

Acknowledgment.—Financial support of this research under Atomic Energy Contract AT-(40-1)-2833 (ORD-2833-22) is gratefully acknowledged. The nmr instrument employed, an A-60 (Varian Corp.), was awarded to Louisiana State University in New Orleans by the National Science Foundation under GP-3674.

(15) The electrochemical bimolecular reduction of *p*-hydroxybenzaldehyde [J. Grimshaw and J. S. Ramsay, *J. Chem. Soc., C*, 653 (1964)] in alkaline aqueous media constitutes a known contradiction to this prediction; an 85% crude yield of the *meso*-hydrobenzoin was isolated with none of the *dl* form reported. This is, however, a rather special case involving a charged aldehyde; *i.e.*, the phenoxide form is undoubtedly involved.

(16) This analysis is admittedly an oversimplification. The 2-acetylpyridine system has proved to be a very "sensitive" system, in contrast to acetophenones which are relatively "insensitive." The individual photochemical and electrochemical results from 2-acetylpyridine are treated in much greater depth in ref 7 and 10, respectively. It should perhaps be emphasized, once again, that results from the various systems by each of the two techniques have been selected to facilitate comparisons.

(17) There is a disparity in the electrochemical and photochemical results for 2-acetylpyridine not found in the other systems. The displacement of the *dl*/*meso* ratios to lower values in the electrochemical studies can be explained by invoking III as the precursor to the methyl-2-pyridylcarbinol observed only in the electrochemical runs. This monomolecular reduction product is the predominant one in acid media; and its production, other factors being constant, is directly proportional to the acidity. To the extent that III is removed to form carbinol, the combination of III and IV is diminished and *dl*/*meso* ratios are decreased in the electrochemical studies.

(18) J. H. Stocker and D. H. Kern, *Chem. Comm.*, 204 (1969).

(19) J. H. Stocker and R. M. Jenevein, *ibid.*, 934 (1968).

The Photochemistry of 5,6-Heptadien-2-one

J. K. CRANDALL AND C. F. MAYER

Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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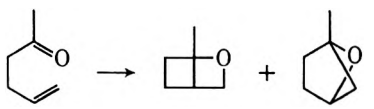
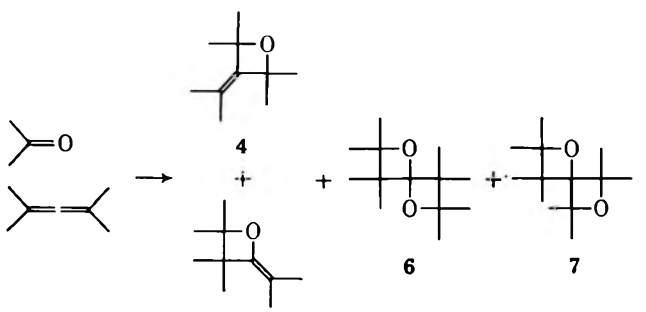
The synthesis and photochemistry of 5,6-heptadien-2-one are described. The major photoproduct is 1-methyl-3-methylene-2-oxabicyclo[2.2.0]hexane. Minor amounts of a second material assigned as isopropenyl 2-butadienyl ether are also observed. Pyrolysis of the bicyclic oxetane yields the minor photoproduct and starting allenic ketone. The first of these thermal products is further rearranged to the second upon standing. The details of these processes are described.

An interesting variation of the Paterno–Büchi[1] reaction (the photochemical 2 + 2 cycloaddition between a ketone and an olefin) is the intramolecular cycloaddition of 5-hexen-2-one (**1**) which yields 1-methyl-2-oxabicyclo[2.2.0]hexane (**2**)[2,3] and 1-methyl-5-oxabicyclo-[2.1.1]hexane (**3**).[3] Several methylated derivatives of **1** have also been found to give analogous products.[3,4]



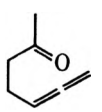
1 **2** **3**

Recent work[5] indicates that allenes can also participate in intermolecular photocycloaddition reactions with carbonyl compounds. For example, Hammond[5a] reports that addition of acetone to tetramethylallene gives monoadducts **4** and **5** and diadducts **6** and **7**. However, in general there appears to be a large preference for carbonyl oxygen to bond to the central carbon of the allene function. In the present study we



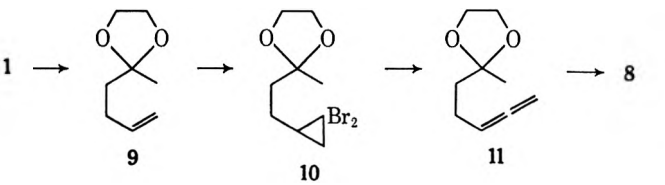
4 **5** **6** **7**

have examined the photochemistry of 5,6-heptadien-2-one (**8**), an analog of **1** which contains isolated carbonyl and allene functions within the same molecule.



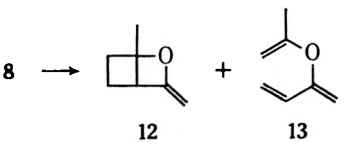
8

5,6-Heptadien-2-one (**8**)[6] was prepared from 5-hexen-2-one (**1**) in a straightforward manner. The ethylene ketal (**9**) of **1** was treated with bromoform and potassium *t*-butoxide in pentane[7] and the resulting adduct **10** was treated with methyllithium to give ketalallene **11**.[8] Careful hydrolysis with 1 *N* sulfuric acid in aqueous tetrahydrofuran gave the desired ketoallene **8**.



9 **10** **11**

A 1% solution of **8** in petroleum ether was irradiated through a Pyrex filter with a 450 W Hanovia lamp. The progress of the reaction was followed by glpc analysis of aliquots taken at intervals. After 46 hr, glpc assay indicated the product to be a 90:6:4 mixture of three materials subsequently identified as 1-methyl-3-methylene-2-oxabicyclo[2.2.0]hexane (**12**), isopropenyl 2-butadienyl ether (**13**), and unreacted starting material. The moderate return of distilled isomeric



12 **13**

materials was accompanied by a fair amount of less volatile residue. Volatile fragmentation products were not observed but probably would not have been visible with the glpc analysis utilized. Samples of the isomeric products were obtained for identification by preparative glpc.

The infrared spectrum of methyleneoxetane **12** exhibits a strong band at 5.92 μ assigned as the C=C stretch of the enol ether.[9,10] The two olefinic protons are coupled to the bridgehead proton and to each other, giving four-line multiplets centered at δ 3.60 and 3.90.[11] The mass spectrum of **12** is very similar to that of ketoallene **8**, except for a significant peak at *m/e* 68

(1) (a) E. Paterno and G. Chieffi, *Gazz. Chim. Ital.*, **39b**, 341 (1909); (b) G. Büchi, C. G. Inman, and E. S. Lipinsky, *J. Amer. Chem. Soc.*, **76**, 4327 (1954); (c) G. Büchi, J. T. Kofron, and D. Rosenthal, *ibid.*, **78**, 876 (1956); (d) G. Büchi and N. C. Yang, *ibid.*, **79**, 2318 (1957); (e) N. C. Yang, *Pure Appl. Chem.*, **9**, 591 (1964).

(2) R. Srinivasan, *J. Amer. Chem. Soc.*, **82**, 755 (1960).

(3) N. C. Yang, M. Nussim, and D. R. Coulson, *Tetrahedron Lett.*, 1525 (1965).

(4) H. Morrison, *J. Amer. Chem. Soc.*, **87**, 932 (1965).

(5) (a) H. Gotthardt, R. Steinmetz, and G. S. Hammond, *J. Org. Chem.*, **33**, 2774 (1968); (b) D. R. Arnold and A. H. Glick, *Chem. Commun.*, 813 (1966).

(6) J. W. Wilson, *ibid.*, 143 (1968).

(7) W. Kirmse, "Carbene Chemistry," Academic Press Inc., London, 1964, p 163.

(8) W. R. Moore and H. R. Ward, *J. Org. Chem.*, **27**, 4179 (1962); L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).

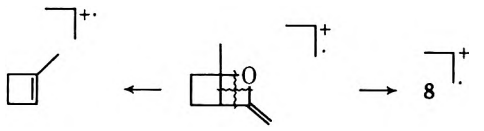
(9) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical—," Holden-Day Inc., San Francisco, Calif., 1962, p 36.

(10) Hammond[5a] observed the corresponding absorption for the monocyclic enol ethers at 5.74–5.79 μ. This difference may be caused by the bicyclic system or the difference in substitution of the double bond.

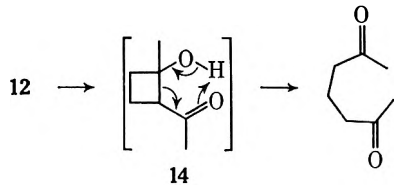
(11) Hammond[5a] reports an AB pattern centered at δ 3.76 for i.

i

(loss of C_2H_2O). This suggests that the important initial mass-spectrometric processes of the molecular ion are the two possible modes of reverse cycloaddition of the oxetane ring.[12]



The spectroscopic evidence for structure **12** is bolstered by the following chemical transformations. Hydrolysis in dilute sulfuric acid gave a single product identified as 2,6-heptanedione. This acyclic material undoubtedly forms by hydrolysis of the enol ether to β-hydroxy ketone **14** which spontaneously isomerizes as indicated.[13] Ozonolysis of **12** gave a neutral product



14

with an intense carbonyl band at 5.49 μ in the infrared[14] consistent with β-lactone structure **15**. The nmr exhibits a one-proton multiplet centered at δ 3.6 appropriate for the bridgehead proton.[14] Further characterization of **15** was not possible because of the tendency for this material to decompose upon glpc purification. The above evidence, however, serves to unambiguously secure structure **15**. Taken together, the above data eliminate **16**, the other possible methyleneoxetane product, as a potential structure for the major photoproduct.

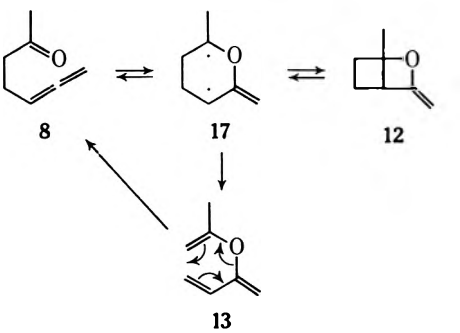
15 **16**

The infrared spectrum of minor photoproduct **13** displays medium-intensity bands at 6.00, 6.12, and 6.29 μ which are assigned to double-bond stretching modes, in addition to strong C–O bands.[9] The only nonolefinic protons in the nmr are those of a methyl group on a double bond (δ 1.84). Absorptions typical for an isolated vinyl group appear at δ 6.14, 5.40, and 5.02 (one proton each), while the four remaining protons appear at δ 4.56 (2), 4.30 (1), and 4.18 (1), positions appropriate for β protons of enol ethers.[15] Insufficient quantities of **13** were isolated for further characterization, but its spectral data, its appearance as a pyrolysis product of methyleneoxetane **12**, and its ready conversion into ketoallene **8** substantiate the proposed structure (*vide infra*).

Vapor phase pyrolysis of methyleneoxetane **12** at 400° gave a mixture of ketoallene **8** and enol ether **13**, whose ratios varied from 7:1 to 3:1 in different runs. When a pyrolysis sample containing an internal standard was allowed to stand at room temperature, **13** decreased by ½ in 6 days and disappeared completely within 12 days. However, the total quantity of **8** plus **13** remained unchanged during this period, thus indicating that enol ether **13** rearranges to ketoallene **8** under rather mild conditions. Pyrolysis of **8** resulted in no change.

Discussion

Photocycloadditions of carbonyls to olefins[1] are thought to be initiated by attack of the electrophilic oxygen of the carbonyl n–π* triplet[16] on the double bond. The resulting biradical species then leads to oxetane by spin inversion and bond formation.[17] In the present instance a similar mechanism is probably operative. Thus, the excited ketone is transformed to biradical **17** which subsequently collapses to bicyclic oxetane **12** by coupling of the transannular radical sites. Alternatively, **17** can fragment to enol ether **13**. Interestingly, no products attributable to oxygen attack at either of the terminal allenic carbons were observed from the photolysis of **8** (*e.g.*, **15**).



8 **17** **12** **13**

Predominance of oxetane products resulting from oxygen bonding to the central carbon of allenes was noted in the earlier work[5] on intermolecular cycloadditions. The most likely explanation for this strong preference is that it reflects the relative stabilities of the intermediate biradicals which result from the different modes of addition.[18] An alternate but less probable rationale is that attack at the terminal allenic carbons occurs competitively with central attack, but that the intermediate from this mode of reaction is not effective in product formation, since its activation energy for reversion to starting material is appreciably less than that for product formation.[19] Superimposed upon this in-

(12) The base peak of the mass spectrum of oxetane results from this type of cleavage: J. H. Beynon in "Advances in Mass Spectrometry," J. D. Waldron, Ed., Pergamon Press, London, 1959, pp 328–354. Cyclobutanones also cleave to olefins and ketenes: H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day Inc., San Francisco, Calif., 1967, pp 145–146.

(13) P. de Mayo, H. Takeshita, and A. B. M. A. Sattar, *Proc. Chem. Soc.*, 119 (1962); P. de Mayo and H. Takeshita, *Can. J. Chem.*, **41**, 440 (1963).

(14) E. J. Corey and J. Streith, *J. Amer. Chem. Soc.*, **86**, 950 (1964).

(15) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1968, p 139.

(16) H. E. Zimmerman, *Advan. Photochem.*, **1**, 183 (1963).

(17) Evidence has been presented which indicates that excited singlet states of ketones also undergo cycloaddition, but orientational features appear to be unchanged. N. J. Turro and P. A. Wriede, *J. Amer. Chem. Soc.*, **90**, 6863 (1968); N. J. Turro, P. A. Wriede, and J. C. Dalton, *ibid.*, **90**, 3274 (1968); N. J. Turro, P. A. Wriede, J. C. Dalton, D. Arnold, and A. Glick, *ibid.*, **89**, 3950 (1967).

(18) Estimates on the energetics for the possible positions of carbonyl oxygen attack on allenes suggest that formation of a vinyl radical by terminal carbon attack should be appreciably less favorable than generation of the radical from central attack, even if significant allylic stabilization is not developed in the transition state for the latter process: B. E. Knox and H. B. Palmer, *Chem. Rev.*, **61**, 247 (1961); T. L. Cottrell, "The Strength of Chemical Bonds," 2nd ed, Butterworths Scientific Publications, London, 1958, pp 173–183; C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, pp 50–53.

(19) A similar explanation has been advanced to account for orientation effects in simple free-radical additions to allenes: D. R. Taylor, *Chem. Rev.* **67**, 317 (1966).

herent orientational preference in the instance of an intramolecular example such as **8** is the effect of the methylene chain which links the interacting functions. An accurate assessment of this feature is difficult, owing to a paucity of information about the geometry and electron distribution of the excited carbonyl function.[20] However, the present results indicate that the intramolecular reaction is, if anything, more selective than its intermolecular counterpart.

The thermal isomerization of oxetane **12** is also of some interest and appears to proceed by initial bond fission to the familiar biradical **17**. This species is capable of reverting to ketoallene **8** or undergoing bond reorganization to produce **13**. Evidently, thermal equilibrium is not achieved in the flow pyrolysis experiment, since **13** would be expected to isomerize completely to **8** by a thermal Cope rearrangement.[23] Indeed, such was found to occur under relatively mild conditions. Pyrolysis of ketoallene **8** does not yield **12**, in consonance with this explanation.

Experimental Section

Infrared spectra were obtained with Perkin-Elmer Infracord Model 137 and 137-G spectrophotometers as neat films unless otherwise noted. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard. Mass spectra were determined using an AEI MS9 spectrometer at 70 eV. Gas–liquid partition chromatography (glpc) was carried out on a Varian-Aerograph Series 1200 chromatograph (analytical, flame ionization detector) using a 10 ft × 1/8 in. 15% Carbowax 20M on 60–80 Chromosorb W column and on an Aerograph Model A700 chromatograph (preparative) using a 5 ft × 3/8 in. 15% Carbowax 20M on 60–80 Chromosorb W column. Percentage composition data were measured using a Disc Model 224 integrator and are not corrected for detector response. Analyses were performed by Midwest Microlab, Inc. All solvents were Fisher reagent grade unless otherwise noted.

5,6-Heptadien-2-one (8).[6]—A stirred mixture of 68 g of 5-hexen-2-one (**1**) (Aldrich Chemical Co.), 50 g of ethylene glycol, 100 ml of benzene, and 53 mg of *p*-toluenesulfonic acid was heated to reflux for 17 hr with removal of 16.5 ml of water by a Dean–Stark trap. The solution was allowed to cool to room temperature and washed with three 75-ml portions of saturated sodium bicarbonate solution and 75 ml of water. The benzene and water were removed at atmospheric pressure. The residue was distilled at reduced pressure to give 84 g (85%) of ethylene ketal (**9**): bp 80–82° (43 mm); glpc purity, 98%; ir 3.22, 6.08, 10.0, and 11.0 μ ($CH{=}CH_2$), and 8.0, 8.2, 8.9, and 9.5 μ (COCOC); nmr δ 5.80 (m, 1, $CH{=}CH_2$), 4.9 (m, 2 $CH{=}CH_2$), 3.82 (s, 4, OCH_2), 2.1 (m, 2), 1.7 (m, 2), and 1.22 ppm (s, 3).

To a stirred slurry of 50 g of potassium *t*-butoxide (MSA Research Corp.) in 50 ml of pentane and 63.5 g of **9** at 0° was added dropwise 113 g of bromoform. Pentane (350 ml total) was added to the reaction mixture as required to keep the slurry thin enough to stir. Stirring was continued for 30 min after the addition time. Water (200 ml) was added and the mixture was suction filtered to remove a brown solid. To the two-phase filtrate was added 100 ml of saturated salt solution, the mixture was shaken, and the layers were separated. The organic layer was washed with two 100-ml portions of saturated salt solution and dried (Na_2SO_4). The solvent was removed at reduced pressure. Most of the unreacted ketal **9** and bromoform were distilled from the mixture at reduced pressure (84 g, bp 76–82°, 40 mm). Nmr analysis shows a 1.4:1.0 mole ratio of **9** to bromoform in this mixture which could be used as starting material for additional **10**.

Further distillation gave 37 g (26%) of the dibromocarbene adduct **10**: bp 101–105° (0.25 mm); ir 8.0, 8.2, 8.6, 9.0, 9.5, and 9.6 μ (COCOC); nmr δ 3.89 (s, 4, OCH_2), 1.26 (s, 3), and 1.2 and 1.7 ppm (m, 7).

A solution of 57 g of methyl iodide in 50 ml of ether was added slowly to a stirred suspension of 8.5 g of lithium wire in 100 ml of ether under nitrogen. The mixture was kept at reflux for 1 hr after addition of the methyl iodide. The mixture was cooled to 25°, the excess lithium was removed with a spatula, and the methyllithium solution was transferred to an addition funnel under a nitrogen atmosphere. This mixture was added slowly to a stirred solution of 32 g of dibromocyclopropane **10** in 150 ml of ether at 0°. The solution was stirred for 30 min after the addition was completed; then 100 ml of water was added. The layers were separated and the organic layer was washed with two 100-ml portions of water. The water solutions were combined and washed with 50 ml of ether. The ether solutions were combined and dried (Na_2SO_4), and the ether was removed to give crude **11**. Distillation afforded 14.0 g (84%) of **11**: bp 96–99° (20 mm); glpc purity, 95%; ir 5.10 and 11.8 μ ($C{=}C{=}CH_2$), and 8.0, 8.2, 8.8, 9.1, and 9.5 μ (COCOC); nmr δ 5.0 (m, 1, $C{=}C{=}CH$), 4.6 (m, 2, $CH_2{=}C{=}C$), 3.82 (s, 4, CH_2O), 1.8 (m, 4), and 1.22 ppm (s, 3).

To a mixture of 25 ml of 6 *N* sulfuric acid and 125 ml of tetrahydrofuran was added 14.0 g of **11** and the homogeneous solution was stirred at 25° for 4 hr. The solution was diluted with 250 ml of water and extracted with three 100-ml portions of pentane. The pentane extract was washed with two 100-ml portions of saturated sodium bicarbonate solution and 100 ml of saturated salt solution. The pentane and most of the tetrahydrofuran were removed. Another 50 ml of pentane was added and the solution was dried (Na_2SO_4). The pentane was removed and the residue was distilled to yield 6.73 g (66%) of 5,6-heptadien-2-one (**8**): bp 64–67° (15 mm); glpc purity, 95%; ir 5.10 and 11.8 μ ($C{=}C{=}CH_2$), and 5.82 μ ($C{=}O$); nmr δ 5.1 (m, 1, $C{=}C{=}CH$), 4.6 (m, 2, $CH_2{=}C{=}C$), 2.3 (m, 4), and 2.07 ppm (s, 3); mass spectrum *m/e* (rel intensity) 110 (4), 95 (9), 67 (15), 58 (10), 53 (12), 43 (100), and 15 (6).

Photolysis of 5,6-Heptadien-2-one (8).—Irradiations were carried out using a Pyrex-filtered 450 W Hanovia Type L medium-pressure mercury arc with a water-cooled quartz immersion well. The solutions were degassed prior to irradiation by bubbling prepurified nitrogen through them for 1 min using a glass tube with a fritted-glass tip, immediately inserting the immersion well, and maintaining a slight positive nitrogen pressure throughout the photolysis. Aliquots were removed by syringe through a serum cap for periodic glpc assay.

Irradiation of a stirred solution of 4.32 g of 98% pure **8** in 410 ml of redistilled 30–60° petroleum ether for 46 hr gave a mixture which glpc analysis indicated to be 91% 1-methyl-2-oxa-3-methylenebicyclo[2.2.0]hexane (**12**), 6% isopropenyl 2-butadienyl ether (**13**), and 4% **8**. Most of the solvent was removed at reduced pressure and the residue was transferred to a Dry Ice–acetone trap at 25° (0.35 mm). A yellow, nonvolatile (0.9 g) remained. After removal of the remaining solvent, the residual 2 ml of colorless liquid was separated by preparative glpc to give 0.38 g of **12**: glpc purity, 98%; ir 5.92 μ ($C{=}C{-}O$); nmr δ 3.9 and 3.6 (m, 2, $O{-}C{=}CH_2$), 3.3 (m, 1, $CH{-}C{=}CH_2$), 2.3 (m, 4), and 1.42 ppm (s, 3); mass spectrum *m/e* (rel intensity) 110 (13), 95 (13), 68 (12), 67 (24), 58 (13), 53 (16), 43 (100), and 15 (5). Re-collection gave an analytical sample.

Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.04; H, 9.37.

A small amount of **13** was also collected: ir (CCl_4) 6.00, 6.12, 6.29, 8.0, and 9.6 μ ($C{=}C{-}O$ and $C{=}C{-}C{=}C$); nmr δ 6.1 (m, 1, $CH{=}CH_2$), 5.4 and 5.0 (m, 2, $CH{=}CH_2$), 4.56 (m, 2, $C{=}CH_2$), 4.3 and 4.18 (m, 2, $CH_3{-}C{=}CH_2$), and 1.84 ppm (d, 3, J = 1 Hz, CH_3).

Vapor Phase Pyrolysis of 12.—The apparatus consisted of a 10 mm i.d. Pyrex tube packed with 0.25 in. o.d. Pyrex helices inserted through a 170 mm E. H. Sargent and Co. tube furnace. The sample was placed in a flask attached at one end of the tube and the vapors were condensed in a Dry Ice–acetone trap at the other end. The pressure in the system was reduced to less than 1 mm by a vacuum pump attached at the trap, and the samples

(20) One reasonable model would utilize the carbonyl group in its ground-state geometry with attack by the half-filled oxygen p orbital in the plane of the carbonyl.[21] However, rehybridization to a nonplanar geometry is also a reasonable possibility.[22]

(21) N. J. Turro and D. S. Weiss, *J. Amer. Chem. Soc.*, **90**, 2185 (1968).

(22) D. E. Freeman and W. Klemperer, *J. Chem. Phys.*, **45**, 52 (1966); J. C. D. Brand and D. G. Wilkinson, *Advan. Phys. Org. Chem.*, **1**, 365 (1963); E. W. Abrahamson, J. G. F. Littler, and K. P. Vo, *J. Chem. Phys.*, **44**, 4082 (1966).

(23) A. C. Cope and E. M. Hardy, *J. Amer. Chem. Soc.*, **62**, 441 (1940); A. C. Cope, K. E. Hoyle, and D. Heyl, *ibid.*, **63**, 1843 (1941); W. von E. Doering and W. R. Roth, *Angew. Chem. Intern. Ed. Engl.*, **2**, 115 (1963).

were allowed to vaporize and pass through the tube. About 40 mg of methyleneoxetane **12** was pyrolyzed at 400°. Less than 5 min was required for passage, and longer pumping reduced the amount of trapped dienol ether **13**. Glpc assay revealed a ratio of 72:28 for **8**:**13**. The nmr of this mixture exhibited the absorptions of **13** at δ 6.14, 5.4, 4.3, 4.18, and 1.84 ppm, the remaining peaks being hidden by the spectrum of **8**. To *ca.* 0.1 ml of a mixture (47% **8**, 47% **12**, and 6% **13**) from photolysis of a 1% solution of **8** in redistilled 30–60° petroleum ether was added ~1 μl of the above pyrolysis mixture. Glpc analysis of this sample on three different columns (10 ft 10% DEGS, 10 ft 15% Carbowax 20M, 5 ft 10% SE-30; all $^1/_8$ in. o.d.) showed only the three peaks originally present in the photolysis mixture.

Another 55-mg sample of **12** was pyrolyzed in the same manner as above. The trapped product mixture was transferred to an nmr capillary microtube and 1 drop of *p*-xylene was added. Integration of the nmr revealed an initial ratio of 6:1 for **8**:**13**. After 6 days at 25°, the corresponding ratio was 12:1; after 12 days, no **13** remained. Standardization against the added *p*-xylene demonstrated that the (**8** + **13**)/*p*-xylene ratio remained constant, thus indicating the conversion of **13** into **8**.

A sample of ketoallene **8** was recovered unchanged from pyrolysis at 400°.

Hydrolysis of 12.—A solution of 100 mg of methyleneoxetane **12** in 1 ml of ether was shaken with 5 ml of 1 *M* sulfuric acid for 5 min. To this was added 20 ml of ether, the mixture was shaken, and the layers were separated. The water layer was washed with two 15-ml portions of ether. The combined ether solutions were washed with 5 ml of saturated sodium bicarbonate solution and dried (Na_2SO_4). Removal of the ether gave 0.13 g of a colorless liquid which was collected by glpc to yield 48 mg (41%) of 2,6-heptanedione: glpc pure; mp 29–32° (lit.[24] mp 30–33°); ir (CCl_4) 5.83 μ (C=O); nmr δ 2.40 (m, 4, CH_2CO), 2.05 (s, 6, CH_3CO), and 1.76 ppm (m, 2, $CH_2CH_2CH_2$).

Ozonolysis of 12.—A solution of 1.00 g of vacuum transferred product mixture from photolysis of **8** (~45% **12** by glpc analysis) in 50 ml of methylene chloride containing 2 ml of pyridine was cooled to −80°. The output of a Welsbach Model T-408 ozonator was bubbled through the solution for 2 hr. The solution was flushed with oxygen for 30 min, allowed to warm to room temperature, and washed with three 25-ml portions of 10% hydrochloric acid. The combined aqueous washings were back extracted with 20 ml of methylene chloride. The combined methylene chloride solutions were shaken vigorously with four 15-ml portions of saturated sodium bicarbonate solution (an unidentified carboxylic acid was removed only with much effort) and dried (Na_2SO_4). The solvent was removed to give 0.24 g (~50%) of 1-methyl-2-oxa-3-oxobicyclo[2.2.0]hexane (**15**): ir 5.49 μ (vs, β-lactone); nmr δ 3.6 (m, 1, CHCO), 2.3 (m, 4), and 1.58 ppm (s, 3). Attempts at glpc analysis or purification of neat samples of **15** gave two peaks with very short elution times and only a relatively small peak with an elution time appropriate for β-lactone **15**. Presumably, decomposition of **15** to carbon dioxide and olefinic products is occurring on the glpc column.

Photolysis of 8 in Methanol.—Irradiation of 1% solutions of ketoallene **8** in methanol on several occasions revealed the presence of methyleneoxetane **12** after a few per cent conversion. However, further irradiation led to disappearance of **12** and formation of several unidentified products with glpc elution times longer than that of **8**. A buffered methanol–water mixture was prepared by adding 5 ml of saturated sodium bicarbonate solution to 105 ml of methanol. The mixture was stirred for 6 hr at 25° to allow equilibration, and the undissolved sodium bicarbonate was removed by gravity filtration. Irradiation of 1.00 g of **8** in this solvent for 28 hr gave 42% conversion (glpc assay) to **12** with only traces of other products. A sample of **12** isolated by preparative glpc gave infrared and nmr spectral data identical with those reported previously for **12**.

(24) S. Danishefsky and R. Cavanaugh, *J. Amer. Chem. Soc.*, **90**, 520 (1968).

Registry No.—**8**, 20449-20-1; **9**, 20449-21-2; **10**, 20449-22-3; **11**, 20449-23-4; **12**, 20500-56-5; **13**, 20449-24-5; **15**, 20455-51-0; 2,6-heptanedione, 13505-34-5.

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Nuclear Magnetic Resonance Studies of Enol–Enol and Keto–Enol Equilibria in Substituted Benzoylacetones[1a,b]

D. J. SARDELLA,[1c,d] D. H. HEINERT,[1e] AND B. L. SHAPIRO[1f]

Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616

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Nmr investigation of a series of *para*-substituted benzoylacetones has established that they exist largely (75–98%) as chelated *cis*-enols. Long-range coupling constants suggest that the benzoyl carbonyl group enolizes, forming the cinnamoyl chromophore, and that little benzoylethylene enol is present. Substituent effects on the keto–enol equilibrium are discussed. It has been found that the rule that electron-releasing groups stabilize adjacent carbonyl groups is valid in these systems.

The tautomerism of benzoylacetone and its derivatives has been investigated by a number of physical methods[2–6] and treated briefly by simple Hückel molecular orbital calculations.[7] Although it is generally accepted that the phenyl group increases the enol content, there is disagreement over the question of whether the stabilization derives from mesomeric electron delocalization[7,8] or inductive electron withdrawal.[9] In an attempt to shed some light on this question, we have undertaken a nuclear magnetic resonance study of substituent effects on the tautomeric equilibria in a series of six *para*-substituted benzoylacetones in chloroform-*d*. Study of the long-range couplings provides evidence for the direction of enolization, and consideration of the concentration and substituent dependence of the hydroxyl resonance position allows us to discuss the probable importance of *trans*-enols.[4,10]

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(2) F. Iimura, *Nippon Kagaku Zasshi*, **77**, 1855 (1956).

(3) R. D. Campbell and H. M. Gilow, *J. Amer. Chem. Soc.*, **84**, 1440 (1962).

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(5) J. U. Lowe and L. N. Ferguson, *J. Org. Chem.*, **30**, 3000 (1965).

(6) M. Gorodetsky, Z. Luz, and Y. Mazur, *J. Amer. Chem. Soc.*, **89**, 1183 (1967).

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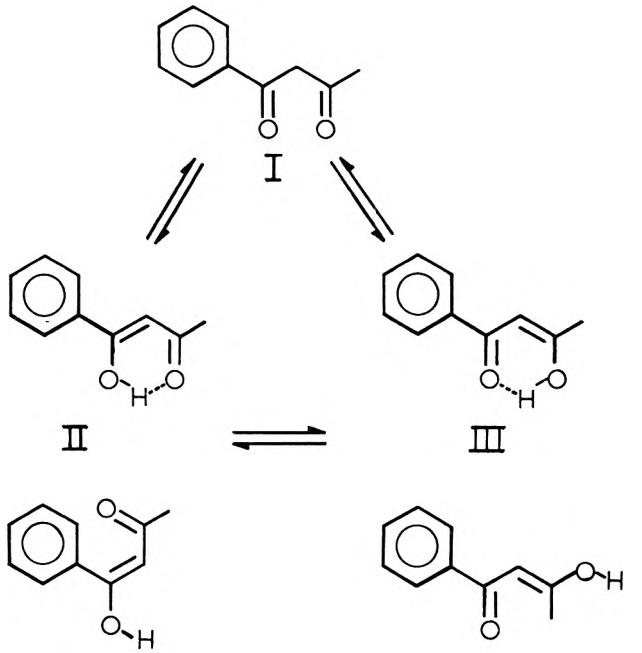
(8) R. L. Lintvedt and H. F. Holtzclaw, *Inorg. Chem.*, **5**, 239 (1966).

(9) J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 2105 (1964).

(10) M. I. Kabachnik, S. T. Ioffe, E. M. Popov and K. V. Vatsuro, *Tetrahedron*, **12**, 76 (1931).

The complete tautomeric equilibrium consists of five possible species (neglecting other species with which they may be associated): diketone I, the pairs of *cis*- and *trans*-enols II (henceforth cinnamoylenol) and III



(henceforth benzoylethyleneenol),[11] and the results thus far accumulated indicate the most stable species in solution to be a *cis*-chelated enol, probably II. The Hückel molecular orbital calculations of Forsen, neglecting the hydrogen bond, indicate the equilibrium constant for II $\rightleftharpoons$ III to be about 12, favoring the cinnamoylenol.[7] Although these results probably reflect more truthfully the relative stabilities of the *trans*-enols, it seems unlikely that the hydrogen bonds in the chelated enols will be so different in strength as to invert the relative stabilities of the enols.

Results

A series of six substituted benzoylacetones (*p*-N,N-dimethylamino-, *p*-methoxy-, *p*-methyl-, *p*-bromo-, *p*-nitro-, and the parent benzoylacetone), examined over the accessible concentration ranges in chloroform-*d*, exhibit the following regularities: two peaks in the region characteristic of acetyl and unsaturated C-methyl groups, one each in the methylene, vinylic, and strongly hydrogen-bonded hydroxyl regions, and an aromatic multiplet. In addition, the substituent groups of *p*-CH_3-BA,[12] *p*-CH_3O-BA, and *p*-$N(CH_3)_2$-BA give rise to the characteristic aromatic C-methyl, O-methyl, and N-methyl resonances, respectively.

Assignment of peaks was unambiguous except for the methyl region of *p*-methylbenzoylacetone, which exhibits peaks at τ 7.64, 7.79, and 7.98. In this case, synthesis of *p*-(trideuteriomethyl)benzoylacetone in 90% isotopic purity established the lowest field methyl resonance (τ 7.64) to be due to the ring methyl, as might be expected from the great deshielding by the benzene ring.

(11) The corresponding enols *cis* II and *cis* III with unchelated hydroxyl are considered to be unimportant in view of the ease with which the hydrogen bond could be formed and the large enhancement of stability which would accompany formation of the hydrogen bond.

(12) Henceforth, benzoylacetone will be abbreviated BA.

Long-Range Coupling.—Couplings across four bonds are sensitive to the nature of the transmitting path, and it was anticipated that they might provide information on the nature of the species present in solution. Long-range proton–proton couplings have been discussed by Sternhell[13] and Burdett.[14] Under close examination, the methylene groups of *p*-H-BA, *p*-CH_3-BA, *p*-CH_3O-BA, and *p*-$N(CH_3)_2$-BA proved to be quartets, and the low-field methyl groups to be triplets.[15] The values for the couplings (at about 0.08-mol of fraction ketone) are summarized in Table I, along with the value reported by Burdett[14] for acetylacetone.

TABLE I
LONG-RANGE COUPLINGS IN DIKETONES

Compd	Coupling, Hz
p-H-BA	0.44 ± 0.02
p-CH_3-BA	0.42 ± 0.03
p-CH_3O-BA	0.42 ± 0.03
p-$N(CH_3)_2$-BA	0.45 ± 0.03
Acetylacetone	0.44

Inspection of the vinylic resonances revealed no discernible splittings, nor was any splitting noticeable in the remaining methyl peaks. However, since it is possible that small couplings, though unresolvable, may manifest themselves by line broadening, we examined the unsplit methyl resonances of *p*-H-BA, *p*-CH_3-BA, *p*-CH_3O-BA, and *p*-Br-BA, comparing their line widths at half-height with the tetramethylsilane line width. The maximum couplings inferred in this manner are tabulated below.[16] In all four cases, the couplings are quite small (Table III). Similar examination of the substituent methyl resonances of *p*-CH_3-BA and *p*-CH_3O-BA indicated maximum couplings of 0.5 and 0.12 Hz, respectively. In no cases was there any evidence for discernible coupling between the hydroxyl proton and any other proton in the molecule, although Burdett[14] has reported a coupling of 0.71 Hz between the hydroxyl and vinyl protons of ethyl acetoacetate.

TABLE II
LONG-RANGE COUPLINGS IN ENOLS

Compd	Maximum coupling, Hz
p-H-BA	0.07
p-CH_3-BA	0.00
p-CH_3O-BA	0.13
p-Br-BA	0.10

Chemical Shifts. Substituent Effects.—The chemical shifts of the six benzoylacetones are listed in Table III for concentrations in the region 0.05–0.08-mol fraction in chloroform-*d*. Since the work of Marcus, Reynolds, and Miller[17] has shown that, in many cases, good correlations exist between chemical shifts and substituent constants for series of related compounds,

(13) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(14) J. L. Burdett, Ph.D. Thesis, Michigan State University, 1963.

(15) Undoubtedly the situation is the same in the remaining compounds; however, there is so little diketone present in these cases that noise obscures the couplings.

(16) The peak was assumed to be the enol methyl resonance, so to be an unresolved doublet. Hence the maximum value the coupling can have must be $W_{1/2}$ (obsd) − $W_{1/2}$ (TMS), where $W_{1/2}$ refers to the widths at half-height of the enol methyl and TMS, respectively.

(17) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).

TABLE III
CHEMICAL SHIFTS OF SUBSTITUTED BENZOYLACETONES (0.05–0.08-MOL FRACTION)

R	$N(CH_3)_2$	CH_3O	CH_3	H	Br	NO_2
σ	−0.83	−0.268	−0.17	0.00	0.232	0.778
CH_3 (enol)	7.90	7.85	7.87	7.85	7.84	7.74
CH_3 (keto)	7.77	7.72	7.73	7.72	7.73	7.63
CH_2 (keto)	6.05	5.98	5.95	5.93	5.97	5.70
CH (enol)	3.95	3.91	3.85	3.85	3.90	3.74
H (*ortho*)	3.37	3.10	2.86	...	2.31	1.61
H (*meta*)	2.22	2.17	2.19	...	2.31	2.10
OH (enol)	−6.52	−6.48	−6.26	−6.27	−6.00	−5.67
CH_3 (substituent)	7.00	6.18	7.61	...	...	...

we attempted to correlate the shifts of each type of proton (except the aromatic protons) with the Hammett σ constants of the substituents, hoping to derive information relating to transmission of electronic effects, especially to the hydrogen-bonded proton. The results of the correlations are summarized in Table IV. The significant datum is the slope obtained for the hydroxyl proton shifts. All other correlations are unexceptional; *i.e.*, resonances shift to lower field with greater substituent electron-withdrawing power. The aromatic protons (whose shifts were obtained by a pseudo-AB analysis of the four principal lines of the multiplet for the five substituted benzoylacetones) were not included in the correlation because it is likely that magnetic anisotropy effects, especially in *p*-NO_2-BA, override the normal electronic effects.

TABLE IV
PARAMETERS FOR HAMMETT-TYPE CORRELATIONS OF CHEMICAL SHIFTS

Peak	Slope	Intercept	Correlation coefficient	Standard deviation
CH_3 (enol)	−0.0939	7.838	0.929	0.0225
CH_3 (keto)	−0.0777	7.713	0.899	0.0226
CH_2 (keto)	−0.1990	5.921	0.890	0.0610
CH (enol)	−0.1174	3.862	0.864	0.0409
OH (enol)	0.5622	−6.174	0.945	0.1168

Chemical Shifts. Solvent Effects.—Each compound was examined over its entire solubility range in chloroform-*d*. In all cases except the hydroxyl resonances, the concentration dependence of the chemical shifts is unexceptional: downfield shifts with increasing dilution in chloroform-*d*. The small shifts most likely arise from the increased separation between the aromatic solute molecules with increasing dilution.

The behavior of the hydroxyl resonances is somewhat erratic: three compounds (*p*-H-BA, *p*-CH_3-BA, and *p*-CH_3O-BA) move upfield on dilution, *p*-$N(CH_3)_2$-BA remains the same, while *p*-Br-BA and *p*-NO_2-BA shift downfield. The data are consistent with either (1) the successive weakening of the intramolecular hydrogen bonds as the electron-withdrawing power of the substituents increases, or (2) a shifting of the *cis*-enol–*trans*-enol equilibrium toward the *trans*-enol side as the more electronegative substituents engage in a competition with the carbonyl group for the hydroxyl proton. Although a choice between these alternatives cannot be made from the data at hand, it is significant that infrared studies of acetylacetone and hexafluoroacetylacetone indicate a weakening of the hydrogen bond by electronegative substituents,[18] and that this weakening seems to be paralleled by an increase in shielding of the hydroxyl proton.[14] The presence of *trans*-enol in benzoylacetones has been inferred from the presence of bands in the 1708–1722-cm^{-1} region by Lowe.[4]

Keto–Enol Equilibrium. Concentration Effects.—The rate of keto–enol interconversion is sufficiently slow at room temperature on the nmr time scale that the position of the equilibrium can be determined by integration of peak areas. The data for the six benzoylacetones (Table V) indicate a moderate concentration dependence of the equilibrium, the percentage of diketone increasing with increasing dilution, consistent with the idea that the enol is less polar than the diketone.

TABLE V
CONCENTRATION DEPENDENCE OF KETO–ENOL EQUILIBRIA OF SUBSTITUTED BENZOYLACETONES IN CHLOROFORM-*d*

	Mol fraction	Per cent enol
p-N,N-Dimethylamino-benzoylacetone	0.095	77.4
	0.143	77.9
p-Methoxybenzoylacetone	0.059	87.7
	0.142	87.7
	0.221	89.0
	0.251	88.8
	0.338	89.8
	0.349	89.7
	0.479	90.1
p-Methylbenzoylacetone	0.065	89.6
	0.16	90.7
	0.35	93.0
	0.47	93.7
	0.71	94.6
	0.81	94.9
	1.00	95.2
Benzoylacetone	0.080	90.5
	0.118	90.7
	0.123	90.2
	0.169	90.4
	0.293	90.8
	0.316	90.4
p-Bromobenzoylacetone	0.071	91.9
	0.103	92.5
	0.223	93.4
p-Nitrobenzoylacetone	0.065	97.5
	0.082	97.8
	0.102	97.2
	0.152	97.8

Keto–Enol Equilibrium. Substituent Effects.—The position of the keto–enol equilibrium is influenced by the nature of the *para*-substituent, the percentage of

(18) H. Ogoshi and K. Nakamoto, *J. Chem. Phys.*, **45**, 3113 (1966).

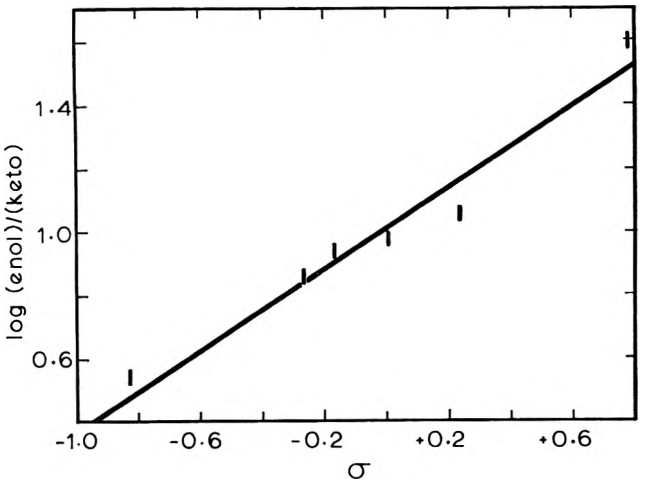


Figure 1.—Plot of log (enol)/(keto) *vs.* the Hammett σ for benzoylacetones.

diketone increasing with the electron-releasing power of the substituent. Figure 1 shows a graph of log (enol)/(diketone) *vs.* the Hammett σ constant for the six benzoylacetones in the concentration range of 0.06–0.10-mol fraction. The best straight-line fit corresponds to the equation

$$\log K = 0.629\,\sigma + 1.019$$

By comparison, application of the Hammett relation to the equilibrium constant data obtained by bromine titrations for series of *meta*- and *para*-substituted benzoylcyclohexanones and benzoylcyclopentanones yielded slopes of 0.70 and 0.93.[3,19]

Discussion

The observation of two methyl resonances, as well as both methylene and vinylic resonances, indicates the equilibrium mixture to consist of at least two species, the less abundant being unenolized β-diketone. This is borne out by the relative intensities of the diketone methylene and methyl groups and the magnitude of the cross-carbonyl coupling constant. Our data do not allow us to infer its conformation.

Nature of the Enol.—Although chemical shift data show clearly that the remainder of the equilibrium mixture is enolic, they cannot indicate the structure of the enol, which can be either II or III. The strongly downfield-shifted hydroxyl resonance indicates most, if not all, of the enol to be intramolecularly hydrogen-bonded, *i.e.*, *cis* II or *cis* III. We cannot, however, rule out the possibility that there may be a small amount of *trans*-enol in solution. Lowe[4] has interpreted the appearance of weak absorption at 3400–3700 cm^{-1} and 1708–1722 cm^{-1} in the infrared spectra of benzoylacetones as indicating the presence of a small amount of *trans*-enol.

Long-range couplings provide a method of estimating the position of the equilibrium *cis* II $\rightleftarrows$ *cis* III. In both cases, allylic couplings are possible: in *cis* II across a formal single bond; in *cis* III across a formal double bond. Couplings across formal single bonds, as in *cis* III are immeasurably small (methyl vinyl ketone <0.2 Hz;[20] methyl styryl ketone <0.2 Hz;[20] 4-methylaminopent-3-en-2-one <0.2 Hz[21]), whereas analogous couplings across formal double bonds are sizable (ethyl acetoacetate, J = 0.77 Hz;[14] 4-methylaminopent-3-en-2-one, J = 0.53 Hz[21]). Assuming rapid interconversion of *cis* II and *cis* III, the averaged allylic coupling constant is given by

$$J\ (\text{avg}) = N_{II}J_{II} + N_{III}J_{III}$$

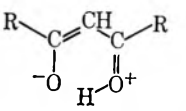
and, if we take J_{II} = 0.1 Hz and J_{III} = 0.6 Hz, then for *p*-methoxybenzoylacetone [J (avg) = 0.13], N_{II} = 0.94. Even for the extreme case where J_{II} = 0, N_{II} = 0.78. Hence, we estimate the amount of *cis* III present in the equilibrium mixture at about 5–10%. This is in excellent agreement with the simple Hückel molecular orbital calculations of Forsen,[7] which indicate the equilibrium constant for the system *cis* II $\rightleftarrows$ *cis* III to be 12. By contrast, the ^{17}O nmr results of Gorodetsky, *et al.*,[6] indicate approximately equal amounts of *cis* II and *cis* III to be present in solution.

Campbell, *et al.*, have concluded on the basis of ultraviolet spectral studies of benzoylcyclohexanones and benzoylcyclopentanones that the dominant enol in both cases contains the cinnamoyl chromophore.[3,19]

Iimura[22] has reported *p*-methoxy- and *p*-nitrobenzoylpinacolone to enolize in the direction of the cinnamoyl chromophore. Paradoxically, the parent benzoylpinacolone is reported to enolize in the opposite direction.

The approximate nature of our discussion of the direction of enolization prevents us from discussing the substituent effect on the enol–enol equilibrium.

The Hydrogen Bond in the Enol.—The substituent effect on the position of the hydroxyl resonance of the enol is completely out of line with substituent effects on all the other resonances, both from the standpoint of its enormous sensitivity (slope = 0.56) and the fact that electron-releasing substituents produce a paramagnetic shift of the hydroxyl peak. The anomalous substituent effect has been noted by other workers,[23,24] and Nonhebel has ascribed it to the fact that "an electron-withdrawing substituent adjacent to a CO group causes the CO oxygen to be less electronegative with consequent strengthening of the bond between the other oxygen and the hydrogen-bonded hydrogen . . . and a consequent weakening of the hydrogen bond."[24] The weakening of the hydrogen bond by the introduction of electron-withdrawing substituents at the terminal positions of a β-diketone is indicated by normal coordinate analyses of the infrared spectra of acetylacetone and hexafluoroacetylacetone; the stretching force constants for the hydrogen bond are 0.300 and 0.128 mdyn/Å, respectively.[18] The corresponding hydroxyl shifts are τ −5.57 and −3.00.[14] The effect may be ascribed to destabilization of canonical forms such as



which are expected to contribute to the hydrogen-bond strength. Hence the anomalous variation in τ (OH)

(19) R. D. Campbell and W. L. Harmer, *J. Org. Chem.*, **28**, 379 (1963).
(20) K. Takahashi, *Bull. Chem. Soc. Jap.*, **37**, 963 (1964).
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(22) F. Iimura, *Nippon Kagaku Zasshi*, **77**, 1855 (1956).
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with substituent in our benzoylacetone series arises from the progressive weakening of the intramolecular hydrogen bond by increasingly electronegative substituents.

Substituent Effects on Keto–Enol Equilibrium.—The question of whether enol stability is due primarily to mesomeric electron delocalization[7,8] or inductive electron withdrawal[9] can be discussed in terms of our results. The ρ value, 0.63, is closely similar to the value of 0.70 found for benzoylcyclohexanones.[3] Although the magnitude suggests some steric hindrance to complete coplanarity, the fact of the correlation and the observed sensitivity of the strength of the hydrogen bond to substituent suggest strongly that there is appreciable overlap between the phenyl group and the remainder of the enol π system.

Experimental Section

Nmr Spectra.—Spectra were measured initially on a Varian Associates A-60 console coupled to a DP-60 power supply and magnet assembly, and later on a standard Varian A-60 instrument. Sample temperature was about 30°.

Chemical shifts, reported in τ values,[25] were obtained by direct reading from the 500-Hz scale and are considered to be accurate to better than 0.02 ppm.

Long-range coupling constants were measured directly from the 50-Hz scale. The values reported are the average of several values, obtained by sweeping in both directions at a sweep speed of 0.1 Hz/sec. The 50-Hz scale was calibrated daily against a 50.0-Hz side band.

Samples were weighed directly in nmr tubes and spectra measured as soon after preparation as possible. No samples were degassed.

Compounds.—All compounds used in this investigation were synthesized by standard methods or obtained commercially.

Melting points were determined with an electrically heated and stirred oil bath, using thermometers calibrated directly in units of 0.2°, and are uncorrected.

Microanalyses were performed in duplicate by Alfred Bernhardt Mikroanalytisches Laboratorium (Germany).

Deuteriochloroform was obtained from Merck Sharp and Dohme of Canada in isotopic purity of better than 99.5% and was used without further purification.

Tetramethylsilane (Anderson Chemical Division, Stauffer Chemical Co.) contained no detectable impurities.

Benzoylacetone (Eastman Organic) was purified by vacuum sublimation and recrystallization from Skellysolve B, giving long, flat needles, mp 55.8–56.5° (lit.[26] mp 57–58°).

***p*-Methylbenzoylacetone.**—*p*-Methylacetophenone (Eastman Organic) was condensed with ethyl acetate by the method of Sprague, *et al.*,[27] using either sodium ethoxide (45.5% yield) or a sodium dispersion (20–25%). Double distillation was performed through a 200-mm vacuum-jacketed fractionation column packed with glass helices. The product had mp 23.3–24.4°; bp 118.0–118.5° (0.75 mm); n^{25}D 1.5925 [lit.[28] bp 154–155°(14 mm)].

***p*-(Trideuteriomethyl)acetophenone.**—Benzotrichloride (Eastman Organic) was reduced with zinc and acetic acid-*d* (prepared by hydrolysis of acetyl chloride with deuterium oxide) to toluene-α,α,α-d_3 in 80% yield by the method of Renaud and Leitch.[29]

To 5.8 g (0.06 mol) of toluene-d_3 in 20 ml of carbon disulfide and 14.8 g (0.11 mol) of aluminum chloride, 5.4 g (0.05 mol) of acetic anhydride was added, with stirring, over a 30-min period. The mixture was heated under reflux for 1 hr, then the complex was decomposed with 200 ml of ice and water and extracted with 200 ml of ether, and the solvent was removed *in vacuo*. The product was recovered by vacuum distillation in 58% yield.

The nmr spectrum of *p*-(trideuteriomethyl)acetophenone is identical with that of undeuterated material, except for loss of the peak at τ 7.75, assigned to the ring methyl group.

***p*-(Trideuteriomethyl)benzoylacetone.**—To 2.8 g (0.12 mol) of powdered sodium under anhydrous ether was added a mixture of 4.1 g (0.02 mol) of *p*-(trideuteriomethyl)acetophenone and 5.1 g (0.06 mol) of ethyl acetate dropwise over a 30-min period with stirring and mild heating. The solution was allowed to sit, with stirring, for 3 hr. Ethanol was added to decompose the excess sodium and the resulting flocculent yellow precipitate was treated with ether and 30% sulfuric acid to effect solution. The aqueous layer was extracted with ether, the combined organic layers were dried ($CaSO_4$), and the solvent was removed *in vacuo*. Double distillation gave a fraction of bp 73–77° (0.01 mm), n^{25}D 1.5906 (39%).

Nmr spectra indicated 90% deuteration. Calcd for 90% deuteration: C, 73.84; H, 8.28. Found: C, 73.43; H, 8.37.

***p*-Methoxybenzoylacetone.**—*p*-Methoxyacetophenone (Eastman Organic) was condensed with ethyl acetate, using the same procedure as for *p*-CH_3-BA. The product sublimed with difficulty from the melt and was recrystallized from Skellysolve B: mp 54.5–55.2° (lit.[28] mp 53–54°).

***p*-(N,N-Dimethylamino)benzoylacetone.**—*p*-N,N-Dimethylacetophenone (16.2 g, 0.099 mol) (Frinton Laboratories) was added slowly and with stirring to a sodium dispersion (4.7 g, 0.204 mol) in 300 ml of tetrahydrofuran (distilled from CaH_2 immediately before use) and allowed to stand overnight. To the resulting yellow solution was added over a 40-min period 27.0 g (0.306 mol) of ethyl acetate, and the reaction was allowed to proceed overnight with mild heating, during which time all the sodium disappeared. The solution was acidified to pH 6 with 20% H_2SO_4, extracted with methylene chloride, and dried ($CaCl_2$). Recrystallization from Skellysolve B gave either dark yellow plates, mp 114–118°, or lemon-yellow powder, mp 118–120°, depending on conditions. On standing after crystallization, the powder was transformed to plates, mp 118–120°. The uv spectra [λ_{max} (log ϵ) 240 (3.91), 247 (3.90), 354 mμ (4.60)] and nmr spectra of the 114–118° and 118–120° materials were identical.

Anal. Calcd for $C_{12}H_{16}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 69.50; H, 7.38; N, 7.05.

***p*-Bromobenzoylacetone.**—A solution containing 25 g (0.125 mol) of *p*-bromoacetophenone (Eastman Organic) dissolved in 89.3 g (0.875 mol) of acetic anhydride at 0°, with stirring, was saturated with boron trifluoride. Boron trifluoride was bubbled in for 2 more hr, and the solution became a slurry and then solidified. Sodium acetate (87 g in 350 ml of water) was added, and the solution was heated under reflux for 30 min, cooled to 0°, filtered, and acidified with glacial acetic acid at 0°. The resulting white precipitate was washed with water and dried ($CaCl_2$). Double recrystallization from hexane, sublimation twice *in vacuo*, and recrystallization from benzene–hexane gave white needles, mp 96° (lit.[30] mp 92.5°). The procedure is a modification of that described by Hauser and Adams.[31] The yield was 44%.

***p*-Nitrobenzoylacetone.**—*p*-Nitroacetophenone (Eastman Organic) was condensed with acetic anhydride in the presence of boron trifluoride by the method of Walker and Hauser.[32] Recrystallization twice from hexane, sublimation twice [110–118° (0.2 mm)], and recrystallization again from hexane gave pale golden yellow needles, mp 112.5–113.0° (lit.[32] mp 112.0–112.8°).

Registry No.—*p*-H-BA, 93-91-4; *p*-CH_3-BA, 4023-79-4; *p*-CH_3O-BA, 4023-82-9; *p*-$N(CH_3)_2$-BA, 20449-17-6; acetylacetone, 123-54-6; *p*-Br-BA, 4023-81-8; *p*-trideuteric methyl)benzoylacetone, 20455-50-9.

Acknowledgment.—We acknowledge gratefully the assistance of Mr. Frank Maurukas in synthesizing several compounds.

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Electron-Transfer Polymers. XXXV. Inductive Effects of Substituents upon Spectral and Redox Properties of *p*-Benzoquinones

GERHARD WEGNER,[1a] THOMAS F. KEYES, III, NOBUO NAKABAYASHI,[1b] AND HAROLD G. CASSIDY

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06520

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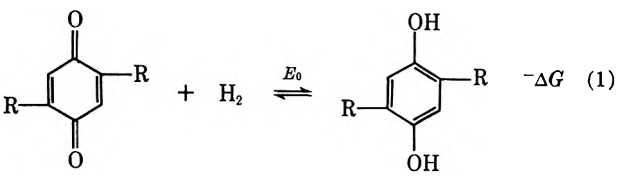
The differences in free-energy change in a series of monosubstituted and of 2,5-disubstituted 1,4-benzoquinones relative to respective reference compounds, ethyl-*p*-benzoquinone and 2,5-dimethyl-1,4-benzoquinone, are correlated with inductive electron-withdrawing effects of the polar substituents upon the position of the *p*-benzoquinone–hydroquinone equilibrium. The effect is correlated to an increase in the ir frequencies of C=C and C=O stretch. The closer the polar group to the ring the greater the effect, giving a fairly clear linear relation between frequencies and standard potentials. The orders of magnitude of the differences in free energy between substituted and reference compounds are comparable to and in the same direction as the changes produced by these substituents upon the free energy of dissociation of acetic acid—the classical case of inductive influence. It is shown with substituents that include hydroquinonyl and *p*-benzoquinonyl as the polar groups that the inductive effect of the polar group falls off with distance and reaches zero when a linear chain of about five CH_2– groups separates polar group and ring. These data thus provide a frame of reference for judging and predicting the behavior of redox polymers related to these models. It seems that the main contribution to the interaction between neighboring redox units is communicated through induction and not through internal charge transfer.

Although many different types of redox polymers have been synthesized during the last twenty years, their redox behavior is still not well understood. This report presents and discusses the properties of new 2,5-disubstituted 1,4-benzoquinones[2a] (*p*-benzoquinones) from which new types of redox polymers have been prepared[2b] and of some hydroquinone dimers. That inductive effects exist, wherein an increase in the number of CH_2 groups inserted between a substituent group and a functional group attenuates in a regular way the effect of the one upon the other, is well known.[3] We present such correlations to redox and spectral properties of *p*-benzoquinones that are new, as far as we can determine. These substituted *p*-benzoquinones serve as models. From their behavior one is able to extrapolate to polymer behavior. If polymers related to these models show behavior not observed with the low molecular weight models, the departure may with firmer reason be discussed as "polymer effect."

The results of redox titrations for different 2,5-disubstituted benzoquinones are listed in Table I.

The titrations were carried out in 90% acetic acid with ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$] in the same solvent as oxidant. From the observed potentials the standard potentials (pH 0, 25°) in Table I were calculated. To bring out effects of substituents, 2,5-dimethyl-1,4-benzoquinone (*p*-xyloquinone) was chosen as reference compound. The difference in potential between this reference compound and the particular substituted quinone is reported in column 5 of Table I. For a given functional group, this difference is greatest when the polar substituent is separated by only one —CH_2— group from the ring. It becomes smaller as more —CH_2— groups separate it from the ring. From the standard potential, ΔG_Q, the change in free energy that takes place in the particular redox reaction is calculated. Again in reference to 2,5-dimethyl-1,4-benzoquinone, the difference in free-energy changes, $\Delta(\Delta G_Q)$, can be calculated. These are shown in column 6 of Table I. For example, from the increase in standard potential of 2,5-bishydroxymethyl-1,4-benzoquinone over the reference compound, it is concluded that it is easier by 1.6 kcal/mol to reduce the hydroxymethyl-substituted compound than the methyl-substituted compound. As the distance of the polar group from the ring is increased, the difference in free-energy change $\Delta(\Delta G_Q)$ approaches zero. The same effect is observed with monosubstituted 1,4-benzoquinones. The relevant quantities for some monosubstituted quinones are presented in Table II, where ethyl-1,4-benzoquinone is used as the reference. Many of the differences in free energy change for the monosubstituted compounds are close to half of those for the disubstituted.

In the following reaction (eq 1) a major part of the driving force is certainly the gain in resonance energy of



the aromatic hydroquinone over the quinone.[4] Other factors, such as inductive effects, hydrogen bonding, charge-transfer interactions, and solvent effects, will enhance, or oppose, this driving force. It is the total free-energy change that determines the potential. In these quinones, the polar groups in the side chains are connected through σ bonds only to the reaction center (the ring system); hence resonance interactions must be excluded. Careful investigations of nmr and ir spectra of the quinonediols, quinone diacids, and hydroquinone esters gave in most cases no evidence of intramolecular hydrogen bonding.[5] No indication for unusual charge-transfer interactions could be found; thus, these two interactions can only have minor effects, insufficient to explain the observed changes. The remaining possibility is inductive effect. Since all titrations were done at pH 0, while the first acid dissociation constant of hydroquinone is above 7, it

(1) (a) Institute for Physical Chemistry, University of Mainz, Mainz, Germany; (b) Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Tokyo, Japan.

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(5) Unpublished work of T. F. Keyes, III.

TABLE I

INFLUENCE OF THE INDUCTIVE EFFECT ON REDOX POTENTIAL AND SPECTRA OF 2,5-DISUBSTITUTED 1,4-BENZOQUINONES

Figure 1 no.	Substituents R (in eq 1)	Registry no.	E_0, mV	ΔE,[a] mV	$\Delta(\Delta G_Q)$,[b] kcal	Ir frequencies,[c] cm^{-1} C=O	Ir frequencies,[c] cm^{-1} C=C	Chemical shift,[d] τ
1	$-CH_3$	137-18-8	602	...	...	1643 (1667)	1620	
2	$-CH_2OH$	13949-75-2	636	34	1.57	1653	1621	3.33
3	$-(CH_2)_2OH$	13949-76-3	620	18	0.83	1656	1611	3.29
4	$-(CH_2)_3OH$	13949-77-4	607	5	0.23	1655	1610	3.43
5	$-(CH_2)_2OCOCH_3$	13949-79-6	635	33	1.54	1660	1618	3.24
6	$-(CH_2)_3OCOCH_3$	13949-80-9	616	14	0.65	1658	1615	3.30
7	$-CH_2-CO_2H$	20452-46-4	655	53	2.45	1665	1625	
8	$-(CH_2)_2CO_2H$	16076-07-6	629	27	1.29	1660	1614	
9	$-CH_2CO_2C_2H_5$	5628-31-9	664	62	2.86	1667	1622	3.18
10	$-(CH_2)_2CO_2C_2H_5$	14053-41-9	623	21	0.97	1658	1611	3.35
	$-H$		706	...	...	1659, 1663	1593	

[a] $\Delta E = E_0$ of substituted quinone $- E_0$ of 2,5-dimethyl-1,4-benzoquinone. [b] See text for explanation. [c] Compounds were dissolved in tetrahydrofuran. [d] Compounds were dissolved in deuteriochloroform.

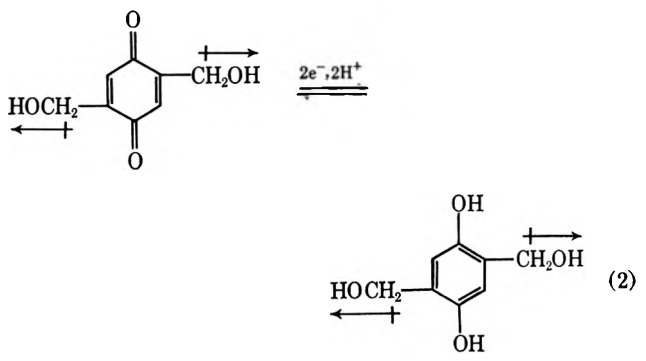
TABLE II

INFLUENCE OF THE INDUCTIVE EFFECT ON REDOX POTENTIAL AND SPECTRA OF MONOSUBSTITUTED BENZOQUINONES

Substituent R	E_0, mV	ΔE,[a] mV	$\Delta(\Delta G_Q)$,[b] kcal	Ir frequencies,[c] cm^{-1} C=O	Ir frequencies,[c] cm^{-1} C=C
$-CH_2-CH_3$	652	..	...	1663	1598
$-(CH_2)_2OH$	669	17	0.78	1663	1601
$-CH_2-CO_2H$	680	28	1.29	1665	1603
$-(CH_2)_2CO_2H$	666	14	0.65	1664	1601
$-CH_2-CO_2C_2H_5$	678	26	1.20	1664	1602
$-(CH_2)_2CO_2C_2H_5$	665	13	0.60	1664	1603

[a-c] See footnotes a–c of Table I.

must be that in every case the reduced forms are un-ionized and therefore comparable. That is, no account need be taken of degrees of ionization due to the substituent.



(2)

In eq 2, a polar group contributes to a permanent dipole, oriented as shown. This influences the charge distribution on the ring in the direction shown (*i.e.*, with the positive pole closer to the ring). In these circumstances, the frequencies of vibration of the —C=C— stretch and —C=O double bond of the quinones should be increased, the more so the closer the polar group to the ring. In Table I, columns 7 and 8, these effects are clearly seen. Further, if the frequencies are plotted against the observed standard potentials, fairly clear straight-line relations are obtained identical in slope within the limits of the measurements. These results recall the correlations found by Goulden[6] between O—H stretching frequencies and pK_a values of carboxylic acids and phenols, and the inductive effects described by Bellamy.[7] An influence of the substituent on the chemical shift of the ethylenic proton due to the substituent is also found, as shown in the last column of Table I.

In the monosubstituted *p*-benzoquinones in solution (Table II) there is only one C=O and one C=C vibration, suggesting that the vibration of the substituted double bond is linked to that of the unsubstituted double bond. The influence of the substituent is not very marked, which suggests that the effect is diluted out by this linkage. A similar supposition applies to the carbonyl absorption for monosubstituted *p*-benzoquinones.

A more important test of the existence of an inductive effect may be made by comparing the effect of a given substituent upon the redox potential with that produced by a substituent on the pK_a value of a carboxylic acid. This comparison invokes the classical example of inductive influence[8] and applies it in this new situation. The comparison is made in Table III. Acetic acid serves as the reference compound for the other carboxylic acids, with the di- and monosubstitued reference compounds as before (Tables I and II). Again the comparison is made in the form of differences in free-energy changes, $\Delta(\Delta G)$. The orders of magnitude are comparable, and the changes occur in the same directions. When, for example, the $-CH_3$ group of acetic acid is replaced by $-CH_2OH$, the free energy of dissociation increases by 1.28 kcal/mol. The corresponding replacement in 2,5-substituted 1,4-quinones raises the free energy of the redox reaction by 1.57 kcal/mol. It may be supposed, in view of the many factors that contribute to the free-energy change in a redox reaction,[4] that the good agreement between columns 3 and 4 of Table III is fortuitous; however, the consistent directions of change, and the similar orders of magnitude of the changes, are probably meaningful. When there is only one substituent present in the redox system, the influence on the free-energy change is less, and in some cases close to half that for the disubstituted compounds. (It must be pointed out that these data are not adequate to allow a decision as to whether ΔG of electron transfer is or is not predominant over ΔG of proton transfer in the oxidation or reduction of these substances.)

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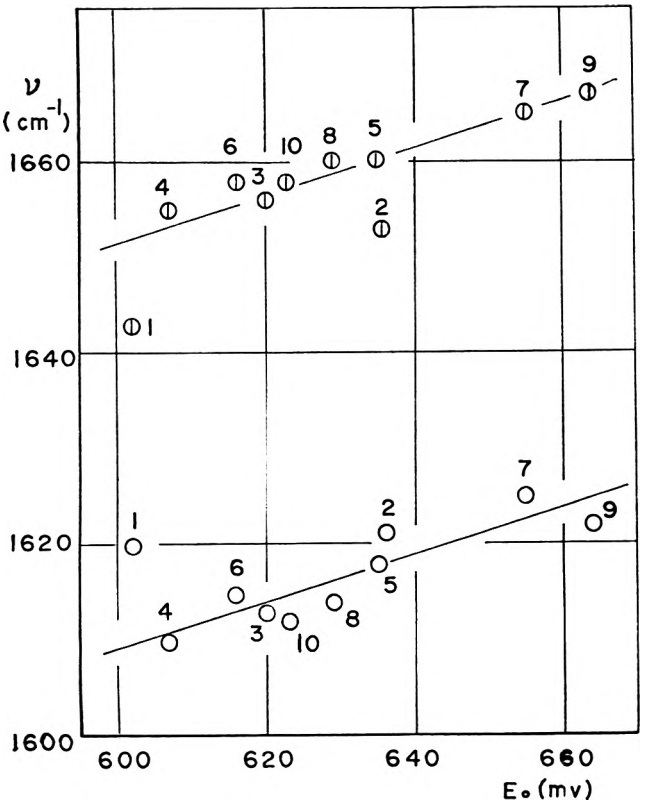


Figure 1.—Plot of ir frequencies of C=O (⊕) and C=C (○) stretching against observed standard potentials of 2,5-disubstituted benzoquinones. Key to the numbers is found in Table I.

TABLE III
COMPARISON OF THE INFLUENCE OF THE INDUCTIVE EFFECT IN SUBSTITUTED *p*-BENZOQUINONES AND SUBSTITUTED CARBOXYLIC ACIDS, R—COOH

		Carboxylic acids	*p*-Benzoquinones	
			2,5-disubstd,	Monosubst,
		$\Delta(\Delta G_a)$,[b]	$\Delta(\Delta G_Q)$,[c]	$\Delta(\Delta G_Q)$,[d]
Substituent R	pK_a[a]	kcal	kcal	kcal
CH_3—	4.76	...	...	...
HO_2C—CH_2—	2.83	2.63	2.45	1.29
$C_2H_5OCOCH_2$—	3.35	1.92	2.86	1.20
$HOCH_2$—	3.83	1.28	1.57	
$HO_2C(CH_2)_2$—	4.19	0.78	1.29	0.65
$C_2H_5OCO(CH_2)_2$—	4.52	0.33	0.97	0.60
$HO(CH_2)_2$—	4.51	0.34	0.83	0.78
$HO(CH_2)_3$—	4.72	0.05	0.23	
C_6H_5—CH_2—	4.31	0.61		0.55[e]
C_6H_5—$(CH_2)_2$—	4.66	0.14		0.37[e]

[a] Values taken from ref 8. [b] Difference in free-energy change of dissociation between the substituted acid and acetic acid. [c] See Table I. [d] See Table II. [e] Values taken from ref 13.

In applying these findings to the behavior of oligomers, there are cases wherein hydroquinonyl or quinonyl groups are the polar substituents on side chains to other such groups. Extending a series already begun by Moser and Cassidy,[9] 1,2-bis(2′,5′-dihydroxyphenyl)-ethane (I) was prepared. The solid line in Figure 2 shows the oxidative titration curve for this compound; the dashed line is that of a theoretical two-electron oxidation with the same midpoint potential. The index potential of the dimer curve is 19 mV instead of the theoretical 14 mV. This implies that more than one

(9) R. E. Moser and H. G. Cassidy, *J. Org. Chem.*, **30**, 2602 (1965).

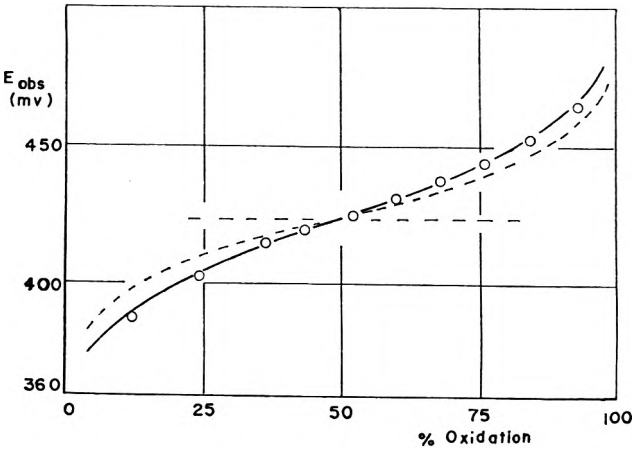
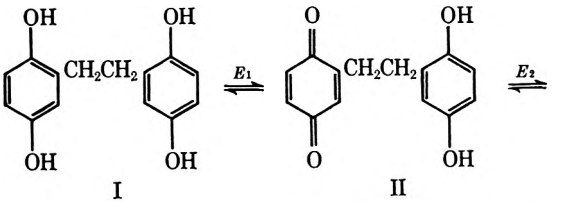
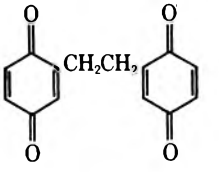


Figure 2.—The solid line connects observed potentials in the oxidative titration of 1,2-(2′,5′-dihydroxyphenyl)ethane. The dashed line is that of a theoretical two-electron oxidation with the same midpoint potential.

species is being titrated. These species are shown in eq 3 and 4. The redox potentials E_1 and E_2 can be calculated



I II



(3)

III

$$\text{I} + \text{III} \overset{K}{\rightleftharpoons} 2\,\text{II} \qquad (4)$$

from the slope of the curve or from the index potentials; and the intermediate-formation constant K can be calculated.[10,11]

Examination of the dimers already prepared by Moser[9] disclosed similar behavior. These data are gathered in Table IV, where it is evident that, when the connecting bridge contains 5 —CH_2— groups, the two rings behave independently of each other. Thus, a bridge longer than about 5 —CH_2— units effectively isolates the redox groups by this criterion. This is supported (Table IV) with an oligomer SD-3 in which the redox units (about nine of them) are each separated from the other by a long bridge containing ester and ether links. The titration curve for this oligomer is ideal, with an index potential of 14 mV.[12] There is evidence, however, that these conclusions from monomers and oligomers must not be extrapolated indiscriminately to polymers.

Finally, with these dimers it becomes possible to compare the differences in free-energy changes $\Delta(\Delta G_Q)$ for a series of compounds in which a *p*-benzoquinone has, within the same distance, either a hydroquinone

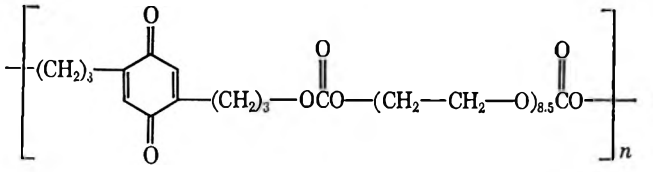
(10) G. Manecke and H.-J. Förster, *Makromol. Chem.*, **52**, 147 (1962).
(11) B. Elema, *J. Biol. Chem.*, **100**, 149 (1933).
(12) G. Wegner, N. Nakabayashi, S. Duncan, and H. G. Cassidy, *J. Polym. Sci., Part A-1*, **6**, 3395 (1968).

TABLE IV

RESULTS OF REDOX TITRATIONS OF VARIOUS OLIGOMERIC p-BENZOQUINONES

Bridge R	E_m, mV	E_i, mV	R	$E_2 - E_1$, mV	E_1, mV	E_2, mV
—$(CH_2)_2$—	652	19	12.8	33	636	669
—$(CH_2)_3$—	652	17.5	9.1	28	638	667
—$(CH_2)_5$—	655	14.0	0	0	655	655
SD-3[a]	616	14.0	0	0	616	616

[a] SD-3 is an oligomer of the structure which appears below.



where $n \approx 9$

E_m is the midpoint potential, E_i the index potential, and K is the intermediate formation constant.

or a p-benzoquinone group. This comparison is made in Table V. The values for the methylene-bridged dimer are from Manecke.[13] Again, $\Delta(\Delta G_Q)$ decreases with distance between the neighboring groups, falling to zero when the bridge reaches 5 —CH_2— groups. This pattern, and the orders of magnitude of the effects when the bridges are short, supports the inference that the effect is inductive. This conclusion is further supported when the influence of hydroquinone and p-benzoquinone substituents upon the pK_a values of the substituted carboxylic acids is examined, as shown in the last two columns of Table V. The influence of these groups on the free energy of dissociation of the acids is about half that for the redox reaction. Possibly the reason for this is that a relatively large p-benzoquinone or hydroquinone group with many internal dipoles may interact to a greater extent with a group of the same size than with a small carboxylic acid group. It seems, in summary, that the main contribution to interaction between neighboring redox units is communicated through induction. Other contributions to the total free-energy change, such as stabilization through internal charge transfer[14] or homoconjugation of adjacent rings,[15] cannot be excluded, but appear to be of minor importance.

Experimental Section

Spectra.—Infrared spectra were obtained with a Perkin-Elmer Model 421 spectrometer. Tetrahydrofuran for infrared measurements was carefully purified and distilled immediately before use. The solutions of the quinones to be measured were about 2% by weight. Ultraviolet spectra were measured with a Bausch & Lomb Spectronic 505 spectrometer.

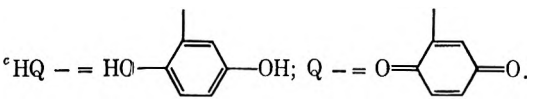
Titrations.—The apparatus used was that described elsewhere.[16,17] Potentials were determined by means of a Leeds and Northrup Speedomax recording potentiometer. The titrations were carried out in a thermostatically controlled water bath at 25°. All reagents were transferred, and titrations were carried out under the usual precautions.[17] Potentials were measured against a saturated calomel electrode which had been calibrated on the hydrogen scale. Thus all potentials are reported on the hydrogen scale and have been calculated to pH 0. The calculations neglect effects of ionization or salt error. Ceric ammonium nitrate, $Ce(NH_4)_2(NO_3)_6$, was used as oxidizing agent and was dissolved in the same solvent as was the hydroquinone being titrated (90% acetic acid, v/v). In a typical run, about 0.1 mmol of a hydroquinone was dissolved in 100 ml of solvent. The end point of titration was reached with about 3.0 ml of the titrant added. During titration, the change in pH was less than 0.1 pH unit (measured with a glass electrode) and was neglected in calculations. The final values for the standard potentials were determined as the middle of several runs. They are exact to ± 2 mV. pK_a values were determined potentiometrically by means of a Leeds and Northrop pH meter. The value of ΔG is good to within 0.1 unit.

TABLE V

INFLUENCE OF A p-BENZOQUINONE OR HYDROQUINONE AS SUBSTITUENT ON THE REDOX POTENTIAL OF A SECOND p-BENZOQUINONE OR ON THE pK_a VALUE OF A CARBOXYLIC ACID, R—COOH

	p-Benzoquinones		Carboxylic acids	
Substituent R[c]	E_0, mV	$\Delta(\Delta G_Q)$,[a] kcal	pK_a	$\Delta(\Delta G_a)$,[b] kcal
HQ—CH_2—	647	1.87[15°]	4.14[23°]	0.89
Q—CH_2—	687		3.49[23°]	
HQ—$(CH_2)_2$—	636		4.49	
		1.52		0.53
Q—$(CH_2)_2$—	669		4.10	
HQ—$(CH_2)_3$—	638			
		1.29		
Q—$(CH_2)_3$	667			
HQ—$(CH_2)_5$—	655			
		0		
Q—$(CH_2)_5$—	655			

[a] $\Delta(\Delta G_Q)$ = difference in free-energy change for oxidation of a hydroquinone with hydroquinone as neighbor and with quinone as neighbor. [b] $\Delta(\Delta G_a)$ was calculated analogously to $\Delta(\Delta G_Q)$.



Materials.—All reaction solvents were of reagent grade, and, except as indicated, were used without further purification. All other reagents were commercial materials freshly recrystallized or distilled before use, unless noted.

2′-Hydroxyethyl-2,5-benzoquinone.—2′-Hydroxyethylhydroquinone[18] [0.31 g (2.0 mmol)]in 40 ml of dry ethyl ether was treated with 0.6 g of silver oxide and 1.0 g of magnesium sulfate. The mixture was stirred for 30 min at room temperature and then filtered. The yellow filtrate gave a yellow crystalline mass upon evaporation of the solvent *in vacuo*. It was recrystallized from normal heptane to give bright yellow needles, mp 36°; 86% yield. Upon reduction with sodium hydrosulfite the starting material was retrieved: ir 1651 (C=O), 1600 (C=C), 3340, 1300, 1050 (CH_2OH) cm^{-1}; nmr τ 3.23 (m), 6.15 (t), 7.31 (m), and 7.93 ppm (d).[19]

1,4-Dimethoxy-2-(2′,2′-dicarbethoxyethyl)benzene (IV).—This substance was prepared from 1,4-dimethoxy-3-chloromethylbenzene by a standard malonic ester synthesis as a colorless liquid, bp 157–160° (0.5 mm); yield, 70%; nmr τ 3.38 (s), 5.92 (qu), 6.26 (s), 6.32 (t), 6.33 (s), 6.42 (d), 8.84 (t).[19]

1,4-Dihydroxy-2(3′-propanoic acid)benzene (V).—Compound IV was refluxed for 4 hr with 48% hydrogen bromide. The hot solution was filtered, diluted with an equal amount of ice, and immediately extracted with several portions of ether. The

(13) G. Manecke and D. Zerpner, *Makromol. Chem.*, **108**, 198 (1967).
(14) R. E. Moser, Dissertation, Yale University, 1965.
(15) S. E. Hunt, A. S. Lindsey, and N. G. Saville, *J. Chem. Soc., B*, 791 (1967).
(16) I. D. Robinson, M. Fernandez-Refojo, and H. G. Cassidy, *J. Polym. Sci.*, **39**, 47 (1959).
(17) K. Kun and H. G. Cassidy, "Oxidation–Reduction Polymers (Redox Polymers)," Interscience Publishers, Inc., New York, N. Y., 1965.
(18) R. Stern, J. English, Jr., and H. G. Cassidy, *J. Amer. Chem. Soc.*, **79**, 5797 (1957).
(19) Elementary microanalyses were carried out by Galbraith Analytical Laboratories. Infrared data in the experimental part were obtained with the substances dissolved in KBr. Nmr data were obtained with a Varian Associates Model A-60 spectrometer. Chemical shifts were given in τ values. The letters in parentheses mean s, singlet; d, doublet; t, triplet; qu, quadruplet; m, multiplet. Analytical grade deuteriochloroform was used as solvent. All melting points are corrected.

combined ether extracts were washed with concentrated sodium chloride solution and dried over magnesium sulfate. Evaporation of the ether gave a brownish crystalline mass. Recrystallization from hot water gave thin white plates, mp 119–120°; yield 40%; ir 1705 (C=O), 1650 (COOH hydrogen bonded), 3380, 3250, 1395, 1190 (OH), 1595, 1500, 1455 (aromatic ring) cm^{-1}.

1,4-Dihydroxy-2-(2′-carbethoxyethyl)benzene.—Compound V was converted to the ethyl ester in anhydrous ethanol with hydrogen chloride gas as catalyst. Recrystallization from toluene–hexane gave small white needles, mp 78–79°; yield, 78%; ir 3350, 1370 (OH), 1610, 1525, 1450 (aromatic ring), 1700, 1200 (ester) cm^{-1}; nmr 3.10 (s), 3.35 (m), 4.14 (s), 5.85 (qu), 7.25 (m), and 8.78 ppm (t).[19]

Oxidation of Hydroquinone Acids and Esters. General Method.—The same general method was used as already reported,[2a] using ferric chloride as oxidizing agent in an ethanol–water mixture.

1,4-Benzoquinone-2,5-bis(3′-propanoic acid).—Recrystallization from tetrahydrofuran by addition of heptane gave yellow needles, mp 191–193°; yield 86%; ir 1710, 1228 (COOH), 1655, 1620 (quinone) cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.25; H, 4.45.

1,4-Benzoquinone-2-(3′-propanoic acid) was obtained as small, dark yellow needles from hexane–tetrahydrofuran, mp 137–139°; yield 72%; ir 1710, 1210 (COOH), 1660, 1598 (quinone) cm^{-1}.

Anal. Calcd for $C_9H_8O_4$: C, 60.25; H, 4.47. Found: C, 60.35; H, 4.30.

2-(2′-Carbethoxyethyl)-1,4-benzoquinone was obtained as a bright yellow oil which crystallized on cooling with a Dry Ice–acetone mixture as long yellow needles, mp 11–15°; yield *ca.* 85%; ir 1730, 1253 (COOH), 1660, 1600 (quinone) cm^{-1}; nmr τ 3.25 (m), 5.82 (qu), 7.3 (m), and 8.74 ppm (t).[19]

1′,2′-Bis(2,5-dimethoxyphenyl)ethane (VI).—1,4-Dimethoxy-2-chloromethylbenzene [27.7 g (0.15 mol)] was dissolved in 120 ml of tetrahydrofuran. This solution was slowly added to a mixture of 1.82 g of magnesium turnings and 40 ml of tetrahydrofuran under vigorous stirring, the usual precautions for the preparation of Grignard compounds being taken. After the addition was finished, the reaction mixture was refluxed for 4 hr, tetrahydrofuran was distilled off, and the residue was heated to 100° for 2 hr on a steam bath. The reaction mixture was then acidified with 6 *N* hydrochloric acid and extracted with ether. Evaporation of the ether gave a slightly yellow oil which soon crystallized. Recrystallization from methanol gave white needles, mp 72°; yield 86%; nmr τ 3.29 (s), 6.20 (s), 6.28 (s), and 7.15 ppm (s).[19]

1′,2′-Bis(2,5-dihydroxyphenyl)ethane (I).—Compound VI, 8.0 g, was refluxed for 4 hr with 75 ml of 48% hydrobromic acid. From the filtered reaction mixture, dark brown crystals separated on cooling. Recrystallization from a large amount of boiling water gave white needles (4.0 g) which were further purified by sublimation at 200° (0.3 mm) bath temperature. They melted at 225° with decomposition. The same compound was simultaneously prepared by Manecke and Zerpner:[13] ir 3210, 1375, 1198 (OH), 1620, 1570, 1455 (aromatic ring) cm^{-1}.

1′,2′-Bis(2,5-benzoquinonyl)ethane (III).—Compound I, 1.2 g, in 50 ml of tetrahydrofuran was oxidized by stirring for 30 min with 5 g of silver oxide and 3 g of magnesium sulfate. The mixture was filtered rapidly, and the solvent was removed *in vacuo*. The dark brown residue, 1.0 g, was purified by sublimation at 160° (0.3 mm) bath temperature to yield microscopic yellow crystals, mp 194°; ir 1660, 1603 (quinone) cm^{-1}.

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 69.18; H, 4.30.

Registry No.—2′-Hydroxyethyl-2,5-benzoquinone, 4082-30-8; III, 20452-50-0; IV, 20452-51-1; V, 10538-47-3; VI, 20306-76-7; 1,4-dihydroxy-2-(2′-carbethoxyethyl)benzene, 20452-54-4; 1,4-benzoquinone-2-(3′-propanoic acid), 20452-56-6; 2-(2′-carbethoxyethyl)-1,4-benzoquinone, 20452-57-7.

Acknowledgment.—We are glad to acknowledge the technical assistance of Mrs. Irmlind Stronkowski in this work, which was supported by a Public Health Service Research Grant GM 10864, National Institutes of Arthritis and Metabolic Diseases.

Nuclear Magnetic Resonance Spectroscopy. Proton Spectra of Diallylmercury[1]

HERMAN E. ZIEGER[2] AND JOHN D. ROBERTS

Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109

Received March 6, 1969

Changes have been observed in the nmr spectra of diallylmercury as a function of temperature which seem explicable in terms of allylic rearrangement and intermolecular exchange. Analysis of the proton spectra of diallylmercury spectra using a modified LAOCOON II computer program gave coupling constant and chemical shift parameters which reproduced the spectra at 60, 100, and 220 MHz.

Analyses of the nmr spectra of three dipropenylmercury compounds have been reported with the objective of establishing their configurations and the stereochemistry of their preparation from propenyllithiums.[3] Similar studies of di-2-propenylmercury (diallylmercury) do not appear to have been published,[4] although it offers the additional possibility of undergoing both intermolecular and intramolecular exchange which, in principle at least, are distinguishable by nmr. Diallylmercury is expected to have a carbon–metal bond intermediate in ionic character between tetraallyltin[5] and diallylcadmium,[6] which have been found to exhibit $ABCD_2$ and AB_4 nmr spectra, respectively. The AB_4 spectra observed for allylmagnesium bromide and diallylmagnesium have been interpreted as indicating a rapid allylic rearrangement (either inter- or intramolecular) between the possible allylic isomers.[7]

It was of particular interest to investigate variations in the nmr spectra of diallylmercury with temperature to see whether rearrangement could be detected and whether or not such rearrangement occurs by intermolecular group exchange and can be distinguished from intramolecular rearrangement by disappearance or retention of the ^{199}Hg satellite lines in the progression

(1) Supported in part by the National Science Foundation.

(2) On sabbatical leave from Brooklyn College of the City University of New York, 1967–1968.

(3) D. Moy, M. Emerson, and J. P. Oliver, *Inorg. Chem.*, **2**, 1261 (1963).

(4) However, see references in P. West, J. I. Purmort, and S. V. McKinley, *J. Amer. Chem. Soc.*, **90**, 797 (1968), to unpublished work of P. West in which conclusions similar to those of this paper were reached.

(5) D. J. Blears, S. S. Danyluk, and S. Cawley, *J. Organometal. Chem.*, **6**, 284 (1964).

(6) K. H. Thiele and J. Kohler, *ibid.*, **7**, 365 (1965).

(7) J. E. Nordlander and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 1769 (1959). G. M. Whitesides, J. E. Nordlander, and J. D. Roberts, *ibid.*, **84**, 2010 (1962); *Discussions Faraday Soc.*, **34**, 185 (1962). H. E. Zieger and J. D. Roberts, *J. Org. Chem.*, **34**, 1976 (1969).

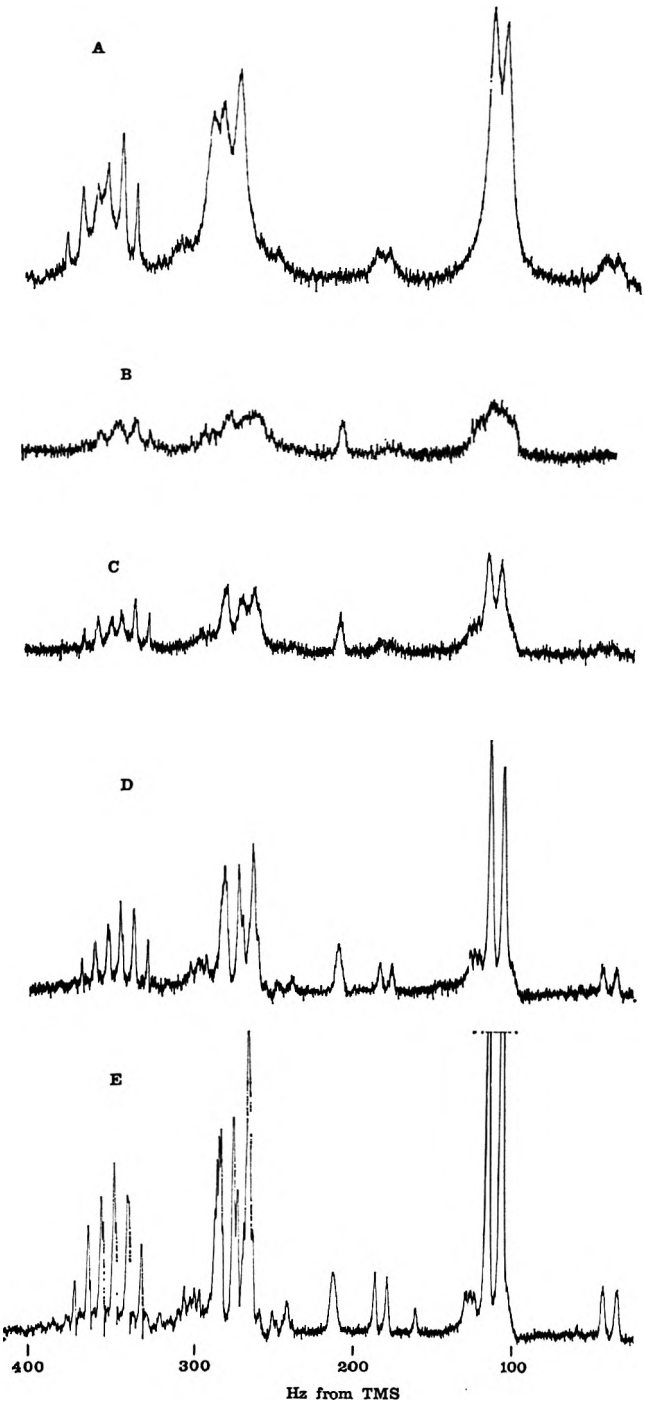


Figure 1.—Proton magnetic resonance spectra of diallylmercury at 60 MHz: A, neat at 39°; B, in perdeuteriotetrahydrofuran solution at 93°; C, at 74°; D, at 39°; and E, at −30°.

of formation of an AB_4-type spectrum from an $ABCD_2$ spectrum.

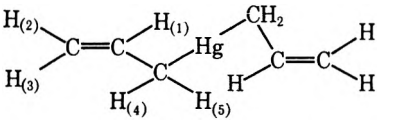
As a prelude to this, analyses were carried out of the 60-MHz and 100-MHz diallylmercury spectra with the aid of a modified LAOCOON II computer program. The coupling constant and chemical shift parameters so obtained were then checked with 220-MHz spectra.

Results

The 60-MHz spectrum of neat diallylmercury (Figure 1) shows relatively broad, poorly resolved lines which result from a superposition of spectra of the $ABCD_2$ and $ABCD_2X$ types.[8] Upon cooling, the spectral lines sharpen noticeably. The same behavior results on dissolution in solvents such as tetrahydrofuran (Figure 1) or carbon tetrachloride. A combination of dilution and cooling was found to provide the maximum achievable resolution. Considerable line broadening was observed on heating in tetrahydrofuran (Figure 1), but even at 108°, the highest temperature attempted, the spectra were essentially of the $ABCD_2$ type and it appeared unlikely that AB_4 (and possibly AB_4X) spectra could be observed at any reasonable temperature for tetrahydrofuran solutions.

These observations, although far from clean-cut, may be interpreted in terms of concomitant allylic rearrangement and intermolecular exchange. The argument for intermolecular exchange is that degradation of the $ABCD_2X$ spectrum in the direction of an $ABCD_2$ spectrum seems qualitatively faster than the degradation of the $ABCD_2$ spectrum in the direction of an AB_4 spectra. Exclusive intramolecular rearrangement would be expected to lead to AB_4 spectra with mercury satellites and probably would be less dependent on concentration than is in fact observed.

The nmr spectra of diallylmercury were analyzed by essentially conventional techniques. Chemical shifts and coupling constants estimated by first-order approximation from 60-MHz and 100-MHz spectra provided trial spectral-line positions for use in the iterative LAOCOON II program.[9,10] The parameters so obtained are given in Table I with the nuclei numbered as in **1**. The theoretical spectrum corresponding to these



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parameters gave an acceptable match to the experimental spectrum (Figure 2).[11] The agreement between the parameters obtained for 60, 100 and 220 MHz is quite satisfactory.

The small variations of some of the coupling constants (Table I) observed on cooling diallylmercury in tetrahydrofuran solution could be caused by small changes in the populations of various conformational isomers.

Experimental Section

Diallylmercury (mp −41 to −40°) was prepared from allylmagnesium bromide, following the literature.[12] The sample used for the spectral analysis was dissolved 1:4 (v/v) in perdeuteriotetrahydrofuran and sealed under pre-purified nitrogen in a thick-wall, precision-bore tube. The 60-MHz spectra were obtained with a Varian Associates A-56/60-A spectrometer equipped with a modified V-6040 variable temperature controller at 39, 57, 63.5, 74, and 93°, and calibrated with a Hewlett-

(8) Naturally occurring mercury contains 16.9% ^{199}Hg of spin $I = 1/2$ which is coupled with the proton spins to give an $ABCD_2X$ spectrum.

(9) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

(10) A. A. Bothner-By, S. Castellano, and H. Gunther, *J. Amer. Chem. Soc.*, **87**, 2439 (1965).

(11) The theoretical spectrum shown in Figure 2 is a computer-produced composite of 83% of an $ABCD_2$ spectrum and 17% of an $ABCD_2X$ spectrum (both with the same $ABCD_2$ parameters) from a slightly modified LAOCOON II program which permits addition of up to six independent spectra in selected proportions.

(12) A. E. Borisov, I. S. Saveljeva, and S. R. Serdyuk, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 896 (1965); original Russiona appears in *Izv. Akad. Nauk SSSR, Ser. Khim.*, **5**, 924 (1965).

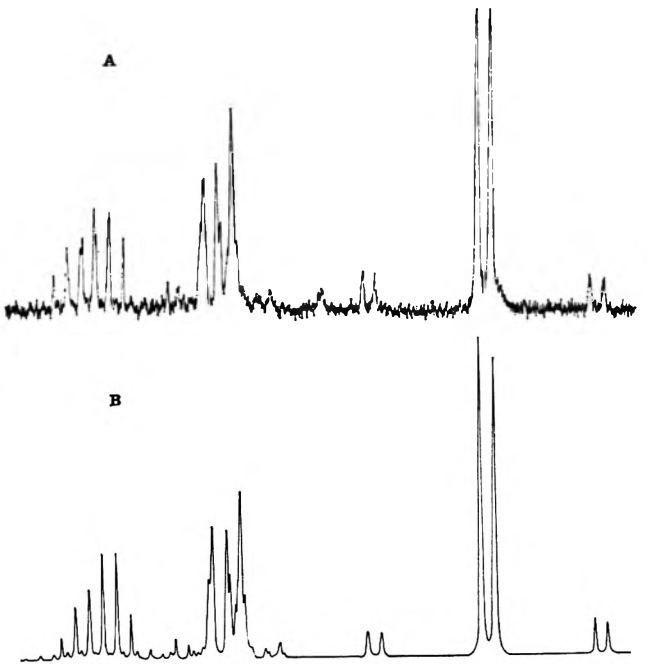

Figure 2.—Experimental proton spectrum (A) of diallylmercury in perdeuteriotetrahydrofuran at 60 MHz and calculated spectrum (B) using the chemical shift and coupling parameters for the 60-MHz analysis as listed in Table I.

Table I
Chemical Shifts and Coupling Constants in Hertz for Diallylmercury (1) in Perdeuteriotetrahydrofuran

	100 MHz[a]	60 MHz[b]
δ_1	598.10	360.24
δ_2	455.38	273.52
δ_3	467.60	281.17
$\delta_4 = \delta_5$	186.48	113.04
J_{12}	9.52[c]	9.43
J_{13}	16.75[d]	17.09
$J_{14} = J_{15}$	8.64	8.81
J_{23}	2.21	2.21
$J_{24} = J_{25}$	−0.66	−0.63
$J_{34} = J_{35}$	−1.04	−0.98
J_{16}[e]		45.85
J_{26}[e]		48.82
J_{36}[e]		49.96
J_{46}		144.30[f]

[a] At 32°. [b] At ~37°. [c] 9.5 Hz from the 220-MHz spectrum. [d] 16.6 Hz from the 220-MHz spectrum. [e] 8.1 Hz at −16.5° and 8.0 Hz at −38°. [f] 147.0 Hz at −16.5° and 147.5 Hz at −38°.

Packard 4204A audiooscillator by linear interpolation between TMS side bands. The 100-MHz spectra were obtained on a Varian Associates HA-100 spectrometer operated in the frequency-sweep mode. A Hewlett-Packard V-4315 frequency counter permitted measurement of the line positions to ±0.1 Hz.

Spin decoupling at 100 MHz of nuclei H-4 and H-5 caused simplification of the H-1 multiplet to a symmetrical quartet centered at −599.3 Hz from TMS with a total separation of 27.2 Hz. The spacing of this quartet suggested that J_{12} was about 10 Hz and J_{13} about 17.2 Hz, which values were used as original input in the LAOCOON computer program.

Subsequently, a 220-MHz spectrum of diallylmercury obtained on a Varian Associates HR-220 spectrometer gave essentially first-order resonances of H-2 and H-3 which gave J_{12} and J_{13} as 16.6 and 9.5 Hz, respectively.

Registry No.—Diallylmercury, 2097-71-4.

Acknowledgment.—We thank Professor S. I. Chan for assistance in securing 100-MHz spectra and for valuable suggestions. Mr. J. H. Prestegard obtained the 220-MHz spectrum and carried out the spin-decoupling experiment.

Bromine Addition to Olefins in Aqueous Solution

DIPAK ACHARYA AND MIHIR NATH DAS

Physical Chemistry Laboratories, Jadavpur University, Calcutta-32, India

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Rates of addition of bromine to methyl acrylate, methyl crotonate, methyl methacrylate, and acrylamide in aqueous solutions have been measured electrometrically in the presence of added bromide at 20, 30, and 40°. The rate constants for addition of Br_2 as well as of Br_3^- have been calculated and hence the corresponding values of activation energy and entropy of activation have been computed for each reaction. The relative reactivities of the four olefins follow the same order (methacrylate > crotonate > acrylamide > acrylate) with respect to both bromine and tribromide ion. For reaction with bromine, activation energy as well as frequency factor lies in the order acrylate > crotonate > acrylamide > methacrylate. For tribromide ion, activation energy lies in the order acrylamide > methacrylate > acrylate > crotonate, the sequence for the frequency factor being acrylamide > methacrylate > crotonate > acrylate. The results are not strictly in conformity with what should be expected from structural considerations.

Rates of addition of bromine to several olefins in aqueous solutions were measured by Kanyaev[1,2] and he concluded that the relative reactivity of molecular bromine and tribromide ion varies continuously with the reactivity of the olefin and also that the proportion of the dibromide in the product is equal to the fraction of reaction effected by tribromide ion. No support for this view has been provided by the studies of Atkinson and Bell.[3] From their kinetic results, coupled with product analysis, Atkinson and Bell postulated a general mechanism which is consistent with their findings. More recently Bell and Pring[4] have reported the kinetic results for addition of bromine to some more olefins in aqueous solution in the presence of added chloride and bromide, which tend to substantiate their earlier conclusions. In general, the velocity constants for reaction with bromine or tribromide ion, varying over eleven powers of ten, show an approximate correlation with the Taft σ^* substituent constants.

The object of the present investigations was to determine the activation energy and the entropy of activation for the reaction with bromine as well as

(1) N. P. Kanyaev, *J. Gen. Chem. USSR*, **26**, 3037 (1956).
(2) N. P. Kanyaev, *ibid.*, **29**, 825 (1959).
(3) J. R. Atkinson and R. P. Bell, *J. Chem. Soc.*, 3260 (1963).
(4) R. P. Bell and M. Pring, *ibid.*, *B*, 1119 (1966).

tribromide ion, for four olefinic substances, from rate measurements at different temperatures. These values should be more useful in providing some insight into the reaction mechanism than relative reactivities alone.

Experimental Section

Materials.—The samples of methyl acrylate (Light & Co., England) and methyl methacrylate (National Chemical Laboratory, Poona, India) were purified by the usual procedure.[5] Methyl crotonate (*trans*) was prepared and purified by the general method.[6] After drying with calcium chloride, the samples were fractionally distilled in an all-glass apparatus, the middle fraction being collected for the work. Acrylamide (Eastman Kodak Co.) was recrystallized from chloroform and dried before use. Inorganic reagents were of G. R. grade (E. Merck). All solutions were made with water which had been redistilled from alkaline potassium permanganate.

The initial concentrations of the olefinic compounds in the reaction mixtures were in the range 5×10^{-3} to 1.25×10^{-2} M for methyl crotonate and acrylamide, 2×10^{-2} to 1×10^{-1} M for methyl acrylate, and nearly 5×10^{-3} M for methyl methacrylate.

Initial bromine concentrations in the reaction mixtures were in the range 6×10^{-4} to 6×10^{-3} M, being about 5–10 times lower than the concentration of the olefinic compound in the reaction mixture.

Perchloric acid concentration was at 0.1 M. The only purpose of using the acid was to maintain the reaction conditions similar to those used by Bell and Atkinson[3] in their studies. They have, however, shown that the acid does not affect the kinetic results. In the presence of 0.1 N perchloric acid, hydrolysis of acrylamide might occur. To investigate this point, 0.01 M acrylamide in 0.1 N perchloric acid was kept overnight at room temperature, and a portion of the mixture was then made just alkaline and treated with Nessler reagent. The test showed absence of ammonia, indicating that hydrolysis of the amide does not occur under the conditions. In alkaline medium however, hydrolysis readily occurs as shown by the Nessler test. Further, in acid medium, any reaction of bromine on the nitrogen of the amide, forming bromamide, is ruled out, so that bromine only adds to the carbon–carbon double bond.

Each reaction was studied with different bromide concentrations (0.02–0.2 M).

Kinetic Measurements.—Kinetic measurements were carried out at 20, 30, and 40° (temperature variation ±0.1°) under dark conditions. The reaction was followed electrometrically, the method adopted being essentially similar to that described by Bell and Ramsden.[7] The reactions were conducted in a cell—a 150-ml beaker tightly closed by a rubber stopper through which were inserted one platinum wire electrode and a dip-type calomel electrode (fibre type, a product of Central Glass and Ceramic Research Institute, Calcutta) ending in a fine capillary tip. Emf measurements were made with a Leeds & Northrup K-type potentiometer and a moving coil galvanometer.

Calculated volumes of perchloric acid, potassium bromide, and bromine solutions were added to the cell vessel which was placed in a thermostat. After some time was allowed the potentiometer readings were noted. When the potentiometer reading became stable, the olefinic compound, kept previously in the same thermostat, was added to the cell vessel by means of a graduated pipet. The final volume of the reaction mixture was usually 40 ml.

The emf plotted against time gave good straight lines over a range of 60 mV, corresponding to a decrase in bromine concentration by a factor of 100. The time taken for this change was 25 to 30 min for methyl acrylate and acrylamide and 5 to 10 min for methyl crotonate and methyl methacrylate. The linearity of the plot of emf against time shows that the reaction is kinetically first order with respect to bromine, being zero order in the olefin which is always present in excess. Typical plots are shown in Figure 1 for illustration.

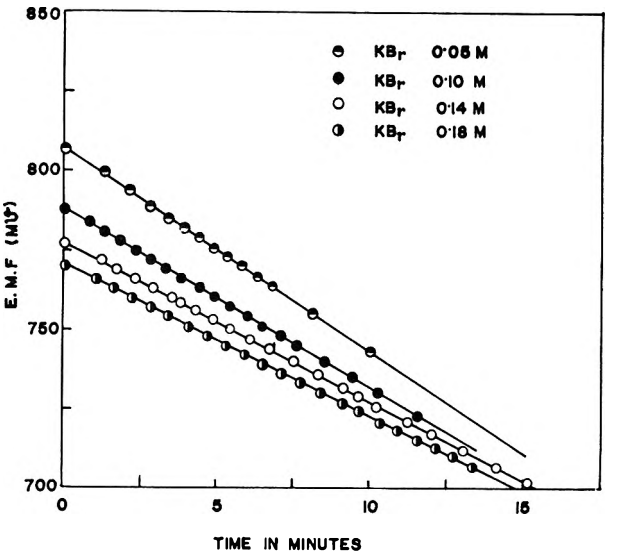

Figure 1.—Bromination of methyl methacrylate (5.0×10^{-3} M) at 20°. The course of a typical experiment.

The second-order rate constants (k) for each reaction at different temperatures have been obtained from eq 1–3 where C is the molar concentration of the olefin.

$$k_{20} = 79.4 \frac{dE}{dt}/C \quad (1)$$

$$k_{30} = 76.8 \frac{dE}{dt}/C \quad (2)$$

$$k_{40} = 74.3 \frac{dE}{dt}/C \quad (3)$$

Results

Assuming that the main product in the reaction between bromine and bromide ion is the tribromide ion and also assuming that Br_2 and Br_3^- are the only brominating species, the observed velocity constant for the bromination of olefin is given[3] by eq 4, where k_1 =

$$k(1 + K[Br^-]) = k_1 + k_1' K[Br^-] \quad (4)$$

second-order velocity constant for the reaction with the species Br_2, k_1' = second-order velocity constant for the reaction with the species Br_3^-, and K, the equilibrium constant, = $[Br_3^-]/[Br_2][Br^-]$. The K values corresponding to the temperatures 20, 30, and 40° are 17.26, 15.89, and 14.69, respectively, as obtained from the linear plot of log K values, as reported by Scaife and Tyrrell,[8] against reciprocals of absolute temperature. Eq 4 predicts a linear relation between the quantity on the left-hand side and the bromide concentration, $[Br^-]$, the values of k_1 and k_1' being obtainable from the intercept and the slope respectively of the straight-line plot. For illustration, the plot for acrylamide is shown in Figure 2.

Table I gives the observed values of the second-order rate constants (k) at different bromide concentrations together with the values of $k(1 + K[Br^-])$. The k_1 and k_1' values are shown in Table II. It should be noted, however, that the equilibrium constant (K) must be subject to salt effects, as also the rate constants (k_1 and k_1'), which have not been considered. Data for salt effects on the tribromide equilibrium are not available. Moreover, Atkinson and Bell[3] found that salt effects on

(5) E. H. Riddle, "Monomeric Acrylic Esters," Reinhold Publishing Corp., 1954.

(6) A. I. Vogel, "A Text Book of Practical Organic Chemistry," Longmans, Green and Co. Ltd., 1956, p 927.

(7) R. P. Bell and E. N. Ramsden, *J. Chem. Soc.*, 161 (1958).

(8) D. B. Scaife and H. J. V. Tyrrell, *ibid.*, 386 (1958).

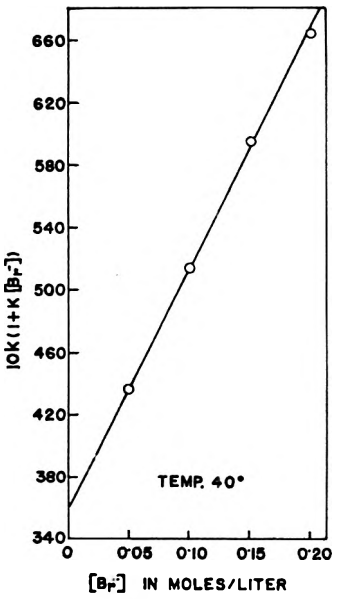

Figure 2.—Bromination of acrylamide.

TABLE I

BROMINATION OF OLEFINS ([H⁺] = 0.10 *M*)

[Br⁻], mol/l.	$10^2 k$, l. mol⁻¹ sec⁻¹ 20°	30°	40°	$10^2 k(1 + K[Br^-])$ 20°	30°	40°
			Acrylamide			
0.05	45.5	112.2	252.5	84.8	201	438
0.10	38.6	92.2	208.0	105.3	239	514
0.15	32.8	81.7	185.8	118.0	277	595
0.20	30.2	76.8	168.4	134.0	321	663
			Methyl Acrylate			
0.02	3.73			5.02		
0.05	3.41	8.63	24.15	6.36	15.5	41.9
0.10	3.18	7.53	20.44	8.66	19.5	50.5
0.14		7.20			23.2	
0.15	3.04		17.95	10.91		57.4
0.18		6.62			26.0	
0.20			16.72			65.9
			Methyl Crotonate			
0.02	82.6			111		
0.05	73.7	189	416	137	339	722
0.10	63.5	158	327	173	410	807
0.15	57.2		282	205		902
0.20		127.5	252		533	992
			Methyl Methacrylate			
0.05	159	384	692	296	689	1200
0.10	151	333	594	410	863	1468
0.14	132			449		
0.15		299	554		1010	1776
0.18	125			532		
0.20		282	535		1177	2107

the observed rate constants are specific so that the problem is not solved by working at a constant ionic strength. Some uncertainties are, therefore, inherent in the values of k_1 and k_1' reported in Table II.

For each olefinic species, the energy of activation for reaction with Br_2 as well as with Br_3^- was obtained by plotting log k_1 and log k_1' against reciprocal of absolute temperature. The plots for acrylamide are shown in Figures 3a and 3b. The entropy of activation ($\Delta S^{\pm}$) at 30° was calculated by equating the experimentally obtained value of the frequency factor A (l. mol^{-1} sec^{-1}) to $e\left(\frac{kT}{h}\right)(e^{\Delta S^{\pm}/R})$. The value of $\Delta S^{\pm}$ so calculated

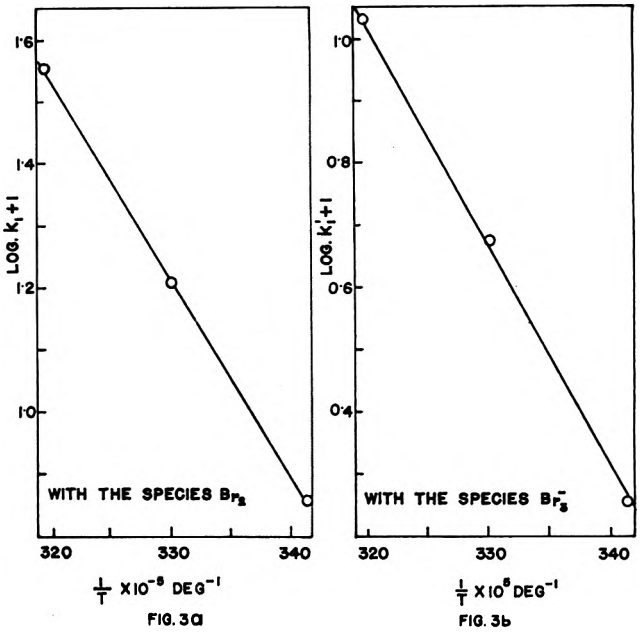

Figure 3.—Dependence of rate constant on temperature for bromination of acrylamide.

refers to the molar scale. The values of activation energy, frequency factor and entropy of activation are shown in Table III.

Discussion

The over-all rates of bromine addition to the three α,β-unsaturated esters lie in the order methacrylate > crotonate ≫ acrylate. The results obtained by Atkinson and Bell[3] with ethyl acrylate and crotonate at 25° are consistent with the present results for other temperatures. Considering separately the rates of addition of free bromine and of tribromide ion, the same sequence is maintained, k_1 being, in each case, considerably higher than k_1'. Thus the effect of the methyl group in the α or β position is in the same direction and is more or less of a similar order of magnitude for the addition of both Br_2 and Br_3^-. This presumably indicates that essentially similar mechanisms operate in both the cases. As expected for an electrophilic reaction, the presence of a methyl group, on either of the ethylenic carbon atoms, facilitates the addition of bromine to the double bond, the methyl group in the α position being slightly more effective than in the β position.

Regarding relative reactivities of several substituted ethylenes, the results of Bell and his coworkers[3,4] show approximate agreement with what is to be expected from the known electron-withdrawing effects of the substituents. The present investigation includes a new type of compound, acrylamide. The rate of bromine addition to acrylamide is much faster than to acrylic ester. The internal mesomeric effect within the amide or ester group should result in a lower over-all electron-withdrawing effect on the part of the amide compared with the acrylic ester. Thus, it fits in with the accepted ideas that electrophilic bromine addition should be faster with acrylamide.

The energy of activation (E) for the addition of free bromine to the three esters studied lies in the order methacrylic < crotonic < acrylic. The order is what is to be expected from the known electron-releasing

TABLE II

RATE CONSTANTS FOR BROMINATION OF OLEFINS

k_1 = second-order rate constant for addition of Br_2

k_1' = second-order rate constant for addition of Br_3^-

Olefin	k_1, l. mol^{-1} sec^{-1}			k_1' l. mol^{-1} sec^{-1}			k_1'/k_1		
	20°	30°	40°	20°	30°	40°	20°	30°	40°
Acrylamide	0.72	1.62	3.58	0.18	0.48	1.08	0.25	0.30	0.30
Methyl acrylate	0.04	0.115	0.35	0.026	0.053	0.102	0.64	0.47	0.29
Methyl crotonate	1.00	2.72	6.20	0.42	0.82	1.53	0.42	0.30	0.25
Methyl methacrylate	2.30	5.24	9.20	0.95	2.04	3.92	0.41	0.39	0.43

TABLE III

COMPARISON OF ACTIVATION ENERGY (E), FREQUENCY FACTOR (A), AND ENTROPY OF ACTIVATION ($\Delta S^{\pm}$)[a] FOR THE REACTION BETWEEN SUBSTITUTED OLEFINS AND BROMINE

Substituted olefins	For reaction with the species Br_2, *i.e.*, for the rate constant k_1			For reaction with the species Br_3^-, *i.e.*, for the rate constant k_1'		
	E, kcal mol^{-1}	A, l. mol^{-1} sec^{-1}	$\Delta S^{\pm}$, cal deg^{-1} mol^{-1}	E', kcal mol^{-1}	A' l./mol^{-1} sec^{-1}	$\Delta S^{\pm\prime}$ cal deg^{-1} mole^{-1}
Acrylamide	14.6	5.8×10^{10}	−11.3	16.2	2.4×10^{11}	−8.5
Methyl acrylate	19.4	1.2×10^{13}	−0.7	12.4	4.2×10^{7}	−25.7
Methyl crotonate	16.5	2.0×10^{12}	−4.3	11.7	2.2×10^{8}	−22.3
Methyl methacrylate	13.3	1.8×10^{10}	−13.7	13.0	5.0×10^{9}	−16.2

[a] $S^{\pm}$ values are reported for 30°.

property of the methyl group. In the addition process, the point of attack is the α-carbon atom, and hence we may reasonably expect the methyl group in the α position (in methacrylic ester) to exert a relatively stronger effect than in the β position (in crotonic ester) The frequency factors lie in the same order as that for the activation energy shown above.

Again, the energy of activation for addition of bromine to acrylamide is appreciably lower than that for the reaction with acrylic ester. This is also in conformity with the relatively smaller electron-withdrawing effect of the amide group, compared with that of the ester group. The frequency factor is, however, much smaller for the amide, leading to a relatively high negative value for the entropy of activation.

Coming to the case of Br_3^- addition, the energy of activation (E') lies in the order crotonic < acrylic < methacrylic. The differences in the values of activation energy are, however, much less pronounced than for molecular bromine addition, and the data may not be accurate enough to justify any detailed discussion on the basis of such small differences. The frequency factors, which lie in the order acrylic > crotonic > methacrylic, are relatively low, the entropy of activation having a large negative value in each case.

The energy of activation for acrylic amide is appreciably higher than for the acrylic ester. For an electrophilic reaction, the reverse should be anticipated. The frequency factor, on the other hand, is much higher for the amide. It is difficult to correlate the results in terms of simple structural considerations.

Registry No.—Bromine, 7726-95-6; acrylamide, 79-06-1; methyl acrylate, 96-33-3; methyl crotonate, 623-43-8; methyl methacrylate, 80-62-6.

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Photobromination of Alkyltrichlorosilanes

K. W. MICHAEL, H. M. BANK, AND J. L. SPEIER

Organic Research Laboratories, Dow Corning Corporation, Midland, Michigan 48640

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Photobromination of *n*-butyl, *n*-propyl, ethyl, 2-propyl, and cyclopentyl groups in butyl-, propyl-, ethyl-, and cyclopentyltrichlorosilanes and 2-propylmethyldichlorosilane was studied. The trichlorosilyl group activated the adjacent position toward bromination and had very little effect upon other positions in the alkyl groups. In contrast, the trichlorosilyl group deactivates the adjacent position toward chlorination. Stabilization of a free radical α to silicon by delocalization of the electron between the carbon and the adjacent silicon atom is suggested to explain these results.

Data concerned with the chlorination of alkylchlorosilanes have been collected and summarized.[1,2] The directive effects of various substituted silyl groups have been studied using sulfuryl chloride as the reagent for chlorination.[3-7] Trimethylsilyl, Me_2ClSi, $MeCl_2Si$, and Cl_3Si groups show an effect upon the near positions of an alkyl group that varies from one of activation by Me_3Si to deactivation by Cl_3Si–. Recent experiments using toluene as a standard for measurement of relative rates.[8,9] verified the above conclusions.

The only example of direct bromination of an alkylsilane in which the distribution of products is known is that of tetraethylsilane which brominated only at the position adjacent to silicon.[10] The results obtained by using mixtures of bromine and chlorine to brominate ethyltrichlorosilane and 1-methylethyltrichlorosilane[11] are best compared with those of chlorination since the chlorine radical abstracts the hydrogen in both cases.[12] This paper reports results of the bromination of several alkyltrichlorosilanes.

Results

The apparatus used for the brominations has been described.[13] In this apparatus a volatile conpound is continually fractionated so that the high boiling halogenated products are collected in a receiver and the unhalogenated compound is refluxed through an illuminated chamber. Halogen is admitted to this chamber in which a large molar ratio of compound to halogen is always maintained. This permits a very high yield of monohalogenated products in most cases.

The results of the bromination of various alkylchlorosilanes are summarized in Table I. The mole fractions of the isomeric monobrominated species were corrected by the appropriate statistical factors for the number of hydrogens at the position of substitution. The amount of the most abundant product in each case was set equal to unity and the amounts of other products shown in Table I are then relative to the most abundant one. No products were detected that could have arisen from skeletal rearrangements or from replacement of chlorine by bromine on silicon.

TABLE I

RELATIVE REACTIVITIES PER C–H BOND IN THE BROMINATION OF ALKYLCHLOROSILANES

Substrate	Registry no.	Position[a] 1	2	3	4
$Cl_3SiCH_2CH_2CH_2CH_2H$	7521-80-4	0.00	1.00	0.96	0.00
$Cl_3SiCH_2CH_2CH_2H$	141-57-1	0.00	1.00	0.00	
$Cl_3SiCH_2CH_2H$	115-21-9	1.00[b]	0.22		
$Cl_3SiCH(CH_3)_2$	4170-46-1	1.00	0.00		
$CH_3Cl_2SiCH(CH_3)_2$	18236-89-0	1.00	0.00		
$Cl_3SiCHCH_2$ (CH$_2$)$_3$	14579-03-4	1.00	0.04	0.00	

[a] The silyl group is at position 1. [b] The amount of the 1-bromo isomer was corrected for that consumed by formation of 1,1-dibromoethyltrichlorosilane.

Discussion

Butyltrichlorosilane was brominated only in the 2 and 3 positions and nearly equally in each position. *n*-Butane under comparable conditions yielded essentially only 2-bromobutane.[14] These results indicate that the orienting effects of a CH_3 group or of a CH_2SiCl_3 group are nearly identical during bromination.

The chlorination of butyltrichlorosilane with sulfuryl chloride in carbon tetrachloride and toluene showed that the 3 position was more reactive than the 2 position and Nagai concluded that this was because of the inductive effect of the trichlorosilyl group removing electron density from the 2 position.[8,9] However, Mironov's[15] study of the same reaction showed that the 2 position was equally or more reactive than the 3 position. The differences in these two reports[9,15] are likely to be not due to the better analyses as suggested by Nagai[9] but due to the effects of carbon tetrachloride and toluene used as solvents by Nagai. Walling and Miller[16] have shown that the presence of carbon tetrachloride alters the selectivity of the chlorine radical and Russell[17] has demonstrated that the presence of aromatic solvents can change the selectivity of the chlorine radical by

(1) C. Eaborn, "Organosilicon Compounds," Butterworths and Co. Ltd., London, 1960, p 379.

(2) V. Bazant, V. Chvalovsky, and J. Rathousky, "Organosilicon Compounds," Vol. 1, Publishing House of the Czechoslovak Academy of Sciences, Prague, 1965, p 269.

(3) L. H. Sommer and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 485 (1946).

(4) L. H. Sommer, E. Dorfman, G. M. Goldberg, and F. C. Whitmore, *ibid.*, **68**, 488 (1946).

(5) L. H. Sommer, D. L. Bailey, W. A. Strong, and F. C. Whitmore, *ibid.*, **68**, 1881 (1946).

(6) L. H. Sommer, D. L. Bailey, and F. C. Whitmore, *ibid.*, **70**, 2869 (1948).

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(8) Y. Nagai, N. Machida, and T.Migita, *Bull. Chem. Soc. Jap.*, **39**, 412 (1966).

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(10) E. Larsson and L. O. Knopp, *Acta Chim. Scand.*, **1**, 268 (1947).

(11) V. Mironov, V. Nepomnina, and L. Leites, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **3**, 461 (1960); 428 CB translation.

(12) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, Chapter 8 and references cited therein.

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(14) P. S. Fredericks and J. M. Tedder, *J. Chem. Soc.*, **25**, 144 (1960).

(15) V. F. Mironov and U. V. Nepomnina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 182 (1955).

(16) C. Walling and B. Miller, *J. Amer. Chem. Soc.*, **29**, 4181 (1957).

(17) G. A. Russell, *ibid.*, **79**, 2977 (1957).

more than a power of ten.[18] Until the nature of these changes[16-19] are understood, evaluation of data obtained in such solvents in terms of only simple inductive effects as done by Nagai[8,9] is unwarranted.

The bromination of propyltrichlorosilane gave mostly 2-bromopropyltrichlorosilane along with a small amount of 2,2-dibromopropyltrichlorosilane. Chlorination has also shown that the 2 position was the most reactive one in propyltrichlorosilane.[4,8,9,20]

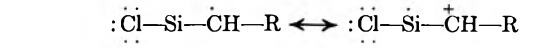
Ethyltrichlorosilane was much less reactive than either propyl- or butyltrichlorosilane. Both positions on the ethyl group were slow to brominate, but the CH_3 group was slower than the Cl_3SiCH_2 group by a factor of about five. Chlorination by sulfuryl chloride showed that the CH_3 was more reactive than the Cl_3SiCH_2 group.[3,8,9] Chlorination with chlorine gave a ratio of 2-chloroethyl to 1-chloroethyltrichlorosilane of about 1.7.[21,22] Correction for the number of hydrogens at each position gives the reactivity at the 2 position as 1.3 times that of the 1 position for chlorination,[23] whereas this study found the 1 position was about 5 times as reactive as the 2 position for bromination.

2-Propyltrichlorosilane and 2-propylmethyldichlorosilane were both brominated exclusively in the 2 position. These results are as expected from the preceding data which indicate a slight activating influence of the silyl groups upon the position adjacent to the silicon atom and the known difficulty of brominating methyl groups in such molecules.

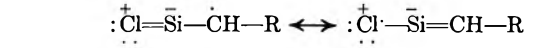
Cyclopentyltrichlorosilane, as expected from the preceding examples, brominated almost entirely in the 1 position with a small amount in the 2 position. The extent of activation of the 1 position may be surprising in this example. The chlorination of cyclopentyltrichlorosilane by sulfuryl chloride has been described[24] as yielding at least 50% 2-chlorocyclopentyltrichlorosilane.

During photohalogenation or other halogenations that proceed by a free-radical mechanism, several factors may determine the distribution of products. The electrophilic halogen atom tends to attack a C–H bond of greatest electron density to form hydrogen halide and an organic free radical.[12] Structural effects upon orientation are greater during brominations than during chlorination for several reasons. Abstraction of a hydrogen atom by a bromine atom is usually endothermic, whereas the corresponding process with a chlorine atom is strongly exothermic.[12] Substituents which influence the stability of the organic radical in these processes will greatly lower the energy of the transition state during brominations, but will have little effect during chlorination.[12] Russell and Brown[25] recognized this when they found that the methyl C–H bonds of toluene were only one-third as reactive as the C–H bonds in cyclohexane toward chlorination, but 230 times as reactive toward bromination. Resonance stabilization of the benzyl free radical is thought to lead to this result in bromination but to have slight effect upon chlorination. Similar effects have been ascribed to halogen substituents during halogenation of haloalkanes.[14,26,27]

No activating influence for bromination having a magnitude comparable with that of an aromatic ring on a methyl group is found in Cl_3Si, Cl_2MeSi, or $ClMe_2Si$ groups as evidenced by the fact that Cl_3SiCH_3, $Cl_2MeSiCH_3$, and $ClMe_2SiCH_3$ are difficult to photobrominate with bromine.[28] However, a small effect of this kind is useful to explain the products obtained in this work. The inductive effect of the Cl_3Si or Cl_2MeSi groups is electron withdrawing leading to deactivation of the positions near silicon during chlorination of alkylsilanes. Resonance stabilization of the intermediate free radicals by delocalizing an electron in the vacant d orbitals of silicon can explain the results of bromination. Delocalization can be thought of in terms of structures such as



Because the silicon chlorine bond has double-bond character,[29] stabilization may also be thought of as involving the chlorine as in structures such as



Experimental Section

A Varan Associates Model A-60 was used to obtain nmr spectra using tetramethylsilane as an internal standard. Analyses by vapor phase chromatography (vpc) were obtained on an F & M Model 720 dual column programmed temperature gas chromatograph equipped with 4 ft × 0.25 in. stainless steel columns packed with 16% Dow Corning® FS-1265 on Chromosorb P.

Materials.—Bromine (Baker Analyzed Reagent), 2-chloropropane (Eastman Organic Chemicals), cyclopentene (Columbia Organic Chemicals), and N-bromosuccinimide (Eastman Organic Chemicals) were used as obtained. Propyltrichlorosilane (bp 123°), methyltrichlorosilane (bp 66.4°), silicon tetrachloride (bp 57.6°), trichlorosilane (bp 31°), and ethyltrichlorosilane (bp 99°) were products of Dow Corning Corp.

1-Methylethyltrichlorosilane was prepared by the method of Sommer and Evans[30] by the reaction of isopropylmagnesium chloride wih silicon tetrachloride.

(1-Methylethyl)methyldichlorosilane was prepared by the reaction of isopropylmagnesium chloride with methyltrichlorosilane and had $n^{25}D$ 1.4250 and d^{25}_4 1.0333 (lit.[31] $n^{20}D$ 1.4270 and d^{20}_4 1.0385).

Cyclopentyltrichlorosilane was prepared by the following method. Cyclopentene (95.7 g, 1.40 mol), trichlorosilane (191 g, 1.40 mol), and chloroplatinic acid (0.1 *N* in isopropyl alcohol, 1.0 ml) were heated at 145–155° for 19 hr in a 1.4-l. strainless steel bomb. Analysis by vpc showed a 75% yield. Distillation gave pure cyclopentyltrichlorosilane, bp 181° (756 mm), $n^{25}D$ 1.4687, d^{25}_4 1.2414 (lit.[32] $n^{25}D$ 1.4688).

Vapor Phase Bromination of Alkylchlorosilanes.—An apparatus described for the chlorination of alkylsilanes was used.[13] Refluxing alkylsilane and bromine were mixed in a chamber illuminated with a 200-W incandescent lamp. Brominated prod-

(18) Walling has also reported significant influences in the presence of carbon disulfide or oxygen.[19]

(19) C. Walling and M. F. Mayahi, *J. Amer. Chem. Soc.*, **81**, 1485 (1959).

(20) S. Munkett and R. Muller, *Chem. Ber.*, **92**, 1012 (1959).

(21) A. D. Petrov, V. F. Mironov. V. A. Ponomarenko, and E. A. Chernyshev, *Dokl. Akad. Nauk SSSR*, **97**, 687 (1954).

(22) C. F. Mironov and V. A. Ponomarenko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 199 (1957).

(23) E. P. Mikheev [*Dokl. Akad. Nauk SSSR*, **117**, 821 (1957)] reports that this reaction at 15–20° in the liquid phase had a reactivity at the 2 position 1.9 times that of the 1 position.

(24) V. F. Mironov, N. G. Maksimova, and V. V. Nepomnina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 329 (1967).

(25) G. A. Russell and H. C. Brown, *J. Amer. Chem. Soc.*, **77**, 4578 (1955).

(26) P. S. Fredericks and J. M. Tedder, *J. Chem. Soc.*, 3520 (1960).

(27) W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963).

(28) J. L. Speier, *ibid.*, **73**, 826 (1951).

(29) C. Eaborn, "Organosilicon Compounds," Butterworths and Co. Ltd., London, 1960, p 96.

(30) L. H. Sommer and F. J. Evans, *J. Amer. Chem. Soc.*, **76**, 1186 (1954).

(31) B. N. Dolgov, S. N. Borisov, and M. G. Vornkov, *Zh. Obshch. Khim.*, **27**, 2062 (1957).

(32) H. M. El-Abbady and L. C. Anderson, *J. Amer. Chem. Soc.*, **80**, 1737 (1958).

ucts were continuously separated by a distillation column. Hydrogen bromide passed the condenser and was vented from the system.

Bromination of Butyltrichlorosilane.—Bromine (335 g, 2.09 mol) and butyltrichlorosilane (534 g, 2.79 mol) gave 675 g of crude product. Analysis by vpc (area per cent) showed 40% butyltrichlorosilane, 30% 2-bromobutyltrichlorosilane, 28% 3-bromobutyltrichlorosilane, and 2% unknowns. The 3-bromobutyltrichlorosilane was isolated by preparatory vpc. The nmr gave a sextet at τ 5.9 for BrCH due to adjacent CH_3 and CH_2 and a doublet at 8.25 for CH_3 in the ratio of 1:2.9. The methylene region was not resolved. The nmr of a fraction obtained by distillation [bp 65° (60 mm)] which was by vpc 80% 2-bromo- and 20% 3-bromobutyltrichlorosilane showed a quintet for BrCH at τ 5.71 due to two CH_2 groups, a triplet for CH_3 at 8.90, and a doublet at 7.74 for $SiCH_2$ in the ratio of 1.0:3.0:2.0 for the 2-bromo isomer. The other methylene unit was not resolved. The neutralization equivalent of this fraction was 71.3 (theoretical value for the 80:20 ratio is 71.6).

Bromination of Propyltrichlorosilane.—Propyltrichlorosilane (1084 g, 6.11 mol) and bromine (719 g, 4.49 mol) gave 1397 g of crude product. Analysis by vpc (area per cent) showed 35% unreacted propyltrichlorosilane, 63% 2-bromopropyltrichlorosilane, and 2,2-dibromopropyltrichlorosilane. Distillation gave 2-bromopropyltrichlorosilane, bp 178.8° (751 mm), $n^{25}D$ 1.4871, d^{25}_4 1.4976, 99% pure by vpc with a neutralization equivalent of 64.3 (theoretical value 64.2). The nmr showed a sextet for BrCH at τ 5.52, $SiCH_2$ at 7.7–7.9, and CH_3 as a doublet at 8.12 in the proton ratio of 1.0:2.0:3.0. The 2,2-dibromopropyltrichlorosilane was identified in a fraction containing 14.5% 2-bromopropyltrichlorosilane from the nmr spectrum which gave a single peak for CH_2CBr_2 at τ 6.75 and a single peak for CBr_2CH_3 at 7.72 in the ratio of 2.0:3.0.

Propyltrichlorosilane (27 g, 0.15 mol) was also brominated with N-bromosuccinimide (18 g, 0.10 mol) in refluxing carbon tetrachloride (75 ml). The color of bromine was stable in the absence of illumination with a 200-W incandescent lamp. After 40 min of illumination, solid succinimide (9.5 g, theoretical value 9.9 g) was removed by filtration. Analysis by vpc showed 2-bromopropyltrichlorosilane as the only significant product. Traces of higher eluting materials were present.

Bromination of Ethyltrichlorosilane.—Bromine (60 g, 0.38 mol) and ethyltrichlorosilane (81.8 g, 0.50 mol) gave 109 g of crude product. The reaction was very slow and it was difficult to avoid excess bromine in the illuminated chamber. Analysis by vpc (area per cent) showed 48% ethyltrichlorosilane, 27% 1-bromoethyltrichlorosilane, 12% 2-bromoethyltrichlorosilane, and 13% 1,1-dibromoethyltrichlorosilane. The material was distilled. The nmr of a fraction which was by vpc 85% 1-bromo- and 15% 2-bromoethyltrichlorosilane, neut equiv 76.2 (theoretical value for 85:15 ratio is 77.7), showed BrCH as a quartet at τ 6.45 and CCH_3 as a doublet at 8.13 in the ratio of 1.0:2.9 for the 1-bromoethyltrichlorosilane. A fraction which was 34% 1-bromo and 66% 2-bromo isomer gave CH_2Br as a triplet at τ 6.46 and CH_2Si as a multiplet at 7.87 in the ratio of 2.0:2.0 for the 2-bromo isomr. The 1,1-dibromoethyltrichlorosilane was a solid (mp 150–153°) with a neutralization equivalent of 107 (theoretical value 107). The nmr showed CCH_3 as a singlet at τ 7.58.

Bromination of 1-Methylethyltrichlorosilane.—Bromine (60 g, 0.38 mol) and 1-methylethyltrichlorosilane (88.8 g, 0.50 mol) gave 118 g of crude product. Analysis by vpc (area per cent) showed 22% unreacted 1-methylethyltrichlorosilane and 77% 1-bromo-1-methylethyltrichlorosilane along with traces of higher eluting materials. Distillation gave pure 1-bromo-1-methylethyltrichlorosilane, mp 100–110°,[33] with a neutralization equivalent of 85.2 (theoretical value 85.5). The nmr showed only a single peak at τ 8.10.

Anal. Calcd for $C_3H_6BrCl_3Si$: C, 14.1; H, 2.23; Si, 10.9. Found: C, 14.2; H, 2.33; Si, 11.0.

Bromination of (1-Methylethyl)methyldichlorosilane.—Bromine (85 g, 0.53 mol) and (1-methylethyl)methyldichlorosilane (100 g, 0.64 mol) gave 142 g of curde product. Distillation gave 98.5 g (0.42 mol, 79% yield) of the monobrominated product as a waxy solid. The nmr showed only (1-bromo-1-methylethyl)methyldichlorosilane with $SiCH_3$ as a singlet at τ 9.06 and CCH_3 as a singlet at 8.16 in the ratio of 3.0:5.9.

Anal. Calcd for $C_4H_9BrCl_2Si$: C, 20.3; H, 3.81; Si, 11.9. Found: C, 20.5; H, 3.92; Si, 11.9.

Bromination of Cyclopentyltrichlorosilane.—Bromine (24 g, 0.15 mol) and cyclopentyltrichlorosilane (41 g, 0.20 mol) at 98 mm gave 53 g of crude product. Distillation gave unreacted cyclopentyltrichlorosilane (13 g, 0.065 mol) and bromocyclopentyltrichlorosilane (35 g, 0.12 mol), bp 110° (49 mm), which had a neutralization equivalent of 90.2 (theoretical value for 83% 1- and 3-bromocyclopentyltrichlorosilane and 17% 2-bromocyclopentyltrichlorosilane, 90). The nmr of the bromocyclopentyltrichlorosilane showed CHBr at τ 5.56 and broad alkyl in the approximate ratio of 1:62. The ratio of CHBr to CH_2 plus SiCH was determined by nmr. Bromocyclopentyltrichlorosilane (6.71 mmol) in 2.30 mmol of chloroform gave a ratio of CHBr to $HCCl_3$ of 0.441 showing that 15% was 2- and 3-bromocyclopentyltrichlorosilane and 85% was 1-bromocyclopentyltrichlorosilane.

(33) The solid underwent a change of structure making the melting point difficult to determine on a Fisher-Johns apparatus.

Direct Liquid Phase Fluorination of Halogenated Aromatic Compounds[1]

V. GRAKAUSKAS

Environmental Systems Division, Aerojet-General Corporation, Azusa, California 91702

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Direct liquid phase fluorination of chlorinated aromatic compounds proceeded by addition and polymerization, yielding the corresponding 1,2,3,4,5,6-hexafluorocyclohexane derivatives, decafluorobicyclohexyls, and low molecular weight polytetrafluorocyclohexenes. The following substrates followed this general reaction sequence: *o*-dichlorobenzene, *p*-dichlorobenzene, 1,2,4-trichlorobenzene, 1,3,5-trichlorobenzene, 1,2,4,5-tetrachlorobenzene, tetrachlorobiphenyl, and hexachlorobiphenyl. The fluorination of tetrachlorophthatic anhydride yielded 1,2,3,4,5,6-hexafluorotetrachlorocyclohexane-1,2-dicarboxylic acid anhydride. Perfluorobicyclohexyl and low molecular weight polydecafluorocyclohexenes were obtained in the fluorination of hexafluorobenzene; the fluorination of chloropentafluorobenzene proceeded in an analgous manner. The chlorofluorocyclohexanes obtained by the fluorination of *o*-dichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene were dehydrohalogenated to give aromatic fluoro and chlorofluoro compounds. Decafluorobiphenyl was obtained in the dehydrohalogenation of decafluorohexachlorobicyclohexyl. Substitution was observed in the fluorination of *o*-dichlorobenzene.

The direct liquid phase fluorination of organic compounds, under investigation in this laboratory since 1958, was utilized in the synthesis of fluoramino[2] and aliphatic fluoronitro compounds.[3] The investigation of the scope and limitation of this fluorination technique with regard to the nature of organic substrates led to the examination of direct liquid phase fluorination of halogenated aromatic compounds reported in this paper.

Early attempts to directly fluorinate aromatic hydrocarbons, and organic compounds in general, resulted in explosions and "burning" of substrates to hydrogen fluoride and carbon tetrafluoride.[4] The differences between direct fluorination and other halogenation reactions were emphasized by Moissan, who predicted that the probability of accomplishing a controllable substitution utilizing elementary fluorine was remote.[5] The attempts to "tame" the reactions of elementary fluorine with organic compounds, however, continued. Bancroft and Jones[6] in 1929 reported explosions in vapor or liquid phase fluorination of benzene and toluene. Several years later, Bancroft and Whearty[7] again investigated the fluorination of benzene, but this time used fluorine diluted with nitrogen. Although explosions were avoided, only tarry, noncharacterizable products were obtained.

Bockemuller[8] investigated the fluorination of several aromatic compounds, but in all cases obtained only nondistillable, high fluorine content tars, and concluded that in direct liquid phase fluorination reactions, aromatic compounds behave as cyclohexatrienes and undergo addition and polymerization rather than substitution reactions.

The fluorination of hexachlorobenzene and 1,3,5-trichlorobenzene was reported[7,9] to give chlorofluorobenzenes by the displacement of one or more chloro groups of the substrates by fluorine. Recently, Brooke, *et al.*,[10] reported excellent yields of hexachlorohexafluorocyclohexane in the liquid phase fluorination of hexachlorobenzene. Bigelow and Pearson[11] also studied the liquid phase fluorination of hexachlorobenzene and obtained small amounts of tetrafluorohexachlorocyclohexene and hexachlorohexafluorocyclohexane.

The differing results obtained by these three groups of investigators under apparently very similar reaction conditions led to a brief reinvestigation of direct liquid phase fluorination of hexachlorobenzene. We confirmed the findings of Brooke, *et al.* Hexachlorobenzene underwent smooth fluorination in either carbon tetrachloride or 1,1,2-trichloro-1,2,2-trifluoroethane solution and consumed approximately 3 mol of fluorine to give a product analyzing for $C_6Cl_6F_6$, practically quantitatively.

The addition of fluorine to hexachlorobenzene suggested that other halogenated aromatic compounds might react similarly, and, consequently, a number of such compounds were examined under direct liquid phase fluorination conditions. 1,2,4-Trichlorobenzene and 1,3,5-trichlorobenzene underwent fluorination in 1,1,2-trichloro-1,2,3-trifluoroethane solution at 0 ± 5°, consuming approximately 3 mol of fluorine rapidly and without burning or explosions. In both cases, the yield of reaction products amounted to the sum of weights of fluorine and the trichlorobenzene employed, indicating that fluorination proceeded by addition rather than by substitution.

The reaction product obtained in the fluorination of 1,2,4-trichlorobenzene was separated into several fractions. The low-boiling fraction amounting to approximately 50% of the total product and analyzing for $C_6H_3Cl_3F_6$, was identified as 1,2,3,4,5,6-hexafluoro-1,2,4-trichlorocyclohexane on the basis of elemental analysis, infrared spectrum, and physical properties. The higher boiling material, amounting to *ca.* 30% of the total product, analyzed for $C_{12}H_6Cl_6F_{10}$. Its molecular weight was determined as 610 ± 60. On the basis of elemental analysis, physical properties, infrared spectrum, and molecular weight, this material was characterized as hexachlorodecafluorobicyclohexyl,

(1) Presented in part at the Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967.

(2) V. Grakauskas, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., September 1961, p 23 M; Third International Symposium on Fluorine Chemistry, Munich, Germany, September 1965.

(3) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

(4) H. Moissan, *Ann. Chim. Phys.*, **19**, 272 (1891).

(5) H. Moissan, "Das Fluor und Seine Verbinderugen," Verlag M. Krayn, Berlin, 1900, pp 236 ff.

(6) W. D. Bancroft and N. C. Jones, *Trans. Amer. Electrochem. Soc.*, **55**, 183 (1929).

(7) W. D. Bancroft and S. F. Whearty, *Proc. Nat. Acad. Sci. U. S.*, **17**, 183 (1931).

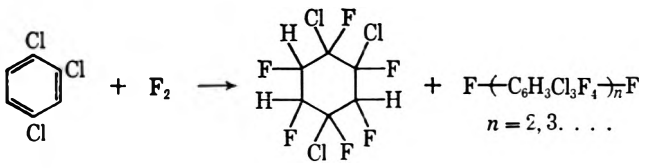
(8) W. Bockemuller, *Ann.*, **506**, 20 (1933).

(9) S. F. Whearty, *J. Phys. Chem.*, **35**, 3121 (1931).

(10) G. M. Brooke, R. D. Chambers, J. Heyes, and W. K. R. Musgrave, *J. Chem. Soc.*, 729 (1964).

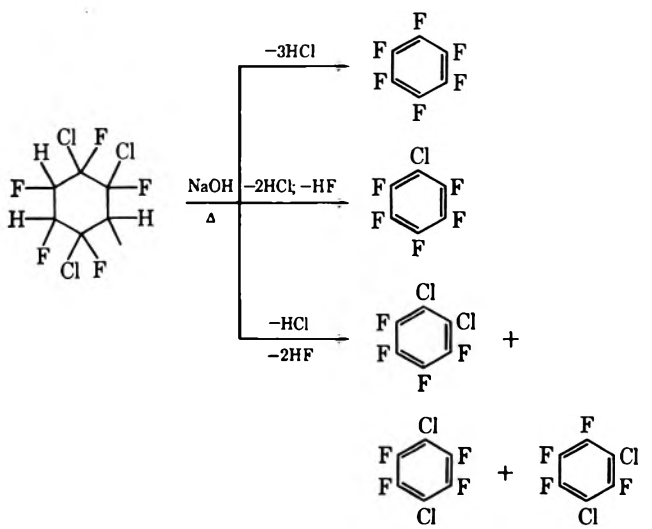
(11) L. A. Bigelow and J. H. Pearson, *J. Amer. Chem. Soc.*, **56**, 2773 (1934).

probably a mixture of several isomers. The remainder of the product, a white solid comprising the distillation residue, analyzed for $C_6H_3Cl_3F_4$. On the basis of elemental analysis and physical properties, this material was characterized as a mixture of polytichlorotetrafluorocyclohexenes, $(C_6H_3Cl_3F_4)_n$.



The fluorination product of 1,3,5-trichlorobenzene was treated in an analogous manner as that above, and the reaction products were identified as 1,2,3,4,5,6-hexafluoro-1,3,5-trichlorocyclohexane, decafluorohexachlorobicyclohexyl, and polytrichlorotetrafluorocyclohexenes.

Additional confirmation of the structures of the above reaction products was obtained in their dehydrohalogenation to aromatic fluorocarbons. 1,2,3,4,5,6-Hexafluoro-1,2,4-trichlorocyclohexane underwent a facile dehydrohalogenation on treatment with sodium hydroxide to give a mixture of hexafluorobenzene, chloropentafluorobenzene, and the three isomers of dichlorotetrafluorobenzene. The individual compounds in the mixture were identified by fluorine nmr spectra (see Experimental Section for details).

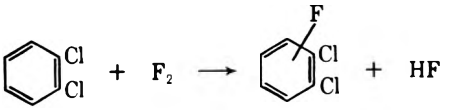


1,2,3,4,5,6-Hexafluoro-1,3,5-trichlorocyclohexane, the monomeric fluorination product of 1,3,5-trichlorobenzene, underwent dehydrohalogenation under similar conditions, and gave a mixture of aromatic compounds similar in composition to that obtained from the 1,2,4-trichloro isomer. *m*-Dichlorotetrafluorobenzene was the only dichlorotetrafluorobenzene isomer in this dehydrohalogenation.

Decafluorohexachlorobicyclohexyls, the dimeric fluorination products of 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene, were dehydrohalogenated with aqueous sodium hydroxide at 80–100°. Decafluorobiphenyl was identified by its fluorine nmr spectrum as one of the components in the dehydrohalogenation mixture.

The fluorination of *o*-dichlorobenzene and *p*-dichlorobenzene was examined next. *o*-Dichlorobenzene underwent fluorination in 1,1,2-trichloro-1,2,2,-trifluoroethane solution and consumed approximately three moles of fluorine. The distillable portion of the fluorination product analyzed for $C_6H_4Cl_2F_6$, and on the basis of elemental analysis and physical properties, the material was characterized as 1,2-dichloro-1,2,3,4,5,6-hexafluorocyclohexane. The distillation residue analyzing for $C_{12}H_8Cl_4F_{10}$, molecular weight 575 ± 60, was characterized as decafluorotetrachlorobicyclohexyl, containing some higher molecular weight condensation products.

Unexpected results were obtained in the dehydrohalogenation of 1,2-dichloro-1,2,3,4,5,6-hexafluorocyclohexane with sodium hydroxide. In addition to pentafluorobenzene, the dehydrohalogenation product mixture also contained hexafluorobenzene and chloropentafluorobenzene. The latter two compounds could be produced only in the dehydrohalogenation of dichloroheptafluorocyclohexane. The formation of dichloroheptafluorocyclohexane in the fluorination of *o*-dichlorobenzene could have taken place by the displacement of hydrogen either before or after the addition. If the latter was the case, *o*-dichlorofluorobenzene must have been produced as a side reaction product from *o*-dichlorobenzene *via* substitution–fluorination.



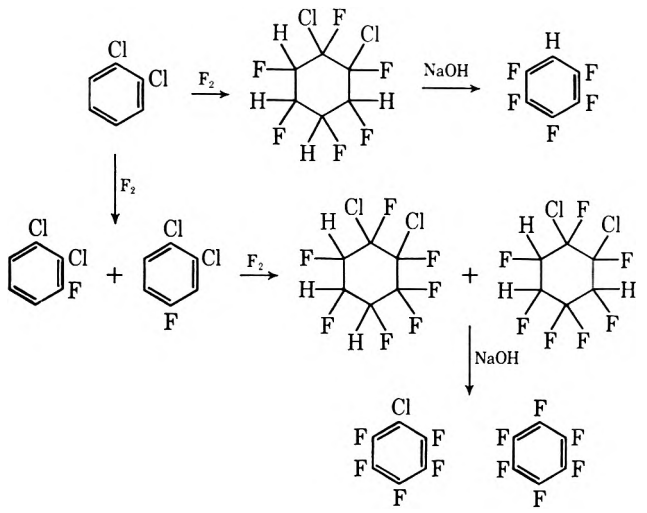
The possibility that *o*-dichlorobenzene underwent aromatic substitution prior to the addition was investigated using a low fluorine to substrate ratio. Neat *o*-dichlorobenzene was used and the fluorination was carried out at somewhat slower rate than that using a diluent. No difficulties were encountered with the control of the exotherm, although occasional blue flashes of light at the tip of the fluorine inlet tube were noticed when attempts were made to increase the rate of fluorination. The fluorine nmr spectrum of this fluorination mixture exhibited two signals at ϕ 108.5 and 110.5. The signal at ϕ 110.5, an eight-line multiplet, was assigned to 1,2-dichloro-4-fluorobenzene by comparing it with the fluorine nmr spectrum of an authentic sample (see Experimental Section for details). The signal at ϕ 108.5 might be due to 1,2-dichloro-3-fluorobenzene, the only other possible dichlorofluorobenzene isomer, but no assignment has been made.

The results of the above experiment not only confirmed the preceding considerations regarding the dehydrohalogenation reactions, but also provided the first example of substitution in an aromatic nucleus under direct liquid phase fluorination conditions.[12]

The fluorination of *o*-dichlorobenzene and the de-

(12) Subsequent to the preliminary report of this work at the Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967, C. L. Coon, M. E. Hill, and D. L. Ross, *J. Org. Chem.*, **33**, 1387 (1968), reported three examples of aromatic fluorine substitution.

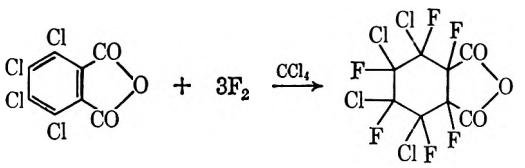
hydrohalogenation of monomeric products is represented by the following equations.



The fluorination of *p*-dichlorobenzene in 1,1,2-trichloro-1,2,2-trifluoroethane proceeded similarly to that of the *ortho* isomer, yielding a mixture of 1,4-dichloro-1,2,3,4,5,6-hexafluorocyclohexane, decafluorotetrachlorobicyclohexyl, and polydichlorotetrafluorocyclohexenes, characterized on the basis of their elemental analyses and their physical properties.

1,2,4,5-Tetrachlorobenzene was fluorinated in carbon tetrachloride to give 1,2,3,4,5,6-hexafluoro-1,2,4,5-tetrachlorocyclohexane, identified by its elemental analysis. The nondistillable fraction of the product, analyzing for $C_6H_2Cl_4F_4$, appeared to be a mixture of polytetrafluorotetrachlorocyclohexenes.

In order to determine if functional groups might interfere in the fluorination of chlorinated aromatic compounds, the fluorination of tetrachlorophthalic anhydride was examined. The fluorination in carbon tetrachloride was relatively sluggish; a considerable amount of unreacted fluorine escaped from the reactor during the course of fluorination and some unreacted starting material was recovered. The fluorination product was characterized as hexafluoro-3,4,5,6-tetrachlorocyclohexane-1,2-dicarboxylic acid anhydride on the basis of its elemental analysis, infrared spectrum, and physical properties. No polymeric material was produced in the fluorination of tetrachlorophthalic anhydride.



The fluorination of halogenated biphenyls was investigated next. Tetrachlorobiphenyl[13] underwent rapid fluorination in 1,1,2-trichloro-1,2,2-trifluoroethane and gave a product analyzing for $C_{12}H_6Cl_4F_{10}$, molecular weight 750 ±75, which was separated into two fractions on distillation. The distillate analyzed for $C_{12}H_6Cl_4F_{12}$, and, on the basis of elemental analysis and physical properties, the material was characterized as dodecafluorotetrachlorobicyclohexyl. Its infrared spectrum was very similar to that of the dimeric fluorination products of dichlorobenzenes. The distillation residue was characterized as a mixture of fluorinated dimers and higher molecular weight condensation products of the general empirical structure $(C_{12}H_6Cl_4F_{10})_n$.

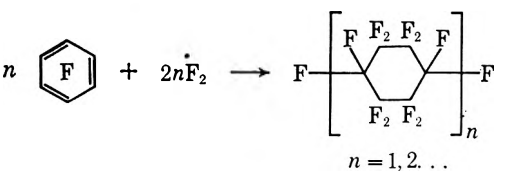
$$C_6H_3Cl_2 - C_6H_3Cl_2 + F_2 \longrightarrow F\text{-}[\text{-}C_6H_3F_5Cl_2 - C_6H_3F_5Cl_2\text{-}]_n\text{F}$$

The fluorination of hexachlorobiphenyl[13] gave a viscous liquid, elemental analysis of which indicated a mixture of the dodecafluoro adduct and higher molecular weight polydecafluorohexachlorobicyclohexenes.

$$C_6H_2Cl_3\text{—}C_6H_2Cl_3 + F_2 \longrightarrow F\text{-}[\text{-}C_6H_2Cl_3F_5\text{—}C_6H_2Cl_3F_5\text{-}]_n\text{F} \quad n = 1, 2, 3.....$$

The facile fluorination of chlorinated aromatic compounds suggested that fluorinated benzenes might also undergo fluorination in an analogous manner, and, consequently, the fluorination of hexafluorobenzene and chloropentafluorobenzene was investigated.

The fluorination of hexafluorobenzene in 1,1,2-trichlo-1,2,2-trifluoroethane at 20° with 3 mol of fluorine gave a viscous oil, which on distillation yielded perfluorobicyclohexyl and several fractions of higher molecular weight products identified on the basis of their elemental analyses as polydecafluorocyclohexenes. The yield of polyperfluorocyclohexenes in this fluorination amounted to only 55%, and, since all hexafluorobenzene was consumed, it was assumed that perfluorocyclohexane comprised the remainder of the product, but the material codistilled with the solvent and was not characterized.



The mode of ring-to-ring junction of decafluorocyclohexyl units in the polymeric products has not been established, and some "residual" unsaturation, if present, would not have been detected by the elemental analyses.

The direct fluorination of hexafluorobenzene differed significantly from that of hexachlorobenzene. Whereas in the latter case, the monomeric hexafluoro adduct was the sole reaction product, the fluorination of hexafluorobenzene yielded predominantly polymeric products. The polymerization in this case was more pronounced in the fluorination of trichlorobenzenes or dichlorobenzenes.

The fluorination of chloropentafluorobenzene in 1,1,2-trichloro-1,2,2-trifluoroethane proceeded similarly to that of hexafluorobenzene. The distillable portion of the fluorination product was identified as $C_{12}Cl_2F_{20}$ on the basis of its elemental analysis and its physical properties. The nondistillable fraction, analyzing for C_6ClF_9, apparently contained a mixture of polychlorononafluorocyclohexenes.

All the above-discussed fluorinations proceeded smoothly even at fast fluorination rates except those of hexafluorobenzene, which in two cases resulted in explosions occurring in the middle of fluorination runs. The causes of these explosions are unknown; it is possible that they were initiated by a sudden polymerization of octafluorocyclohexadiene intermediate.

(13) Tetrachlorobiphenyl and hexachlorobiphenyl were obtained from Monsanto Chemical Co. under the trade name Aroclor. Both compounds were mixtures of isomers, as determined by their nmr spectra.

Experimental Section

Apparatus.—Fluorinations were carried out in glass standard taper three-necked flasks equipped with a mechanical stirrer, a glass inlet tube extending below the liquid level, and a standard taper thermometer well with an opening for gas exit. Standard fluorine handling hardware[14] was used, and fluorine was diluted with nitrogen (1:3 to 1:5 ratio).

1,2,3,4,5,6-Hexachlorohexafluorocyclohexane.—A solution–suspension of 57 g (0.2 mol) of hexachlorobenzene in 350 ml of carbon tetrachloride was fluorinated at 0 ± 5° with 0.6 mol of fluorine (4.5 hr). The reaction mixture was concentrated and degassed at 45° (0.1 mm) to give 75 g of a pale yellow oil.

Anal. Calcd for $C_6Cl_6F_6$: C, 18.5; Cl, 53.9; F, 28.5. Found: C, 18.1; Cl, 53.6; F, 28.5.

Fluorination of 1,3,5-Trichlorobenzene.—A solution of 36.3 g (0.2 mol) of 1,3,5-trichlorobenzene in 350 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at 0 ± 5° with 0.6 mol of fluorine (2.0 hr) and the fluorination mixture was distilled to give (1) 18.5 g of colorless liquid, bp 38–41° (0.1 mm); and (2) 38 g of distillation residue which solidified at room temperature.

Anal. Calcd for $C_6H_3Cl_3F_6$: C, 24.4; H, 1.0; F, 38.6. Found (1): C, 23.9; H, 0.9; F, 36.9. Calcd for $C_{12}H_6Cl_6F_{10}$: C, 26.0; H, 1.1; F, 34.4. Found (2): C, 26.6; H, 0.9; F, 33.7.

Fluorination of 1,2,4-Trichlorobenzene.—A solution of 54.5 g (0.3 mol) of 1,2,4-trichlorobenzene in 400 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at −5 ± 5° with 0.9 mol of fluorine (1.5 hr) and the fluorination mixture was distilled to give (1) 40 g of a colorless liquid, bp 72–76° (25 mm); (2) 21.5 g of colorless viscous oil, bp 130–135° (0.1 mm); and (3) 19 g of distillation residue (white solid).

Anal. Calcd for $C_6H_3Cl_3F_6$: C, 24.4; H, 1.0; F, 38.6. Found (1): C, 23.8; H, 1.1; F, 37.4. Calcd for $C_{12}H_6Cl_6F_{10}$: C, 26.0; H, 1.1; F, 34.4; mol wt, 553. Found (2): C, 26.6; H, 0.9; F, 34.8; mol wt, 610 ± 60. Calcd for $(C_6H_3Cl_3F_4)_n$: C, 28.0; H, 1.2; F, 29.5. Found (3): C, 27.8; H, 0.9; F, 31.2.

Dehydrohalogenation of 1,2,3,4,5,6-Hexafluoro-1,2,4-trichlorocyclohexane and 1,2,3,4,5,6-Hexafluoro-1,3,5-trichlorocyclohexane.—A solution of 20 g of sodium hydroxide in 25 ml of water and 21 g of 1,2,3,4,5,6-hexafluoro-1,2,4-trichlorocyclohexane was placed into a 100-ml round-bottoned flask equipped with a stirrer and a reflux condenser and heated at 95–100° for 3 hr. A colorless liquid began to reflux when the reaction temperature was reached. The reaction mixture was cooled to 50° and distilled at 25 mm. The distillate was separated from a small amount of water and distilled to give (1) 6.2 g of a colorless liquid, bp 80–100°; (2) 3.8 g of a colorless liquid, bp 110–125°; and (3) 2.6 g of a colorless liquid, bp 135–140°. All fractions were analyzed by nmr.

The fluorine nmr spectra were obtained using undiluted samples. Fraction 1 exhibited four signals. A singlet at ϕ 163.1 was assigned to hexafluorobenzene on the basis of the reported[15] fluorine nmr spectrum for the compound, and also by comparing the spectrum with that of an authentic sample of hexafluorobenzene. The other three signals, multiplets at ϕ 141.3 and 162.2 and a triplet at ϕ 157.0, were assigned to *ortho*, *meta*, and *para* fluorines, respectively, of chloropentafluorobenzene. The reported[16] ϕ values for the compound was 140.8, 161.5, and 156.3, respectively. The approximate ratio of hexafluorobenzene to chloropentafluorobenzene was 1.3:1.

The fluorine nmr spectrum of fraction 2 consisted of the same four signals as fraction 1, but chloropentafluorobenzene was by far the predominant component in the mixture. The ratio of chloropentafluorobenzene to hexafluorobenzene, 40:1, was obtained by triangulation.

The fluorine nmr spectrum of fraction 3 consisted of a doublet of doublets at ϕ 135.1, a multiplet at ϕ 160.3, and a pair of triplets at ϕ 118.2, assigned to the fluorines of *m*-dichlorotetrafluorobenzene (reported[16] ϕ 134.5, 160.6, and 118.4, respectively); A_2X_2 patterns at ϕ 136.7 and 156.2 assigned to the fluorines of *o*-dichlorotetrafluorobenzene (reported[16] ϕ 136.1 and 155.6), and a sharp singlet at ϕ 140.2 assigned to the fluorines of *p*-dichlorotetrafluorobenzene (reported[16] ϕ 140.0). The approximate ratio of *meta*/*ortho*/*para* isomers in the mixture was 1:2:1.

The dehydrohalogenation of 1,2,3,4,5,6-hexafluoro-1,3,5-trichlorocyclohexane was carried out under identical reaction conditions with those of the 1,2,4-trichloro isomer. The reaction products, characterized by nmr, were identical with those above, with the exception that *m*-dichlorotetrafluorobenzene was the only dichlorotetrafluorobenzene isomer.

Dehydrohalogenation of Decafluorohexachlorobicyclohexyl.—Decafluorohexachlorobicyclohexyl, 17 g, obtained in the fluorination of 1,3,5-trichlorobenzene, was dehydrohalogenated with aqueous sodium hydroxide, following the reaction conditions described above. The reaction product was extracted with methylene chloride and distilled to give 4.0 g of pale yellow liquid, bp 60–85° (0.1 mm). The distillation residue, amounting to 5.0 g, was not characterized.

The fluorine nmr spectrum in carbon tetrachloride consisted of multiplets at ϕ 138.2, 150.8, and 161.6, of a 2:1:2 area ratio attributed to the *ortho*, *para*, and *meta* fluorines, respectively, of decafluorobiphenyl, in good agreement with those reported[17] for the compound: ϕ 138.1, 150.2, and 160.6. The concentration of decafluorobiphenyl in the mixture was estimated at 30–50%.

Fluorination of 1,2,4,5-Tetrachlorobenzene.—A solution–suspension of 86.5 g (0.4 mol) of 1,2,4,5-tetrachlorobenzene in 650 ml of carbon tetrachloride was fluorinated at 10 ± 5° with 1.3 mol of fluorine and the fluorination mixture was distilled to give (1) 70 g of colorless liquid, bp 52–55° (0.1 mm); and (2) 58 g of distillation residue.

Anal. Calcd for $C_6H_2Cl_4F_6$: C, 21.8; H, 0.6; Cl, 43.0; F, 34.5. Found (1): C, 22.4; H, 0.5; Cl, 46.4; F, 30.7. Calcd for $(C_6H_2Cl_4F_4)_n$: C, 24.7; H, 0.7; Cl, 48.7; F, 25.9. Found (2): C, 25.3; H, 0.6; Cl, 47.5; F, 26.2.

1,2,3,4,5,6-Hexafluorotetrachlorocyclohexane-1,2-dicarboxylic Acid Anhydride.—A suspension of 67 g (0.2 mol) of tetrachlorophthalic anhydride in 600 ml of carbon tetrachloride was fluorinated at 25° with 1 mol of fluorine. The fluorination was sluggish, and a considerable amount of unreacted fluorine escaped from the reactor. The reaction mixture was filtered and the filter cake was washed with 50 ml of carbon tetrachloride. The solid, amounting to 32 g, was identified as the starting material by its melting point. The combined tetrachloride filtrate and washings were distilled to give 45 g of a colorless liquid: bp 63–66° (0.1 mm); ir, characteristic anhydride absorption peak at 5.54 μ.

Anal. Calcd for $C_8Cl_4F_6O_3$: C, 24.0; Cl, 35.5; F, 28.5. Found: C, 23.8; Cl, 36.0; F, 30.0.

Fluorination of Tetrachlorobiphenyl.[13]—A solution of 40 g (0.137 mol) of tetrachlorobiphenyl in 650 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at −5° with 0.76 mol of fluorine (3.0 hr), and the fluorination mixture was concentrated to give 67 g of a white solid, mp 64–68°, molecular weight 755 ± 70. A portion of the material, 40 g, was distilled to give (1) 9.8 g of a colorless viscous oil, bp 122–125° (0.2 mm); and (2) 28.5 g of distillation residue which solidified at room temperature.

Anal. Calcd for $(C_{23}H_6Cl_4F_{10})_n$: C, 29.9; H, 1.2; F, 39.4. Found: C, 29.5; H, 1.2; F, 39.8.

Anal. Calcd for $C_{12}H_6Cl_4F_{12}$: C, 27.7; H, 1.2; F, 43.8. Found (1): C, 28.4; H, 0.9; F, 45.5. Calcd for $C_{12}H_6Cl_4F_{10}$: C, 29.9; H, 1.2; F, 39.4. Found (2): C, 30.4; H, 1.0; F, 41.0.

Fluorination of Hexachlorobiphenyl.[13]—A solution of 12 g (0.034 mol) of hexachlorobiphenyl in 350 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at −5° with 0.25 mol of fluorine and the fluorination mixture was concentrated to give 19 g of viscous oil.

Anal. Calcd for $C_{12}H_4Cl_6F_{12}$: C, 24.4; H, 0.6; F, 38.7. Calcd for $C_{12}H_4Cl_6F_{10}$: C, 26.1; H, 0.71; F, 34.5. Found: C, 25.8; H, 0.4; F, 34.8.

Fluorination of *o*-Dichlorobenzene.—A solution of 44.1 g (0.3 mol) of *o*-dichlorobenzene in 650 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at −20 ± 5° with 0.93 mol of fluorine (3.5 hr) and the product was distilled to give (1) 31 g of a colorless liquid, bp 35–45° (0.1 mm); and (2) 39.5 g of viscous distillation residue which solidified at room temperature.

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Anal. Calcd for $C_6H_4Cl_2F_6$: C, 27.5; H, 1.5; F, 43.7. Found (1): C, 27.2; H, 1.2; F, 41.8. Calcd for $C_{12}H_8Cl_4F_{10}$: C, 29.7; H, 1.6; F, 39.2; mol wt, 484. Found (2): C, 30.3; H, 1.3; F, 40.6; mol wt, 575 ±60.

In another experiment, 50 g (0.34 mol) of undiluted *o*-dichlorobenzene was fluorinated at −10 to −15° with 0.15 mol of fluorine (2.5 hr). The fluorination mixture was washed with three 50-ml portions of water and distilled to give 48 g of a colorless liquid, bp 31–33° (0.1 mm). The fluorine nmr spectrum exhibited two signals at ϕ 108.5 and 110.5. The signal at ϕ 110.5, an eight-line symmetrical multiplet, was assigned to 1,2-dichloro-4-fluorobenzene. The fluorine nmr spectrum of an authentic sample of 1,2-dichloro-4-fluorobenzene consisted of an identical signal at ϕ 110.5; $J_{H\text{-}o\text{-}F}$ = 8.3 cps, $J_{H\text{-}p\text{-}F}$ = 7.6 cps and $J_{H\text{-}m\text{-}F}$ = 5.4 cps.

Fluorination of *p*-Dichlorobenzene.—A solution of 73.5 g (0.5 mol) of *p*-dichlorobenzene in 650 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at −20 ± 5° with 1.5 mol of fluorine and the fluorination mixture was distilled to give (1) 35 g of a colorless liquid, bp 33–38° (0.1 mm); (2) 21 g of a colorless liquid, bp 123–128° (0.1 mm); and (3) 52 g of distillation residue which solidified to a white solid.

Anal. Calcd for $C_6H_4Cl_2F_6$: C, 27.5; H, 1.5; F, 43.7. Found (1): C, 28.7; H, 1.5; F, 40.4. Calcd for $C_{12}H_8Cl_4F_{10}$: C, 29.7; H, 1.6; F, 29.2. Found (2): C, 30.4; H, 1.3; F, 41.2. Calcd for $(C_6H_4Cl_2F_4)_n$: C, 32.3; H, 1.8; F, 34.1. Found (3): C, 31.8; H, 1.2; F, 36.3.

Dehydrohalogenation of 1,2-Dichloro-1,2,3,4,5,6-hexafluorocyclohexane.—A mixture of 9.5 g of sodium hydroxide and 9.0 g of 1,2-dichloro-1,2,3,4,5,6-hexafluorocyclohexane was heated at 90–95° in a distillation apparatus for 2.0 hr. The reaction mixture turned pale yellow and sodium hydroxide pellets gradually disintegrated. The reaction mixture was distilled at 40–70° (25 mm), and the distillate was separated from a small amount of water and distilled to give 4.5 g of liquid, bp 75–100°, and 1.5 g of liquid, bp 50–70° (25 mm).

The material of the first fraction, examined by nmr, contained pentafluorobenzene, hexafluorobenzene, and chloropentafluorobenzene in a 5:1:05 ratio, estimated by the triangulation of the signals. Hexafluorobenzene and pentafluorobenzene were isolated from the mixture by gas chromatography. The proton nmr spectrum of pentafluorobenzene in carbon tetrachloride exhibited a symmetrical doublet, J = 3.1 cps; a doublet of triplets, J = 6.5 cps; and a doublet of triplets, J = 10.1 cps; at δ 6.90. The fluorine nmr spectrum exhibited a doublet of triplets at ϕ 138.9 for *ortho* fluorines, a triplet at ϕ 153.5 for the *para* fluorine, and a symmetrical multiplet at ϕ 162.1 for the *meta* fluorine. The reported[15] ϕ values are 139.1, 154.0, and 162.6, respectively. The fluorine nmr spectrum of hexafluorobenzene exhibited a singlet at ϕ 163.1; reported[15] ϕ 162.9. The two remaining multiplet signals at ϕ 141.3 and 157.1 of the spectrum of the mixture were assigned to chloropentafluorobenzene on the basis of the reported[16] values for the *ortho* and *meta* fluorines of the compound, ϕ 141.3 and 157.0. The signal of the *para* fluorine at ϕ 162.2 was obscured by the hexafluorobenzene singlet.

The second fraction of dehydrohalogenation product, also examined by nmr, contained chloropentafluorobenzene and pentafluorobenzene in a 3:1 ratio.

Fluorination of Hexafluorobenzene.—A solution of 55.8 g (0.3 mol) of hexafluorobenzene in 750 ml of 1,1,2-trichloro-1,2,2-trifluoro-ethane was fluorinated at 20° with 0.9 mol of fluorine (1.5 hr) and the fluorination mixture was fractionated to give: (1) 15.8 g of colorless liquid, bp 30–35° (0.1 mm) (solidified to a white solid, mp 70–75°); (2) 12.5 g of colorless oil, bp 90–95° (0.1 mm); (3) 10.0 g of a viscous oil, bp 130–135° (0.1 mm); and (4) 8.5 g of distillation residue which solidified to a white solid at room temperature.

The material of fraction 1 was identified as perfluorobicyclohexyl, reported[18] mp 74–75°.

Anal. Calcd for $C_{12}F_{22}$: C, 25.6; F, 74.4. Found: C, 26.0; F, 75.5.

The elemental analyses of fractions were practically identical.

Anal. Calcd for $(C_6F_{10})_n$: C, 27.5; F, 72.5. Found (2–4): C, 27.6; F, 23.6.

1,1,2-Trichloro-1,2,2-trifluoroethane, removed in the concentration of the fluorination mixture, was examined by nmr and and did not contain hexafluorobenzene.

Fluorination of Chloropentafluorobenzene.—A solution of 40.5 g (0.2 mol) of chloropentafluorobenzene in 650 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated with 0.7 mol of fluorine at 25° (1.5 hr) and the fluorination mixture was distilled to give 21.5 g of colorless liquid, bp 60–80° (0.05 mm), and 10.5 g of distillation residue, a viscous oil. The elemental analyses of both fractions were identical.

Anal. Calcd for C_6ClF_9: C, 25.8; F, 61.4. Calcd for C_6ClF_{10}: C, 24.2; F, 33.9. Found: C, 26.5; F, 59.6.

Registry No.—1,2,3,4,5,6-Hexachlorohexafluorocyclohexane, 308-11-2; 1,2,3,4,5,6-hexafluoro-1,3,5-trichlorocyclohexane, 20643-01-0; 1,2,3,4,5,6-hexafluoro-1,2,4-trichlorocyclohexane, 20643-02-1; hexafluorobenzene, 392-56-3; chloropentafluorobenzene, 344-07-0; *o*-dichlorotetrafluorobenzene, 1198-59-0; *m*-dichlorotetrafluorobenzene, 1198-61-4; *p*-dichlorotetrafluorobenzene, 1198-62-5; 1,2,3,4,5,6-hexafluoro-1,2,4,5-tetrachlorocyclohexene, 20643-03-2; 1,2,3,4,5,6-hexafluorotetrachlorocyclohexane-1,2-dicarboxylic acid anhydride, 20643-05-4; 1,2,3,4,5,6-hexafluoro-1,2-dichlorocyclohexane, 20643-04-3; 1,2,3,4,5,6-hexafluoro-1,4-dichlorocyclohexane, 20643-06-5.

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Direct Fluorination of Substituted Carbamates[1]

VYTAUTAS GRAKAUSKAS AND KURT BAUM

Environmental Systems Division, Aerojet-General Corporation, Azusa, California

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The fluorination of N-substituted carbamates was shown to be a general method for the synthesis of difluoramino compounds and substituted fluorocarbamates. Substituents included alkyl and cycloalkyl groups as well as alkyl groups containing ester, nitro, or nitramino groups. The fluorination of carboalkoxyguanidines gave carboalkoxytetrafluoroguanidines, and the fluorination of 1,3-dicarboalkoxyguanidines gave carboalkoxytetrafluoroguanidines as well as 1,3-dicarboalkoxytrifluoroguanidines. 1-Carbethoxy-3-cyanoguanidine gave carbethoxytetrafluoroguanidine, ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate, and ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate.

We have previously reported the synthesis of alkyl fluorocarbamates and alkyl difluorocarbamates by the direct liquid phase fluorination of alkyl carbamates.[2] Only one example of the fluorination of an N-substituted carbamate, ethyl methylcarbamate, has been reported, and the only product isolated was difluoraminomethane.[3]

The present paper describes the fluorination of a variety of N-substituted carbamates to give fluorocarbamates as well as difluoramino compounds. The products obtained by the fluorination of alkylcarbamates, cycloalkylcarbamates, and alkylidenedicarbamates are shown in Table I. These reactions represent successive fluorination of NH and fluorinolysis of carboalkoxy groups. The rates of the two reactions are of the same order of magnitude; the use of less than a stoichiometric amount of fluorine resulted in the isolation of a considerable amount of the difluoramino compound as well as the fluorocarbamate and starting material.

$$\mathrm{RNHCOR'} \xrightarrow{F_2} \mathrm{RNFCOR'} \xrightarrow{F_2} \mathrm{RNF_2}$$

Fluorinations were conducted using solutions or suspensions of the substrates in water or acetonitrile. One example, methyl butylcarbamate, was fluorinated as a neat liquid. The presence of the substrate as a separate base required a reduced rate of fluorine input to avoid localized ignition at the inlet.

The products were characterized by elemental analysis and spectral data or by comparison with authentic samples. Ethyl N-fluoro-N-methylcarbamate, ethyl N-cyclopentyl-N-fluorocarbamate, and ethyl N-cyclohexyl-N-fluorocarbamate were prepared previously by the alkylation of ethyl fluorocarbamate.[2] Difluoraminocyclohexane was prepared previously by the addition of difluoramine to cyclohexene[4] as well as by the direct fluorination of buffered aqueous cyclohexylamine.[5] Methyl β-difluoraminopropionate has been synthesized from difluoramine and methyl acrylate.[6] Difluoraminobutane and 2-difluoraminobutane were prepared previously by the reaction of butane with tetrafluorohydrazine.[7] The infrared spectrum of difluoraminocyclopentane, which was fully characterized in the present work, did not correspond to that of the tentatively assigned compound in the literature.[5]

The only product which was not sufficiently stable for isolation was ethyl difluoraminoacetate, which underwent partial dehydrofluorination under the conditions of synthesis. Attempts to separate ethyl difluoraminoacetate from ethyl cyanoacetate by gas chromatography resulted in further dehydrofluorination. On the other hand, no problems were encountered in the isolation of methyl α-difluoraminobutyrate.

This method for the synthesis of difluoramino compounds has advantages of generality and convenience compared with other reported methods. The alkylation of difluoramine[4,6,8] does not yield simple primary derivatives, and remote manipulation is required because of the high sensitivity of difluoramine. Reactions of tetrafluorohydrazine are somewhat less hazardous but are also limited in scope[9-11] or selectivity[7,12] depending on the class of substrate. The fluorination of buffered amines was reported to give impure products.[5]

The technique of using a carboalkoxy group as a leaving group in fluorinolysis was also applied to the synthesis fluorinated guanidines, a class of compounds that has recently been investigated by several groups.[13-18]

Products of the fluorination of carboalkoxyguanidines, 1,3-dicarboalkoxyguanidines, and 1-carboethoxy-3-cyanoguanidine are shown in Table II. Carboalkoxyguanidines gave carboalkoxytetrafluoroguanidines, whereas 1,3-dicarboalkoxyguanidines gave both dicarboalkoxytrifluoroguanidines and carboalkoxytetrafluoroguanidines. The carboalkoxytetrafluoroguanidines were obtained as mixtures of *syn* and *anti* isomers which could be distinguished on the basis of fluorine nmr spectra. For one set of isomers, —NF_2, =NF, and —NF— signals appeared at close to ϕ^* −42.5, −32, and 44.5, while, for the other set, the signals appeared at −45.5, −25, and 52, respectively. The doublet coupling constants between —N=F and —NF—, resolvable only for the —NF— signals, were 6 cps for the former set of isomers and 9 cps for the latter set. Since *trans* coupling constants to fluorines

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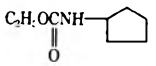
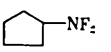
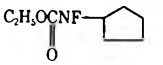
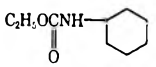
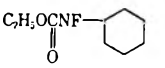
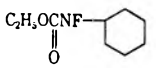
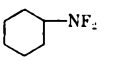
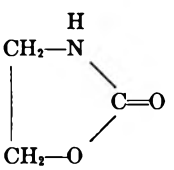
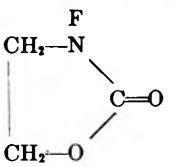
TABLE I

FLUORINATION OF CARBAMATES

Starting material	Registry no. of product	Products	Bp, °C (mm)
$C_2H_5OCNHCH_3$ (O)	21298-14-6	$C_2H_5OCNFCH_3$ (O)	50 (25)
$CH_3OCNH(CH_2)_3CH_3$ (O)	17832-42-7	$CH_3OCNF(CH_2)_3CH_3$ (O)	68–69 (25)
	10524-16-0	$F_2CNH_2CH_2CH_2CH_3$	74
$CH_3OCNHCH(CH_3)CH_2CH_3$ (O)	10524-17-1	$CH_3CH(NF_2)CH_2CH_3$	64–65
	14182-80-0		24–25 (25)
	21298-19-1		39 (0.2)
	21298-20-4		50–51 (0.1)
	14182-78-6		34 (12)
$C_2H_5OCNH(CH_2)_3NHCOC_2H_5$ (O, O)	21298-22-6	$F_2NCH_2CH_2CH_2NF_2$	25–32 (25)[a]
	21298-23-7	$C_2H_5OCNF(CH_2)_3NFCOC_2H_5$ (O, O)	95–96 (0.2)
$C_2H_5OCNHCH_2CH_2NHCOC_2H_5$ (O, O)	17832-43-8	$C_2H_5OCNFCH_2CH_2NFCOC_2H_5$ (O, O)	78–79 (0.2)
	21298-25-9	$C_2H_5OCNFCH_2CH_2NF_2$ (O)	60 (0.1)[a]
$CH_3OCNHCH_2COC_2H_5$ (O, O)	21298-26-0	$F_2NCH_2CO_2C_2H_5$	33–42 (25)[b]
$CH_3OCCHCH_2CH_3$ (O, $NHCOOCH_3$)	21298-27-1	$CH_3OCCHCH_2CH_3$ (O, $N{\equiv}CCO_2C_2H_5$)	48–49 (0.3)
	21298-28-2	$CH_3OCCHCH_2CH_3$ (O, NF_2)	52–53 (4)
$CH_3OCCH_2CH_2NFCOC_2H_5$ (O, O)	20955-65-1	$CH_3OCCH_2CH_2NF_2$ (O)	47 (20)
$(C_2H_5OCNHCH_2CH_2)_2N$ (O, NO_2)	21298-30-6	$(F_2NCH_2CH_2)_2N$ (NO_2)	70–71 (0.1)
$CH_3OCNHCH_2C(NO_2)_2F$ (O)	21297-31-7	$CH_3OCNFCH_2C(NO_2)_2F$ (O)	59–61 (0.1)
	21298-32-8		47–48 (0.1)
	21298-33-9	$F_2NCH_2CH_2OH$	40–42 (25)

[a] Impure distillate; analytical sample was isolated by gas chromatography. [b] Dehydrofluorinated during attempted purification. Spectral identification

TABLE II

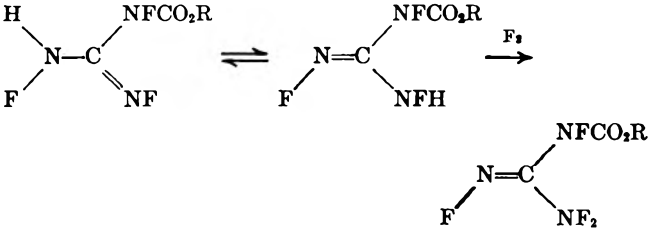
FLUORINATION OF CARBOALKOXYGUANIDINES

Starting material	Registry no. of product	Products	Bp, °C (mm)
$C_4H_9OCNHCNH_2$ (O, NH)	21298-01-1	$C_4H_9OCNFCNF_2$ (O, NF)	70 (40)[a]
	21298-02-2	$C_4H_9OCNFCNF_2$ (O, FN)	
$(CH_3)_2CHOCNHCNH_2$ (O, NH)	21298-03-3	$(CH_3)_2CHOCNFCNF_2$ (O, NF)	20–23 (0.3)[a]
	21298-04-4	$(CH_3)_2CHOCNFCNF_2$ (O, FN)	
$C_2H_5OCNHCNHCOC_2H_5$ (O, NH, O)	21298-34-0	$C_2H_5OCNFCNFCOC_2H_5$ (O, NF, O)	72 (0.1)
	21298-05-5	$C_2H_5OCNFCNF_2$ (O, NF)	25–28 (0.1)[a]
	21298-06-6	$C_2H_5OCNFCNF_2$ (O, FN)	
$[(CH_3)_2CHOCNH]_2C{=}NH$ (O)	21298-35-1	$[(CH_3)_2CHOCNF]_2C{=}NF$ (O)	80 (0.1)
$C_2H_5OCNHCNHCN$ (O, NH)	21298-36-2	$C_2H_5OCNFCF_2NF_2$ (O)	
	21298-37-3	$C_2H_5OCNFC{=}N$ (O, F, F)	40–60 (25)[a]
		$C_2H_5OCNFCNF_2$ (O, NF)	
		$C_2H_5OCNFCNF_2$ (O, FN)	

[a] Impure distillate; analytical sample was isolated by gas chromatography.

in olefins[19] as well as fluorimonium ions[4] are larger than *cis* coupling constants, the configurations can be assigned.[18]

The predominant isomer of the carboalkoxyguanidines depended upon whether a carboalkoxyguanidine or a dicarboalkoxyguanidine was used as the starting material. The ratio of NF_2CNFCO_2R (NF) / NF_2CNFCO_2R (FN) was 1:2 and 1:5 for the butyl and isopropyl derivatives prepared from carboalkoxyguanidines and 1.8:1 for the ethyl derivative prepared from the dicarboalkoxyguanidine. These results are qualitatively in accord with the expected stepwise fluorination path. The last step for the carboalkoxyguanidine reactions involves fluorination of a mobile tautomeric system in which the sterically favored position of the fluorimino fluorine is *anti* to the carboalkoxy group. Replacement of the last NH by fluorine would then prevent further equilibration. On the other hand, the last step for the dicarboalkoxyguanidine reactions most likely is fluorinolysis of acarboalkoxy group of the dicarboalkoxytrifluoroguanidine. The least hindered such group is *anti* to the fluorimine fluorine.



The fluorination of 1-carbethoxy-2-cyanoguanidine gave carbethoxytetrafluoroguanidine, ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate, and ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate. The carbethoxytetrafluoroguanidine is a product of the fluorinolysis of the cyano group, and the other products represent elimination of the –NHCN group. The nmr spectrum of the last product showed that only one isomer was present. The magnitude of the –CF=NF coupling constant indicated that these fluorine atoms

(19) J. A. Pople, W. O. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 335.

were in the *syn* configuration.[20] The same configuration was reported for tetrafluoroformamidine obtained in the fluorination of guanylurea sulfate.[17] The reaction of fluorine with cyanoguanidine[13] has been reported to give products of fluorinolysis of the cyano or amino groups as well as products of fluorine addition to the cyano group.

Infrared and nmr spectra of the products are detailed in the Experimental Section.

Experimental Section

General.—Fluorinations were conducted as described previously[2,21] using fluorine diluted fourfold to tenfold with nitrogen. Safety shielding should be used in handling neat NF compounds. *The guanidine derivatives are extremely sensitive explosives and must be handled remotely.*

Method A. Ethyl N-Fluoro-N-methylcarbamate.—A solution of 26 g (0.25 mol) of ethyl methylcarbamate in 350 ml of water was fluorinated at 0–5° with 0.4 mol of fluorine. The product was extracted with four 150-ml portions of methylene chloride, dried over sodium sulfate, and distilled to give 16 g (53% yield) of ethyl N-fluoro-N-methylcarbamate with physical properties identical with reported values.[2]

Method B. 2-Difluoraminobutane.—Fluorine (1 mol) diluted with nitrogen was passed into a solution of 66.5 g (0.50 mol) of methyl 2-butylcarbamate in 350 ml of acetonitrile at −20° over a 3-hr period. The solution was diluted with 1 l. of ice–water, and the insoluble material was washed with three 70-ml portions of ice–water. The product was dried over sodium sulfate and distilled to give 25 g (46% yield) of 2-difluoraminobutane, bp 64–65°.

Anal. Calcd for $C_4H_9NF_2$: C, 44.03; H, 8.31; N, 12.83; F, 34.82. Found: C, 43.62; H, 8.60; N, 13.0; F, 33.8.

The proton nmr spectrum of 2-difluoraminobutane consisted of a triplet (J = 8 cps) at δ 1.01 for CH_3CH_2–, a doublet (J = 8 cps) of triplets (J = 1 cps) at δ 1.26 for $CH(NF_2)CH_3$, a multiplet with maximum intensity at δ 3.33 for the methine, and a multiplet at δ 1.61 for the methylene. The fluorine spectrum consisted of a broadened AB pattern centered at ϕ^* −39.1, with J_{FF} = 569 cps, and inner members separated 116 cps. Infrared peaks in the NF region were 10.23 (m), 10.5 (s), 11.5 (s), 11.8 (s), and 12.37 μ (m).

Fluorination of Methyl Butylcarbamate.—Fluorine (0.71 mol) diluted fourfold with nitrogen was passed into 131 g (1.0 mol) of neat methyl butylcarbamate with stirring at 0 to −10° over a 3.5-hr period. More rapid fluorination resulted in localized firing at the inlet. The product was washed with three 200-ml portions of ice–water, dried over sodium sulfate, and distilled to give 21.2 g (0.195 mol) of 1-difluoraminobutane, bp 74°; 26.0 g (0.175 mol) of methyl butyl-N-fluorocarbamate, bp 68–69° (25 mm), $n^{25}D$ 1.4010; and 34 g (0.26 mol) of starting material, bp 45° (0.1 mm).

Anal. Calcd for $C_4H_9NF_2$: C, 44.03; H, 8.31; N, 12.83; F, 34.82. Found: C, 44.30; H, 8.21; N, 12.8; F, 35.0.

The proton nmr spectrum of 1-difluoroaminobutane consisted of an irregular triplet at δ 0.99 for the methyl, a triplet of triplets (J_{HH} = 7 cps, J_{HF} = 28.9 cps) at δ 3.43 for CH_2NF_2, and a multiplet with maximum intensity at δ 1.57 for the other methylenes. The fluorine spectrum consisted of a broad signal at ϕ^* −55.58. Infrared peaks in the NF region were 9.87 (m), 10.12 (m), 10.40 (m), 10.91 (s), 11.47 (m), 12.0 (s), and 12.6 μ (s).

Anal. Calcd for $C_6H_{12}NO_2F$: C, 48.31; H, 8.11; N, 9.39; F, 12.74. Found: C, 48.40; H, 8.47; N, 9.4; F, 12.6.

The proton nmr spectrum of methyl butyl-N-fluorocarbamate in CCl_4 consisted of a singlet at δ 3.79 for the methoxy, an irregular triplet at δ 0.96 for the other methyl, a doublet (J_{HF} = 34.7 cps) of triplets at δ 3.63 for $-CH_2-NF-$, and a multiplet at δ 1.55 for the other methylenes. The fluorine spectrum consisted of a triplet (J = 33.8 cps) at ϕ^* 70.92.

Fluorination of Ethyl Cyclopentylcarbamate.—Fluorination of 64 g (0.50 mol) of ethyl cyclopentylcarbamate by method B (350 ml of acetonitrile, 1 mol of fluorine, 0 to −10°, 3 hr) and distillation through a 25-cm Holzmann column gave 30 g (50% yield) of difluoraminocyclopentane, bp 24–25° (25 mm).

Anal. Calcd for $C_5H_9NF_2$: C, 49.58; H, 7.49; N, 11.56; F, 31.37. Found: C, 49.22; H, 7.80; N, 11.4; F, 31.0.

The proton nmr spectrum (CCl_4 solution) showed a triplet of multiplets (J_{HF} = 24 cps) at δ 3.90 for the methine and a multiplet at δ 1.81 for the methylenes. The fluorine spectrum showed a signal at ϕ^* −52.3. Infrared peaks in the NF region were 10.04 (w), 10.60 (w), 10.83 (m), 11.0 (sh), and 11.75 μ (s).

Method A (42.6 g, 0.3 mol, of ethyl cyclopentylcarbamate in 650 ml of water, 0.6 mol of fluorine, 3 hr) gave 7.5 g of somewhat impure difluoraminocyclopentane, 11.5 g (22% conversion) of ethyl N-cyclopentyl-N-fluorocarbamate,[2] and 8 g of starting material.

Ethyl N-Cyclohexyl-N-fluorocarbamate.—The fluorination of 100 g (0.585 mol) of ethyl cyclohexylcarbamate by method A (1200 ml of water, 1.0 mol of fluorine, 5–10°) gave 35 g of impure difluoraminocyclohexane, bp 36–42° (25 mm); 7.0 g (6.3% conversion) of ethyl N-cyclohexyl-N-fluorocarbamate,[2] and 20 g of starting material.

Difluoraminocyclohexane.—Fluorination of 5.2 g (0.030 mol) of ethyl N-cyclohexyl-N-fluorocarbamate by method A (200 ml of water, 0.030 mol of fluorine) gave 1.0 g (25% conversion, 54% yield) of difluoraminocyclohexane, bp 34° (12 mm), identical with an authentic sample,[4] and 2.8 g (54% recovery) of starting material.

Fluorination of Diethyl Trimethylenedicarbamate.—Fluorination of 34.7 g (0.16 mol) of diethyl trimethylenedicarbamate by method A (650 ml of water, 0.6 mol of fluorine) gave 0.80 g of 75% pure 1,3-bis(difluoramino)propane, bp 25–32° (26 mm), containing five other compounds (2.6% yield). An analytical sample was isolated by gas chromatography (15 ft × $^3/_{16}$ in. column of 10% dioctyl phthalate on Chromosorb P, 80°, 60 ml/min helium flow).

Anal. Calcd for $C_3H_6N_2F_4$: C, 24.66; H, 4.14; N, 19.18. Found: C, 25.10; H, 5.10; N, 18.9.

The proton nmr spectrum (CCl_4 solution) consisted of a triplet of triplets (J_{HF} = 28 cps, J_{HH} = 6.5 cps) at δ 3.64 for the α-methylenes and a quintet (J = 7 cps) at δ 2.18 for the central methylene. The fluorine spectrum consisted of a triplet (J = 25 cps) at ϕ^* −53.9. The infrared spectrum showed bands in the NF region at 9.8 (m), 10.2 (m), 10.9 (s), 11.23 (s), and 12.0 μ (s).

Distillation of the above residue gave 5.0 g of colorless liquid, bp 43–45° (0.2 mm); 2.5 g, bp 45–80° (0.2 mm); and 4.5 g, bp 95–105° (0.2 mm). The first of these fractions appeared to consist mainly of ethyl (3-difluoraminopropyl)fluorocarbamate on the basis of infrared and nmr spectra (NF_2 triplet at ϕ^* −54.8, J = 29 cps; –NFC=O triplet at ϕ^* 69.5, J = 34 cps), but a pure sample was not obtained on redistillation. The second fraction was indicated likewise to be impure ethyl (3-difluoraminopropyl)carbamate (NF_2 triplet at ϕ^* −54.19, J = 29.0 cps). Redistillation of the 95–105° fraction gave 3.8 g (9.4% yield) of diethyl N,N′-difluorotrimethylenedicarbamate, bp 95–96° (0.2 mm), $n^{25}D$ 1.4265.

Anal. Calcd for $C_9H_{16}N_2F_2O_4$: C, 42.52; H, 6.34; N, 11.12. Found: C, 42.02; H, 6.11; N, 11.2.

The proton nmr spectrum (CCl_4 solution) consisted of a triplet at δ 1.34 and a quartet at δ 4.27 for the ethoxy groups, a quintet at δ 2.08 for the internal methylene, and a doublet of triplets (J_{HF} = 35 cps) at δ 3.79 for the α-methylenes. The fluorine spectrum consisted of a triplet (J = 35 cps) at ϕ^* 69.5. The infrared spectrum showed a carbonyl band at 5.8 μ.

Fluorination of Diethyl Ethylenedicarbamate.—Fluorination of 40.5 g (0.20 mol) of diethyl ethylenedicarbamate by method A (650 ml of water, 0.7 mol of fluorine, 15–20°) gave 12 g of liquid, bp 20–65° (0.1 mm); and 2.0 g (4.2% yield) of diethyl N,N′-difluoroethylenedicarbamate, bp 78–79° (0.2 mm). The infrared spectrum showed carbonyl bands at 5.69 and 5.79 μ (s) and no NH.

Anal. Calcd for $C_8H_{14}N_2F_2O_4$: C, 40.00; H, 5.87; N, 11.66; F, 15.82. Found: C, 39.8; H, 5.76; N, 11.80; F, 15.4.

Gas chromatography ($^3/_8$ in. × 6 ft column of 5% ethylene glycol succinate on Chromosorb W, 90°, 200 ml/min helium flow) of the low-boiling fraction showed seven components. The major component (85% of the total, 7-min retention time) was identified as ethyl (2-difluoraminoethyl)fluorocarbamate (27% yield). The infrared spectrum showed carbonyl bands at 5.69 and 5.79 μ (s) and no NH.

(20) D. H. Dybvig, *J. Inorg. Chem.*, **5**, 1795 (1966).
(21) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

Anal. Calcd for $C_5H_9N_2F_3O_2$: C, 32.66; H, 4.87; N, 15.05; F, 30.62. Found: C, 32.49; H, 4.82; N, 14.8; F, 30.8.

Fluorination of Ethyl N-Carbomethoxyglycine.—Fluorination of 48.3 g (0.30 mol) of ethyl N-carbomethoxyglycine by method A (650 ml of water, 0.6 mol of fluorine, 75 min) gave 11 g of colorless liquid, bp 33–42° (25 mm), each fraction of which was found by nmr spectroscopy to be a mixture of ethyl difluoraminoacetate and ethyl cyanoformate. Attempts to isolate ethyl difluoraminoacetate by gas chromatography resulted in further dehydrofluorination. Proton nmr signals assigned to ethyl difluoraminoacetate follow: a triplet at δ 1.32 and a quartet at δ 4.24 for the ethoxy, and a triplet (J = 28 cps) at δ 4.24 for NF_2CH_2–. The fluorine spectrum of the mixture consisted of a broad triplet at ϕ^* −56.4 (J = 26 cps).

Methyl N-Carbomethoxy-α-aminobutyrate.—Methyl chloroformate (190 g, 2.0 mol) was added over 1 hr to a solution of 205 g (2.0 mol) of DL-α-aminobutyric acid and 160 g (4.0 mol) of sodium hydroxide in 500 ml of water at 15–20°. The product was extracted with 300 ml of methylene chloride, dried over sodium sulfate, stripped of solvent, and refluxed for 4 hr in 500 ml of methanol containing 2 drops of concentrated sulfuric acid. Dilution with 1 l. of ice–water, extraction with three 100-ml portions of methylene chloride, and distillation gave 297 g (85% yield) of methyl N-carbomethoxy-α-aminobutyrate, bp 75–76° (0.1 mm).

Anal. Calcd for $C_7H_{13}NO_4$: C, 48.00; H, 7.44; N, 8.00. Found: C, 47.82; H, 7.78; N, 8.40.

Fluorination of Methyl N-Carbomethoxy-α-aminobutyrate.—Fluorination of 70 g (0.40 mol) of methyl N-carbomethoxy-α-aminobutyrate by method B (300 ml of acetonitrile, 0.7 mol of fluorine, 0–5°) gave 22 g (36% conversion) of methyl α-difluoraminobutyrate, bp 52–53° (40 mm), and 34 g (44% conversion) of methyl N-carbomethoxy-N-fluoro-α-aminobutyrate, bp 48–49° (0.3 mm).

The proton nmr spectrum ($CDCl_3$ solution) of methyl α-difluoraminobutyrate consisted of a singlet at δ 3.81 for the methoxy, a triplet at δ 1.03 for CH_3CH_2 a quintet at δ 1.95 for the methylene, and a doublet (J_{HF_A} = 25.7 cps) of doublets (J_{HF_B} = 24.4 cps) of triplets (J_{HH} = 6.5 cps) for the methine at δ 4.10. The fluorine spectrum consisted of an AB quartet (ϕ^*_B = 43.10, ϕ^*_A = −50.66, J_{FF} = 592.4 cps) with additional doublet splitting (J_{HF_A} = 25.5 cps, J_{HF_B} = 24.0 cps). The infrared spectrum showed a carbonyl band at 5.73 μ and bands in the NF region at 9.84 (m), 10.61 (s), 10.53 (s), 10.7 (m), 11.0 (w), 11.15 (m), 11.6 (v, s), and 12.42 μ (s).

Anal. Calcd for $C_5H_7NF_2O_2$: C, 39.20; H, 5.92; 9.15. Found: C, 39.49; H, 6.10; N, 9.5.

The proton nmr spectrum of methyl N-carbethoxy-N-fluoro-α-aminobutyrate ($CDCl_3$ solution) consisted of a triplet at δ 1.10 for CH_3CH_2, a multiplet at δ 2.67 for the methylene, singlets at δ 3.79 and 3.92 for the methoxy groups, and a doublet of doublets of doublets at δ 4.59 for the methine with unequal coupling constants to the adjacent methylene hydrogens (J_{HF} = 40.5 cps, J_{HH} = 6.8, 9.8 cps). The infrared spectrum showed carbonyl bands at 5.63 (s) and 5.77 μ (s) and bands in the NF region at 9.95 (m), 10.45 (w), 11.40 (w), 11.98 (m), 12.5 (m), and 12.9 μ (m).

Anal. Calcd for $C_7H_{12}NFO_4$: C, 43.52; H, 6.22; N, 7.27. Found: C, 43.49; H, 6.20; N, 7.4.

Methyl β-(Difluoramino)propionate.—Fluorination of 3.2 g (0.0166 mol) of methyl N-carbethoxy-N-fluoro-β-aminopropionate[2] by method A (200 ml of water, 0.022 mol of fluorine) gave 0.7 g (30% yield) of methyl β-(difluoramino)propionate identical with an authentic sample.[6]

1,5-Bis(difluoramino)-3-nitrazapentane.—Fluorination of 45 g (0.15 mol) of diethyl 3-nitraza-1,5-pentanedicarbamate[22] by method A (650 ml of water, 0.6 mol of fluorine) gave, after removal of methylene chloride, a viscous oil. Extraction with five 50-ml portions of carbon tetrachloride gave an insoluble solid (25 g), which was found to be impure starting material. Distillation of the carbon tetrachloride solution gave 4.4 g (13% conversion) of 1,5-bis(difluoramino)-3-nitrazapentane, bp 70–71° (0.1 mm). The infrared spectrum showed peaks at 6.58 (s), 6.9 (m), 7.08 (m), 7.6 (m), 7.83 (s), 8.3 (w), 8.8 (w), 9.7 (m), 10.4–10.5 (m), 10.8 (w), 11.12 (w), and 11.8 μ (s).

Anal. Calcd for $C_4H_8N_4F_4O_2$: C, 21.82; H, 3.66; N, 25.45; F, 34.52. Found: C, 21.50; H, 3.71; N, 24.9; F, 35.0.

Methyl N-Fluoro-N-(2-fluoro-2,2-dinitroethyl)carbamate.—Fluorination of 2.8 g (0.0133 mol) of methyl(2-fluoro-2,2-dinitroethyl)carbamate[23] by method A (350 ml of water, 0.04 mol of fluorine) gave 1.0 g (33% conversion, 52% yield) of methyl N-fluoro-N-(2-fluoro-2,2-dinitroethyl)carbamate, bp 59–61° (0.1 mm), and 1.0 g of starting material.

Anal. Calcd for $C_4H_5N_3F_2O_6$: C, 20.97; H, 2.20; N, 18.34; F, 16.59. Found: C, 21.21; H, 2.32; N, 18.0; F, 16.8.

The proton nmr spectrum (CCl_4 solution) consisted of a singlet at δ 3.94 for the methoxy and a doublet of doublets (J_{H-NF} = 30.0 cps, J_{H-CF} = 15.5 cps) at δ 5.05 for the methylene. The fluorine spectrum consisted of a triplet (J_{HF} = 30.2 cps) of doublets (J_{FF} = 10.2 cps) at ϕ^* 58.14 for the NF and a broad band at ϕ^* 108.5 for the CF. The infrared spectrum showed carbonyl at 5.75 μ (s), nitro at 6.30 μ (s), and the following bands in the 10–13-μ region: 10.11 (w), 10.5 (w), 11.22 (w), 11.79 (m), 12.03 (m), 12.5 (m), and 13.0 (m).

Fluorination of 2-Oxazolidone.—Fluorination of 42 g (0.50 mol) of 2-oxazolidone by method A (250 ml of water, 0.5 mol of fluorine, extraction with methylene chloride and of ether) gave, after distillation through a 25-cm Holzmann column, 4.1 g (8.5% yield) of 2-difluoraminoethanol, bp 40–42° (25 mm); and 18 g (41% yield) of N-fluoro-2-oxazolidone, bp 47–48° (0.1 mm).

The fluorine nmr spectrum of 2-difluoraminoethanol ($CDCl_3$ solution) consisted of a triplet (J = 26 cps) at ϕ^* −54.88. Infrared bands in the NF region were 10.42 (s), 11.10 (m), 11.90 (s), and 12.60 μ (s).

Anal. Calcd for $C_2H_5NF_2O$: C, 24.74; H, 5.16; N, 14.44; F, 39.15. Found: C, 24.61; H, 5.30; N, 14.3; F, 38.5.

The fluorine nmr spectrum of N-fluoro-2-oxazolidone ($CDCl_3$ solution) consisted of a triplet (J = 15.4 cps) at ϕ^* 69.48. The infrared spectrum showed peaks at 5.5–5.6 (s), 6.8 (m), 7.27 (m), 8.4 (s), 9.0 (m), 9.2 (m), 9.53 (s), 9.88 (s), 10.4 (m), and 12.8 μ (s).

Anal. Calcd for $C_3H_4NFO_2$: C, 34.28; H, 3.84; N, 13.33; F, 18.08. Found: C, 34.59; H, 4.11; N, 13.2; F, 18.2.

Carboalkoxyguanidines and Dicarboalkoxyguanidines.—1,3-Dicarbethoxyguanidine hemihydrate was prepared by the method of Nencki.[24] 1-Carboisopropoxyguanidine and 1,3-dicarboisopropoxyguanidine were prepared by adding 491 g (4.0 mol) of isopropyl chloroformate at 20° to a solution of 360 g (2.0 mol) of guanidine carbonate and 8 mol of potassium hydroxide in 1500 ml of water. After 45 min, the product was filtered at 5° and recrystallized from water to give 180 g (62% conversion) of carboisopropoxyguanidine, mp 143–145°, and 60 g of crude 1,3-dicarboisopropoxyguanidine which was insoluble in hot water. Recrystallization of the latter from methanol gave 45 g (10% conversion), mp 170°.

Anal. Calcd for $C_6H_{11}N_3O_2$: C, 41.38; H, 7.59; N, 29.0. Found: C, 41.51; H, 7.73; N, 28.3.

Anal. Calcd for $C_9H_{17}N_3O_4$: C, 46.74; H, 7.41; N, 18.17. Found: C, 46.60; H, 7.51; N, 18.2.

Carbobutoxyguanidine, mp 130°, was prepared in 70% yield using an equimolar amount of butyl chloroformate.

Anal. Calcd for $C_6H_{13}N_3O_2$: C, 45.38; H, 8.18; N, 26.40. Found: C, 45.42; H, 8.09; N, 26.7.

1-Carbobutoxytetrafluoroguanidine.—Fluorination of 63.6 g (0.40 mol) of carbobutoxyguanidine by method B (750 ml of acetonitrile, 1.6 mol of fluorine, 0–5°) gave 6.0 g of 70% pure (gc analysis) 1-carbobutoxytetrafluoroguanidine, bp 70° (40 mm). Careful control of the rate of fluorine input was required to avoid localized firing. An analytical sample was isolated by gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80).

Anal. Calcd for $C_7H_9N_3F_4O_2$: C, 31.17; H, 3.99; N, 18.18; F, 32.88. Found: C, 31.20; H, 4.12; N, 17.8; F, 31.2.

The proton nmr spectrum ($CDCl_3$ solution) consisted of a triplet at δ 4.42 for the α-methylene, a multiplet at δ 1.57 for the β-methylene, and a triplet at δ 0.97 for the methyl. The fluorine spectrum indicated a 1:2 mixture of NF_2CNFCO_2R and NF_2CNFCO_2R, with NF_2 signals at ϕ^* −42.4 and −25.4, –NF– doublets at 44.1 (J = 6 cps) and 51.5 (J = 9 cps), and =NF signals at ϕ^* −32.8 and −25.0, respectively. The infrared spectrum showed carbonyl bands at 5.53 (s) and 5.64 μ (s), a fluorimine

(22) M. B. Frankel, *J. Chem. Eng. Data*, **7**, 410 (1962).

(23) V. Grakauskas and K. Baum, paper in preparation.

(24) M. Nencki, *Ber.*, **7**, 1588 (1874).

band at 6.13 μ (w), and bands in the NF region at 10.2 (m), 10.72 (m), and 11.40 μ (m).

1-Carboisopropoxytetrafluoroguanidine.—Fluorination of 46 g (0.30 mol) of carboisopropoxyguanidine by method B (350 ml of acetonitrile, 0.7 mol of fluorine, 0–5°, 2.5 hr) gave 5.5 g (7.6% yield) of 1-carboisopropoxytetrafluoroguanidine, $NF_2C(=NF)NFCO_2C_3H_7$, bp 20–23° (0.3 mm), 90% pure by gc analysis. An analytical sample was obtained by gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80).

Anal. Calcd for $C_5H_7N_3F_4O_2$: C, 27.66; H, 3.24; N, 19.35; F, 35.0. Found: C, 27.41; H, 3.12; N, 19.1; F, 35.0.

The proton nmr spectrum (CH_2Cl_2 solution) consisted of a doublet for the methyl at δ 1.39 and a septet for the methine at δ 5.21. The fluorine spectrum indicated a 1:5 mixture of *syn–anti* isomers, NF_2CNFCO_2R and NF_2CNFCO_2R, with NF_2 signals

NF_2CNFCO_2R (NF) and NF_2CNFCO_2R (FN)

at ϕ^* −42.68 and −45.52, –NF– doublets at ϕ 44.69 (J = 6 cps) and 52.26 (J = 9 cps), and =NF signals at ϕ^* −31.6 and −24.24, respectively. The infrared spectrum showed carbonyl bands at 5.53 (s) and 5.69 μ (m), a fluorimine band at 6.2 μ (w), and bands in the NF region at 9.9 (w), 10.21 (w), 10.81 (m), 11.11 (m), 11.41 (m), 12.0 (m), and 12.83 μ (m).

1-Carbethoxytetrafluoroguanidine and 1,3-Dicarbethoxytrifluoroguanidine.—Fluorination of 20.3 g (0.10 mol) of 1,3-dicarbethoxyguanidine by method B (300 ml of acetonitrile, 0.35 mol of fluorine, 0°, 2 hr gave 2.5 g (11.7% yield) of 95% pure (gc analysis) 1-carbethoxytetrafluoroguanidine, bp 25–28° (0.1 mm); and 4.5 g (17.5% yield) of 1,3-dicarbethoxytrifluoroguanidine, bp 72° (0.1 mm). Analytical sample of 1-carbethoxytetrafluoroguanidine was prepared by gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80).

The proton nmr spectrum ($CDCl_3$ solution) showed a quartet at δ 4.48 and a triplet at δ 1.41. The fluorine spectrum indicated a 1.8:1 mixture of *syn–anti* isomers, NF_2CNFCO_2R and NF_2CNFCO_2R, with NF_2 signals at ϕ^* −42.4 and −45.4, –NF– doublets at ϕ^* 44.1 (J = 6 cps) and 51.4 (J = 9 cps), and =NF signals at ϕ^* −32.8 and −25.0, respectively. The infrared spectrum showed carbonyl bands at 5.57 (s) and 5.69 μ (s), a fluorimino band at 6.2 μ (w), and bands in the NF region at 10.0 (w), 10.28 (m), 10.88 (m), 11.4 (m), and 11.7 μ (m).

Anal. Calcd for $C_4H_5N_3F_4O_2$: C, 23.65; H, 2.50; N, 20.69. Found: C, 24.02; H, 2.80; N, 21.09.

The proton nmr spectrum ($CDCl_3$ solution) of 1,3-dicarbethoxytrifluoroguanidine showed a quartet at δ 4.45 and a triplet at δ 1.40. The fluorine spectrum showed a broadened band at ϕ^* −18.6 for the fluorimino and a triplet at 54.05 (J = 7 cps) and a doublet of doublets at 59.58 (J = 8.0, 12.1) for the geometrically nonequivalent –NF– groups.

Anal. Calcd for $C_7H_{10}N_3F_3O_4$: C, 32.69; H, 3.92; N, 16.34; F, 22.17. Found: C, 32.60; H, 4.11; N, 16.4; F, 21.9.

1,3-Dicarboisopropoxytrifluoroguanidine.—Fluorination of 23 g (0.10 mol) of 1,3-diisopropoxyguanidine by method B (350 ml of acetonitrile, 0.3 mol of fluorine, 1 hr, 0 to −10°) gave 12 g (42% yield) of 1,3-dicarboisopropoxytrifluoroguanidine, bp 80° (0.1 mm).

Anal. Calcd for $C_9H_{14}N_3F_3O_4$: C, 37.90; H, 4.95; N, 14.73; F, 19.19. Found: C, 37.90; H, 4.71; N, 15.0; F, 20.0.

The proton nmr spectrum ($CDCl_3$ solution) showed a doublet at δ 1.40 and a septet at δ 5.17. The fluorine spectrum consisted of a broadened band at ϕ^* −18.54 for =NF, and a doublet of doublets (J = 5.9, 7.9 cps) at ϕ^* 53.65 and a doublet of doublets (J = 8.8, 11.0 cps) at ϕ^* 60.25 for the *syn* and *anti* –NFCO groups.

Redistillation of the forecuts gave 2.6 g of 1-carboisopropoxytetrafluoroguanidine, identified by its infrared spectrum.

Fluorination of 1-Carbethoxy-3-cyanoguanidine.—Fluorination of 31.2 g (0.20 mol) of 1-carbethoxy-3-cyanoguanidine by method B (350 ml of acetonitrile, 1.2 mol of fluorine, 0 to −10°) gave 18 g of slightly yellow liquid, by 40–60° (25 mm). Gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80) showed that the distillate was a 26:50:24 mixture of ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate, ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate, and 1-carbethoxytetrafluoroguanidine, respectively, in the order of their retention times.

The fluorine nmr spectrum of ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate (CCl_4 solution) consisted of a broadened signal at ϕ^* −19.8 for NF_2, a broadened signal at ϕ^* 77.4 for –NF–, and a doublet (J = 12 cps) at ϕ^* 97.9 for CF_2. Irradiation at −19.8 resolved the 77.4 signal to a triplet (J = 12 cps). The infrared spectrum showed carbonyl bands at 5.55 and 5.62 μ (s) and bands in the NF region at 10.0 (m), 10.70 (m), 10.88 (s), and 11.68 μ (w).

Anal. Calcd for $C_4H_5N_2F_5O_2$: C, 23.08; H, 2.42; N, 13.46. Found: C, 23.39; H, 2.70; N, 13.6.

The fluorine nmr spectrum of ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate (CCl_4 solution) consisted of a broad signal at ϕ^* 15.0 for =NF, a doublet (J = 26 cps) at 53.2 for –NF–C=O, and a doublet of doublets (J = 26, 13 cps) at 63.4 for CF. Irradiation at 15.0 simplified the 63.4 signal to a doublet (J = 13 cps). The infrared spectrum showed carbonyl bands at 5.54 (s) and 5.64 μ (s), a fluorimino band at 5.98 μ (s), and bands in the NF region at 10.0 (m), 10.70 (s), 11.49 (m), and 11.70 μ (m).

Anal. Calcd for $C_4H_5N_2F_3O_2$: C, 28.24; H, 2.96; N, 16.47; F, 33.51. Found: C, 28.40; H, 3.02; N, 16.9; F, 33.6.

Registry No.—Ethyl (3-difluoraminopropyl)fluorocarbamate, 21298-38-4; ethyl (3-difluoraminopropyl)-carbamate, 21298-39-5; methyl N-carbomethoxy-α-aminobutyrate, 21298-40-8; carboisopropoxyguanidine, 21298-42-0; 1,3-dicarboisopropoxyguanidine, 21298-43-1; carbobutoxyguanidine, 21298-44-2; 1-carbobutoxytetrafluoroguanidine, 21298-45-3; 1-carboisopropoxytetrafluoroguanidine, 21298-46-4; 1-carbethoxytetrafluoroguanidine, 21298-47-5.

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Halogenated Ketenes. IX. Ketene Carbodiimide Cycloadditions[1,2]

WILLIAM T. BRADY, EDWIN D. DORSEY, AND FRED H. PARRY, III

Department of Chemistry, North Texas State University, Denton, Texas

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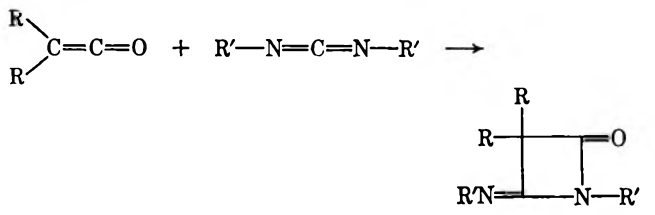
The cycloaddition of various types of ketenes with dicyclohexyl- and diisopropylcarbodiimides to produce imino-β-lactams has been investigated. A large difference in the ketene reactivities was found. The ketenes studied include fluoro-, chloro-, dibromo-, methylchloro-, phenylchloro-, diphenyl-, phenylethyl-, butylethyl-, and dimethylketenes as well as ketene itself. The mechanism of this reaction is discussed in terms of a dipolar intermediate. The preparation of phenylethyl- and phenylchloroketenes and cycloaddition of the latter with cyclopentadiene are also described.

There are many reports which date back to the early investigations of Staudinger on the reaction of ketenes with imino compounds across the C=N linkage to give β-lactams.[3] However, the cycloaddition with carbodiimides has only recently appeared; and in the first two reports no structures were given and, furthermore, one report indicated that the adducts were not isolated owing to decomposition.[4,5] Hull has more recently described the reaction of dichloroketene with a couple of carbodiimides to yield the corresponding azetidinones (β-lactams).[6] In connection with a study of monohaloketenes, one of us has quite recently communicated on the cycloaddition of fluoroketene and diisopropylcarbodiimide.[7]

We now wish to report on a study of the reaction of dicyclohexyl- and diisopropylcarbodiimides with different types of ketenes, with particular emphasis on halogenated ketenes. As a part of this study, the previously unknown phenylethyl- and phenylchloroketenes were synthesized; and cycloaddition of the latter with cyclopentadiene is also described.

The reaction of ketenes and carbodiimides is a 1,2-cycloaddition reaction and can be generally represented as follows.

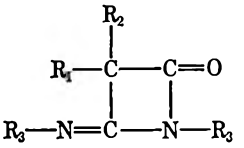


The imino-β-lactams and the yields of the preparations are shown in Table I. The infrared spectra of the cycloadducts revealed the carbonyl absorptions at 1810–1832 cm^{-1} and the C=N absorptions at 1690–1716 cm^{-1}.

Since we have been unable to isolate the halogenated ketenes, these materials were generated by dehydrohalogenation of the appropriately substituted acid halide with triethylamine in the presence of the carbodiimide. The optimum conditions for these cycloadditions appears to be in refluxing hexane. At lower temperatures, the rate of cycloaddition is considerably slower, and the more unstable ketenes undergo polymerization rather than cycloaddition. Diphenylketene is an exception, as a benzene solution of this ketene and diisopropylcarbodiimide at room temperature loses the characteristic yellow color due to ketene after only about 30 min. Difficulty was experienced in the isolation and purification of the adducts from chloro- and butylethylketenes, but the spectral data established that these β-lactams were produced.

TABLE I

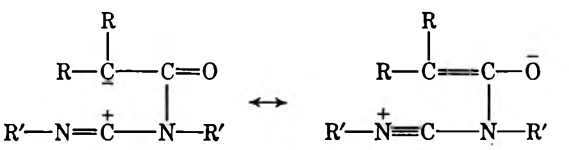
CYCLOADDUCTS FROM KETENES AND CARBODIIMIDES



Compd	Registry No.	R_1	R_2	R_3	Yield, %
I	20452-63-5	C_6H_5	C_6H_5	C_6H_{11}	90
II	20452-64-6	C_6H_5	C_6H_5	i-C_3H_7	88
III	20452-65-7	C_6H_5	Cl	C_6H_{11}	65
IV	20452-66-8	Br	Br	C_6H_{11}	59
V	20452-68-0	C_6H_5	C_2H_5	i-C_3H_7	57
VI	20452-69-1	F	H	i-C_3H_7	40
VII	20452-70-4	CH_3	CH_3	i-C_3H_7	32
VIII	20452-71-5	CH_3	Cl	C_6H_{11}	25
IX	20452-72-6	Cl	H	i-C_3H_7	20
X	20452-73-7	C_4H_9	C_2H_5	i-C_3H_7	15
XI	20452-74-8	H	H	i-C_3H_7	5

The treatment of dicyclohexylcarbodiimide with an excess of diphenylketene did not produce a detectable amount of the 2:1 adduct, nor was there any evidence of such an adduct in any of the other preparations.

We have already presented evidence which indicates that the mechanistic pathway for this reaction involves a dipolar intermediate represented below.[8]



It is interesting to note that the phenyl-substituted ketenes and the dihaloketenes give considerably better yields of the β-lactams than the other ketenes. This is apparently a result of these ketenes having substituents capable of stabilizing or smearing out the negative charge on the α carbon, thus making these materials

(1) Paper VIII. W. T. Brady, W. L. Vaughn, and E. F. Hoff, *J. Org. Chem.*, **34**, 843 (1969).

(2) Support of this investigation by The Robert A. Welch Foundation and a National Science Foundation Grant (GP-7386) is gratefully acknowledged.

(3) R. N. Lacey, "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1207.

(4) Fabrenfabriken Bayer Akt. Ges., British Patent 797,972 (1958); *Chem. Abstr.*, **53**, 3059 (1959).

(5) R. Hofmann, E. Schmidt, K. Wamsler, A. Reichle, and F. Moosmuller, German Patent 960,458 (1957); *Chem. Abstr.*, **53**, 16077 (1959).

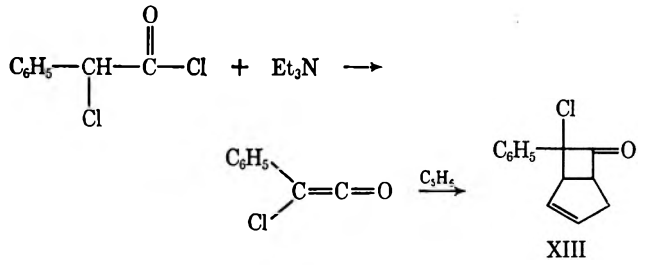
(6) R. Hull, *J. Chem. Soc., C*, 1967, 1154.

(7) W. T. Brady and E. F. Hoff, *J. Amer. Chem. Soc.*, **90**, 6256 (1968).

(8) W. T. Brady and E. D. Dorsey, *Chem. Comm.*, 1638 (1968).

more reactive than the others studied. Ketene itself is less reactive than all of the ketenes investigated, and this is certainly consistent with the dipolar mechanism. It should be emphasized that all of these reactions are uncatalyzed, and that cycloadditions effected in the presence of Lewis acid catalysts would be expected to show a decrease in the reactivity differences.

Phenylchloroketene is readily prepared by the dehydrochlorination of α-chloro-α-phenylacetyl chloride with triethylamine. When the dehydrochlorination is effected in the presence of the reactive cyclopentadiene, the corresponding 1,2 cycloadduct, XII, is obtained in 80% yield along with a quantitiative amount of amine salt.



XIII

Cycloaddition of phenylchloroketene with cyclohexene, an unactivated olefin, proceeded with difficulty as expected. The adduct was obtained in about 20% yield, but difficulty was experienced in purification.

Phenylethylketene was readily obtained by the dehydrochlorination of α-phenylbutyryl chloride with triethylamine and was easily distilled under reduced pressure.

Experimental Section

The solvents employed in these preparations were benzene and hexane, which were previously dried by refluxing and distilling from calcium hydride. Diphenylketene was obtained by the dehydrochlorination of diphenylacetyl chloride with triethylamine.[9] α-Chloro-α-phenylacetyl chloride was prepared from *dl*-mandelic acid and phosphorus pentachloride according to the method of Walden.[10] All of the other acid halides were also prepared from the corresponding acids and an appropriate reagent according to standard procedures. Dimethylketene was obtained by the pyrolysis of the commercially available ketene dimer, tetramethyl-1,3-cyclobutanedione, and ketene was prepared by the pyrolysis of acetone.[11,12] We are grateful to Eastman Chemical Products, Inc., for supplying us with butylethylketene in the form of a 20% solution in toluene.

1-Cyclohexyl-4-cyclohexylimino-3,3-diphenylazetidin-2-one (I).—A 13.2-g (0.068-mol) portion of diphenylketene was added to a stirred solution containing 14 g (0.068 mol) of dicyclohexylcarbodiimide in 100 ml of hexane at room temperature. After several hours, the reaction mixture was filtered to yield 23.6 g (90%) of I: mp 158–159°; ir 1810 (C=O) and 1695 cm^{-1} (C=N); nmr (CCl_4) δ 1.57 (m, 20 H), 3.4 (m, 2 H), and 7.12 ppm (m, 10 H).

Anal. Calcd for $C_{27}H_{32}N_2O$: C, 80.9; H, 8.05; N, 6.95. Found: C, 80.8; H, 8.35; N, 6.71.

3,3-Diphenyl-1-isopropyl-4-isopropyliminoazetidin-2-one (II).—A solution containing 6.4 g (0.033 mol) of diphenylketene and 4.2 g (0.033 mol) of diisopropylcarbodiimide in 100 ml of benzene was allowed to stand at room temperature for 2 hr. Upon removal of the solvent and recrystallization of the solid residue from ether, II was obtained in 88% yield: mp 108.5–109.5°; ir 1810 (C=O) and 1690 cm^{-1} (C=N); nmr (CCl_4) δ 0.80 (d, 6 H), 1.45 (d, 6 H), 3.66 (m, 1 H), 4.03 (m, 1 H), and 7.3 ppm (m, 10 H).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.7; H, 7.56; N, 8.75. Found: C, 79.0; H, 7.58; N, 8.74.

3-Chloro-1-cyclohexyl-4-cyclohexylimino-3-phenylazetidin-2-one (III).—A solution of 13.3 g (0.070 mol) of α-chloro-α-phenylacetyl chloride in 30 ml of hexane was added dropwise to a refluxing solution of 14.5 g (0.070 mol) of dicyclohexylcarbodiimide and 14.2 g (0.141 mol) of triethylamine in 200 ml of dry hexane. After the addition was complete, the mixture was allowed to continue refluxing for 2 hr. The amine salt was removed by filtration and the hexane was evaporated to yield 16 g (65%) of III, recrystallized from methanol: mp 86–88°; ir 1822 (C=O) and 1700 cm^{-1} (C=N); nmr (CCl_4) δ 1.5 (m, 20 H), 3.4 (m, 2 H), and 7.42 ppm (m, 5 H).

Anal. Calcd for $C_{21}H_{27}ClN_2O$: C, 70.30; H, 7.52; Cl, 9.90; N, 7.81. Found: C, 70.53; H, 7.83; Cl, 9.82; N, 8.08.

3,3-Dibromo-1-cyclohexyl-4-cyclohexyliminoazetidin-2-one (IV).—To a refluxing solution of 12.2 g (0.059 mol) of dicyclohexylcarbodiimide and 6.55 g (0.065 mol) of triethylamine in 100 ml of hexane was added over a period of 2 hr a solution of 16.6 g (0.059 mol) of dibromoacetyl chloride in hexane. After refluxing an additional 30 min, the solution was cooled and filtered and the solvent was evaporated on a rotatory evaporator. The residue was recrystallized from 95% ethanol to yield 14.5 g (59%) of IV: mp 121.5–122°; ir 1822 (C=O) and 1716 cm^{-1} (C=N); nmr (CCl_4) δ 1.7 (m, 20 H), and 3.7 ppm (m, 2 H).

Anal. Calcd for $C_{15}H_{22}N_2OBr_2$: C, 44.3; H, 5.42; N, 6.90. Found: C, 44.5; H, 5.63; N, 6.73.

Phenylethylketene.—A solution of 11.1 g (0.11 mol) of triethylamine in 20 ml of hexane was added dropwise to 18.2 g (0.10 mol) of α-phenylbutyryl chloride in 50 ml of hexane at room temperature. Stirring was continued for several hours after the addition was complete. The salt was removed by filtration, the solvent was evaporated, and the phenylethylketene was distilled at 32–34° (0.04 mm) to yield 7 g (48%) of product: ir 2110 cm^{-1} (ketene absorption).

3-Ethyl-1-isopropyl-4-isopropylimino-3-phenylazetidin-2-one (V).—A 4.2-g (0.029 mol) portion of phenylethylketene was added to 20 ml of dry benzene containing 3.62 g (0.029 mol) of diisopropylcarbodiimide at room temperature. The solution was allowed to stand at this temperature for 48 hr, after which time the yellow color of the ketene had disappeared. The solvent was evaporated and the residue was recrystallized from ether to yield 4.5 g (57%) of V: mp 35–36°; ir 1830 (C=O) and 1710 cm^{-1} (C=N); nmr (CCl_4) δ 0.95 (d, 3 H), 1.10 (d, 3 H), 1.12 (t, 3 H), 1.45 (d, 6 H), 2.28 (m, 2 H), 3.42 (heptet, 1 H), 4.05 (heptet, 1 H), and 7.25 ppm (m, 5 H).

Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.25; H, 8.93; N, 10.23.

3-Fluoro-1-isopropyl-4-isopropyliminoazetidin-2-one (VI).—A solution containing 11.4 g (0.12 mol) of fluoroacetyl chloride in 60 ml of hexane was added dropwise to a refluxing solution containing 24 g (0.24 mol) of triethylamine and 15.5 g (0.12 mol) of diisopropylcarbodiimide in 100 ml of hexane. Refluxing was continued for 2 hr after the addition. The amine salt was removed by filtration and the filtrate was vacuum distilled to yield 8.9 g (40%) of VI: bp 50–51° (0.7 mm); ir 1832 (C=O) and 1710 cm^{-1} (C=N); nmr (CCl_4) δ 1.32 (m, 12 H). 3.85 (m, 2 H), and 5.94 ppm (d, 1 H, J_{HF} = 55 cps).

Anal. Calcd for $C_9H_{15}FN_2O$: C, 58.1; H, 8.07; N, 15.5. Found: C, 58.37; H, 8.26; N, 15.21.

3,3-Dimethyl-1-isopropyl-4-isopropyliminoazetidin-2-one (VII).—To a solution of 40 ml of hexane containing 18.2 g (0.144 mol) of diisopropylcarbodiimide was added 10.1 g (0.144 mol) of dimethylketene. This solution was refluxed for 8 hr, and then the solvent and unreacted carbodiimide were removed by vacuum distillation. The residue was recrystallized from ligroin to yield 9.1 g (32%) of VII. The cycloadduct was further purified by sublimation at room temperature and 0.01-mm pressure: mp 75–76°; ir 1815 (C=O) and 1695 cm^{-1} (C=N); nmr (CCl_4) δ 1.10 (d, 6 H), 1.35 (s, 6 H), 1.35 (d, 6 H), and 3.7 ppm (m, 2 H).

Anal. Calcd for $C_{11}H_{20}N_2O$: C, 67.3; H, 10.2; N, 14.3. Found: C, 67.06; H, 9.99; N, 14.45.

3-Chloro-3-methyl-1-cyclohexyl-4-cyclohexyliminoazetidin-2-one (VIII).—A 11.3-g (0.066-mol) portion of α-chloropropionyl bromide in 50 ml of hexane was added to a stirred refluxing solution of 13.6 g (0.066 mol) of dicyclohexylcarbodiimide and 13.3 g (0.132 mol) of triethylamine in 150 ml of hexane over 2 hr. After refluxing for an additional 5 hr. and cooling, the amine

(9) H. Staudinger, *Ber.*, **44**, 1619 (1911).
(10) P. Walden, *ibid.*, **28**, 1287 (1895).
(11) W. E. Hanford and J. C. Sauer, *Org. Reaction*, **3**, 136 (1946).
(12) W. E. Hanford and J. C. Sauer, *ibid.*, **3**, 108 (1946).

salt was removed. The solvent was removed on a rotatory evaporator and the residue was recrystallized from 95% ethanol to yield 4.8 g (25%) of VIII. Further purification was obtained by sublimation at 56° *in vacuo:* mp 61–62°; ir 1825 (C=O) and 1705 cm^{-1} (C=N); nmr (CCl_4) δ 1.6 (m), 1.85 (s), and 3.55 ppm (m). The singlet was superimposed on the 1.6 multiplet. The areas were in the ratio of 2:23.

Anal. Calcd for $C_{16}H_{23}N_2OCl$: C, 64.8; H, 8.45; N, 9.46. Found: C, 64.8; H, 8.77; N, 9.40.

3-Chloro-1-isopropyl-4-isopropyliminoazetidin-2-one (IX).—A 10.1-g (0.065 mol) portion of chloroacetyl bromide in 25 ml of hexane was slowly added to a refluxing solution of 8.2 g (0.065 mol) of diisopropylcarbodiimide and 6.5 g (0.13 mol) of triethylamine in 100 ml of hexane. The reaction mixture was refluxed for 2 hr after the addition was completed. Upon removal of the salt by filtration and evaporation of the solvent, the residue was distilled to yield 2.4 g (20%) of impure IX: ir 1820 (C=O) and 1705 cm^{-1} (C=N).

3-*n*-Butyl-3-ethyl-1-isopropyl-4-isopropyliminoazetidin-2-one (X).—To a refluxing solution consisting of 9.95 g (0.079 mol) of diisopropylcarbodiimide in 50 ml of hexane was slowly added 9.95 g (0.079 mol) of butylethylketene in 50 ml of hexane. This solution was refluxed for an additional 2 hr. The solvent was evaporated and the residue was distilled at 80–89° (0.025 mm) to yield 2.3 g (12%) of impure X: ir 1810 (C=O) and 1690 cm^{-1} (C=N).

1-Isopropyl-4-isopropyliminoazetidin-2-one (XI).—An excess of ketene was bubbled into a solution of 8.1 g (0.07 mol) of diisopropylcarbodiimide over a period of 8 hr. The solvent was evaporated to yield predominantly unreacted carbodiimide with only a very small amount (5%) of XI: ir 1820 (C=O) and 1700 cm^{-1} (C=N).

7-Chloro-7-phenylbicyclo[3.2.0]hept-2-en-6-one (XII).—A 17.25-g (0.17 mol) portion of triethylamine in 30 ml of benzene was added dropwise with stirring to a solution containing 29.35 g (0.155 mol) of α-chloro-α-phenylacetyl chloride, 102.5 g (1.55 mol) of cyclopentadiene, and 100 ml of dry benzene. After the addition was complete, the mixture was refluxed for 1 hr. The amine salt was removed by filtration and the filtrate was concentrated and distilled *in vacuo* to yield 27 g (80%) of XII: bp 113–113.5° (0.9 mm); ir 1784 (C=O) and 1600 cm^{-1} (C=C); nmr (CCl_4) δ 2.55 (m, 2 H), 4.18 (m, 2 H), 5.6 (m, 2 H), and 7.4 ppm (m, 5 H).

Anal. Calcd for $C_{13}H_{11}ClO$: C, 71.40; H, 5.08. Found: C, 71.3; H, 5.07.

Registry No.—Phenylethylketene, 20452-67-9; XII, 20452-75-9.

Thermal Cleavage Reactions of N-Chloroketimines. Behavior of Imino Radicals

MARVIN L. POUTSMA AND PEDRO A. IBARBIA

Union Carbide Research Institute, Union Carbide Corporation, Tarrytown, New York

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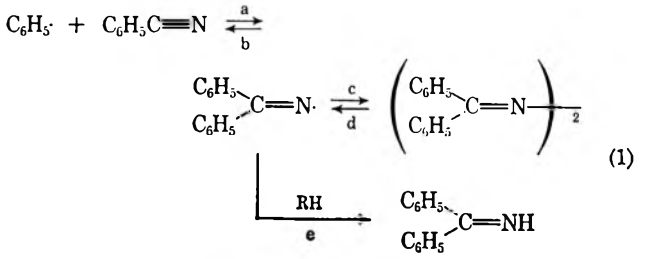
In contrast to the relatively stable diphenyl N-chloroketimine (**1**), phenyl benzyl N-chloroketimine (**2**) in chlorobenzene solution (<0.04 *M*) undergoes cleavage at 130° to form benzonitrile and benzyl chloride along with small amounts of bibenzyl. The reaction is accelerated by slow addition of benzoyl peroxide and inhibited by oxygen. A radical chain sequence is postulated involving β scission of phenyl benzyl ketimino radical (**13**) as the key step. The intermediate benzyl radical has been trapped by added 1-octene to form 1-phenyl-3-chlorononane (**12**) and by added tri-*n*-butyltin hydride (Bu_3SnH) to form toluene. At 35–40°, radical **13** can be partially intercepted by Bu_3SnH before cleavage. Phenyl α-methylbenzhydryl N-chloroketimine (**3**) gives benzonitrile, 1,1-diphenylethylene, and hydrogen chloride on thermolysis, the latter two products apparently derived from 1,1-diphenyl-1-chloroethane (**10**). In concentrated solution, additional products from the thermolysis of **2** included ammonium chloride and 2,3,4,5-tetraphenylpyrrole (**9**). The reduction of **1** with Bu_3SnH at 50–60° could be inhibited by oxygen and accelerated by di-*t*-butyl peroxyoxalate as anticipated for a radical chain process. Silver ion catalyzed Beckmann rearrangement of **2** gave N-phenylphenylacetamide (**4**) free from N-benzylbenzamide (**5**), so that chlorine appears to be *syn* to the benzyl group. Similar treatment of **3** gave no amides but only benzonitrile and 1,1-diphenylethylene. Attempts to prepare the N-chloroketimine from phenyl benzhydryl ketimine by the same procedures which were successful for **1**, **2**, and **3** gave initial chlorination on carbon rather than on nitrogen.

The methylenimino radical ($H_2C{=}N\cdot$), produced by addition of hydrogen atoms to hydrogen cyanide in a low-temperature matrix, has been observed by esr spectroscopy.[1] However, methods of formation and typical reactions of substituted ketimino radicals ($RR'C{=}N\cdot$) are not well known. We wish to report some reactions of N-chloroketimines which involve the intermediacy of such radicals.

Generation of cyclohexyl or phenyl radicals in the presence of benzonitrile gives small amounts of ketimines;[2] a ketimino radical produced by addition of the carbon radical to the nitrile group (step 1a) is a reasonable intermediate if it is assumed to be able to abstract hydrogen (step 1e) to give the observed product. Among the products from pyrolysis of benzophenone azine at 375–500° are benzene, biphenyl, benzonitrile, and benzophenone ketimine;[3] initial N–N bond homolysis (step 1d) followed by β scission of a ketimino radical (step 1b) was invoked to explain nitrile formation. A similar scheme would rationalize the



(1)

pyrolysis of acetone azine to form acetonitrile and ethane[4] as well as the use of certain azines as polymerization initiators.[5,5a] Other reactions which apparently involve radical addition to the nitrile function and the intermediacy of ketimino radicals [$R(X)C{=}N\cdot$] which either undergo β scission (X = Cl) or abstract hydrogen

(1) E. L. Cochran, F. J. Adrian, and V. A. Bowers, *J. Chem. Phys.*, **36**, 1938 (1962).

(2) J. R. Shelton and C. W. Uzelmeier, *J. Amer. Chem. Soc.*, **88**, 5222 (1966).

(3) S. S. Hirsch, *J. Org. Chem.*, **32**, 2433 (1967).

(4) J. L. Anderson, U. S. Patent 2,770,643 (1956).

(5) M. J. Roedel, U. S. Patent 2,439,528 (1948).

(5a) NOTE ADDED IN PROOF.—Photolysis of benzalazine has also been postulated to proceed through imino radicals: R. W. Binkley, *J. Org. Chem.*, **34**, 2072 (1969).

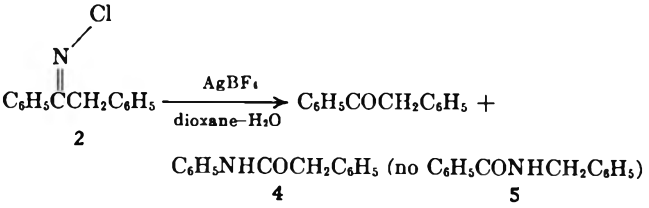
(X = CN) are the introduction of cyano groups into hydrocarbons by reaction with cyanogen chloride[6a,b] and of α-cyanoimino groups by reaction with cyanogen.[6b] A similar addition–β scission sequence may explain the addition of trifluoroacetonitrile to simple olefins.[6c]

Curtin and McCarty[7] observed free-radical halogenation of hydrocarbons by benzophenone N-halimines; the evidence did not, however, allow a clear distinction between reaction through ketimino radicals as hydrogen-abstracting chain carriers and reaction through halogen atoms in which the N-halimine only served as a halogen source by reaction with hydrogen halide. Photolysis of hexafluoroacetone N-bromimine gave hexafluoroacetone azine,[8] possibly by radical coupling (an analog of step 1c).

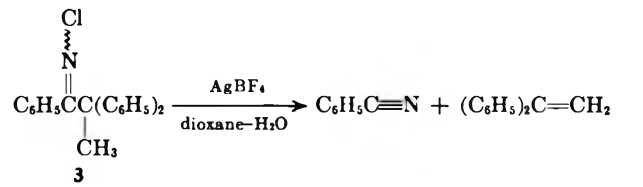
Aldimino radicals and their conversion to nitriles by donation of a hydrogen atom to molecular oxygen have been postulated[9a] in the conversion of aldehydes to nitriles by reaction with ammonia, base, oxygen, and a copper salt; the evidence seems circumstantial at best. An aldimino radical and a 1,2-hydrogen shift within it have been suggested[9b] in the base-catalyzed rearrangement of arylhydrazones of aromatic aldehydes to amidines; this proposal, however, provides no role for the base which is obviously vital to the reaction.

Results

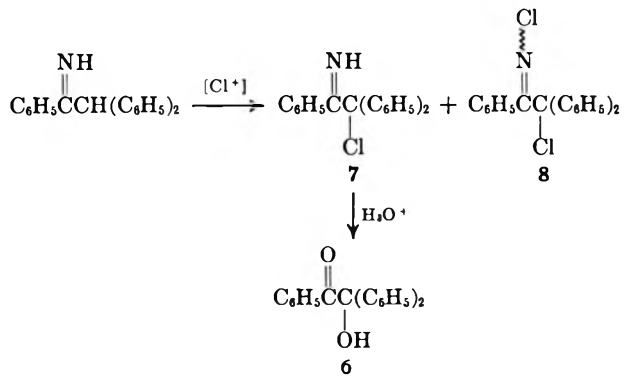
N-Chloroketimines.—Treatment of the respective ketimines with *t*-butyl hypochlorite gave diphenyl N-chloroketimine (**1**),[10] phenyl benzyl N-chloroketimine (**2**),[11] and phenyl α-methylbenzhydryl N-chloroketimine (**3**), whose purity could be determined by iodometric titration for active chlorine. The nmr spectrum of **2** showed only one singlet (4.37 ppm) for the benzylic protons in deuteriochloroform solution, even down to −60°, whereas two signals would have been expected for a mixture of *syn* and *anti* forms[12-14] in the absence of rapid interconversion. Since *syn–anti* isomerization of similarly constituted N-halimines has been shown to be slow at room temperature,[12,13] the predominance of a single isomer is suggested.[15] Treatment of **2** with silver tetrafluoroborate in dioxane–water gave, in addition to partial hydrolysis to deoxybenzoin, rearrangement only to N-phenylphenylacetamide (**4**) free from N-benzylbenzamide (**5**). Since this Beckmannlike rearrangement has been shown in similar cases to occur with concerted stereospecific migration of the group *trans* to chlorine,[13] we assign **2** with the chlorine *syn* to the benzyl group.



This argument would not be valid if the migratory aptitude of phenyl was considerably greater than that of benzyl in this particular reaction; then the isomer with chlorine *trans* to phenyl could have given **4** while that with chlorine *trans* to benzyl was being hydrolyzed. However, the migratory aptitudes of phenyl and *s*-butyl have been shown to be quite similar;[13] this fact, coupled with the nmr evidence, makes the assignment reasonable. The nmr spectrum of **3** showed only a single methyl group. Treatment with silver tetrafluoroborate in dioxane–water gave no amide formation, but rather conversion to benzonitrile and 1,1-diphenylethylene. Apparently the normal Beckmannlike rearrangement[13] is superseded by the "abnormal Beckmann rearrangement"[16] when a leaving cation as stable as 1,1-diphenylethyl is possible. Thus this reaction cannot be used to assign configuration to **3**.



Treatment of phenyl benzhydryl ketimine with positive chlorine donors gave both a monochloride and a dichloride. The monochloride gave erratic values for active chlorine and failed to show the expected benzhydrylic proton in the nmr spectrum. Hydrolysis gave phenyl α-hydroxybenzhydryl ketone (**6**) rather than the parent ketone. Therefore, we formulate the monochloride as **7** and suggest that the initial attack of positive chlorine occurred on carbon of an enamine tautomer of the imine rather than on nitrogen of the imine itself. As a precedent, we note that the imine of diphenylacetaldehyde seems to be more stable in its enamine tautomeric form.[17] The dichloride would



(6) (a) E. Müller and H. Huber, *Chem. Ber.*, **96**, 670, 2319 (1963). (b) D. D. Tanner and N. J. Bunce, *J. Amer. Chem. Soc.*, **91**, 3028 (1969). (c) B. Hardman and G. J. Janz, *ibid.*, **90**, 6272 (1968); J. B. Flannery and G. J. Janz, *ibid.*, **88**, 5097 (1966).

(7) D. Y. Curtin and C. G. McCarty, *J. Org. Chem.*, **32**, 223 (1967).

(8) W. J. Middleton and C. G. Krespan, *ibid.*, **30**, 1398 (1965).

(9) (a) W. Brackman and P. J. Smit, *Rec. Trav. Chim.*, **82**, 757 (1963); (b) I. I. Grandberg, Y. A. Naumov, and A. N. Kost, *J. Org. Chem. USSR* (Engl. Trans.), **1**, 809 (1965).

(10) P. P. Peterson, *Am. Chem. J.*, **46**, 325 (1911).

(11) K. N. Campbell, *J. Amer. Chem. Soc.*, **59**, 2058 (1937).

(12) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *ibid.*, **88**, 2775 (1966).

(13) R. N. Loeppky and M. Rotman, *J. Org. Chem.*, **32**, 4010 (1967).

(14) G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *J. Amer. Chem. Soc.*, **86**, 3351 (1964), and references therein.

(15) A single form may have preferentially crystallized. A dilute solution of **2** in carbon tetrachloride was heated at reflux for 1 hr; after the solution was cooled and concentrated, no changes in the nmr spectrum were observed. If the rate of interconversion is similar to that for diaryl cases,[12] this may still have not been drastic enough treatment to effect isomerization. However, more severe thermal treatment was precluded by the thermal instability discussed below.

(16) C. A. Grob and P. W. Shiess, *Angew. Chem. Intern. Ed. Engl.*, **6**, 9 (1967).

(17) D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 863 (1965).

TABLE I

THERMAL DECOMPOSITION OF PHENYL BENZYL N-CHLOROKETIMINE

Entry	Temp, °C	Concn, solvent[a]	Conditions	$t_{1/4}$, min[b]	$t_{1/2}$, min[c]	t_f, min[d]	Yield, % C_6H_5CN	Yield, % $C_6H_5CH_2Cl$
1	81	0.020, B	N_2	>2800				
2	105	0.020, C	N_2	>1500[e]				
3	131	0.020, C	N_2	70	200	<1500	97	92
4[f]	131	0.020, C	N_2	200[g]	280[g]	<1500	97	91
5[f]	131	0.020, C	N_2	40	85	~250	97	78[h]
6	131	0.010, C	N_2	90	120	<1500	100	69
7	131	0.040, C	N_2	65	140	360	95	90
8	131	1.03, C	N_2			<105	22[i]	17[i]
9	131	0.020, C	O_2	>360		<1500	95	20[j]
10	131	0.020, C	O_2	>330		<1500	77	25[k]
11	131	0.020, C	*l*		75	240	80	34
12	131	0.020, C	Bz_2O_2,[m]	18	42	180	100	73
13	131	0.020, C	Bz_2O_2[n]		15	120	84	68
14	81	0.020, B	Bz_2O_2[o]	>360				
15	131	0.020, C	*p*	45	100		99	80
16	28	0.020, C	*hν*[q]	~150		<1500	9	4

[a] Molarity in benzene (B) or chlorobenzene (C). [b] Time for 25% loss of active chlorine. [c] Time for 50% loss of active chlorine. [d] Time for total loss of active chlorine; "<1500" signifies reactions incomplete after ~400 min but complete after standing overnight at the stated conditions. [e] Increasing temperature to 131° at this point led to decomposition with $t_{1/2}$ ~200 min. [f] These entries represent extremes of behavior with respect to inhibition periods; different batches of 2 were used. [g] Significant inhibition period observed. [h] 0.065 mol of bibenzyl formed per mol of chlorimine. [i] 0.27 mol of ammonium chloride and 0.165 mol of 2,3,4,5-tetraphenylpyrrole formed per mol of chlorimine. [j] 16% unknown product. [k] 25% unknown product. [l] 10 mol % 4-*t*-butylcatechol added. [m] 10 mol % Bz_2O_2 (benzoyl peroxide) added at steady rate over 120-min period. [n] 11 mol % added at steady rate over 50-min period. [o] 12 mol % present initially. [p] 10 mol % *t*-butyl peroxide present initially. [q] Three 275-W sun lamps through Pyrex at ~6 in.

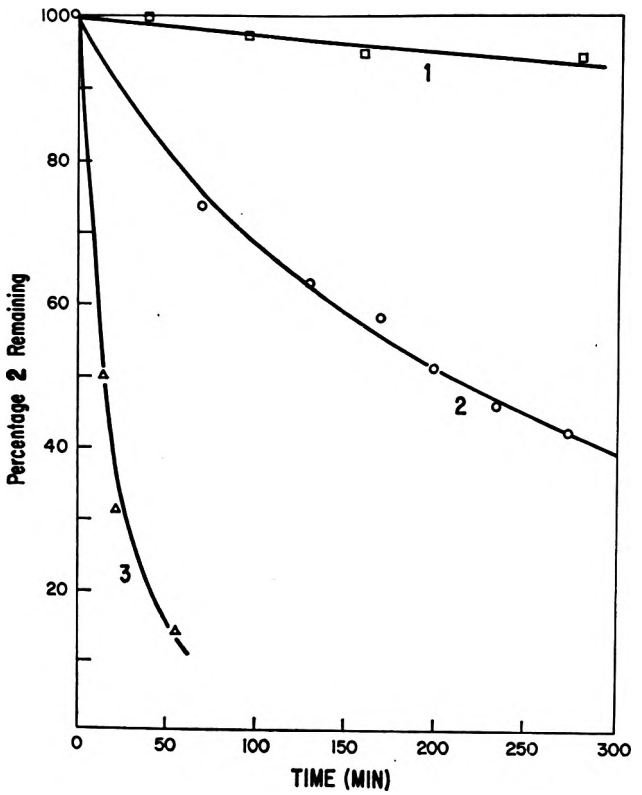
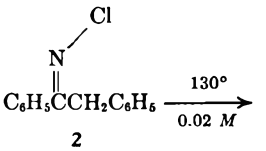


Figure 1.—Typical rate profiles for thermal decomposition of phenyl benzyl N-chloroketimine (2) at 131° (0.02 *M* solution in chlorobenzene): curve 1 (□), oxygen atmosphere, entry 9, Table I; curve 2 (○), nitrogen atmosphere; curve 3 (△), slow addition of benzoyl peroxide, entry 13, Table I.

appear to be **8**, but this material was not investigated extensively.

Thermal Stability.—Diphenyl N-chloroketimine (**1**) was heated in chlorobenzene solution (0.02 *M*) at 130–131° under nitrogen for 6 hr without detectable loss of active chlorine; such thermal stability of diaryl N-chloroketimines has been noted previously.[12,13]

In contrast, heating a dilute solution (<0.04 *M*) of the phenyl benzyl analog 2 in chlorobenzene under comparable conditions led to loss of active chlorine after occasionally observed induction periods. The products were benzonitrile (95–100%) and benzyl chloride (70–95%) as measured by glpc analysis; minor amounts

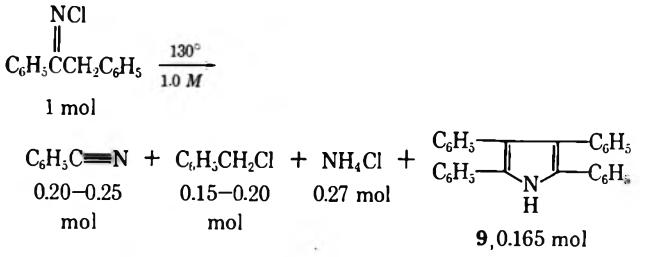


$$C_6H_5C{\equiv}N + C_6H_5CH_2Cl + C_6H_5CH_2CH_2C_6H_5$$
95–100% 70–95% ~5%

of bibenzyl were detected. Results under a variety of conditions are shown in Table I and typical data are plotted in Figure 1. Although individual concentration *vs.* time plots for runs under nitrogen were impossible to reproduce exactly (different batches of 2 were used and variable amounts of oxygen may have been present since rigorous degassing techniques were not used), the inhibition by added oxygen was so marked as to be unmistakable; runs under oxygen carried to total loss of active chlorine gave benzonitrile in good yield but gave benzyl chloride in diminished amounts (20–25%). Slow addition of benzoyl peroxide solution ($t_{1/2}^{130°}$ <5 min) led to considerable enhancement of initial rates. Thermal cleavage at low concentration could also be conveniently carried out by slow addition of 2 to refluxing chlorobenzene at a rate such that the concentration never exceeded 0.04 *M*. Reaction was extremely slow at 80°; loss of active chlorine did occur on photolysis at 28°, but <10% of benzonitrile and benzyl chloride were produced.

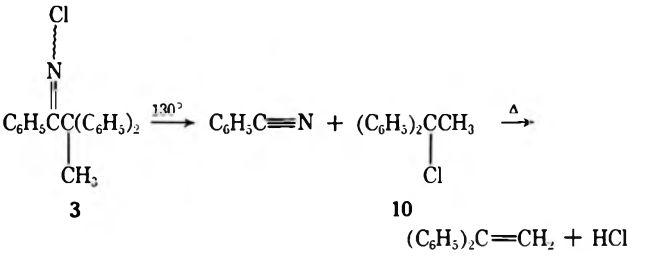
Thermal decomposition of 2 at 130–131° under nitrogen in 1.0 *M* chlorobenzene solution was much more rapid than that in dilute solution, but produced only 20–25% of benzonitrile and 15–20% of benzyl chloride. A new set of products was formed: ammonium chloride

(27% based on nitrogen and chlorine; 54% based on available hydrogen in 2) and 2,3,4,5-tetraphenylpyrrole (9) (16.5% based on nitrogen; 33% based on



phenyl groups in 2). This obviously rather complex condensation at higher concentrations was not explored further; however, it may be noted that pyrrole 9 has been prepared from treatment of the ketazine of phenyl benzyl ketone with hydrogen chloride at 180°.[18]

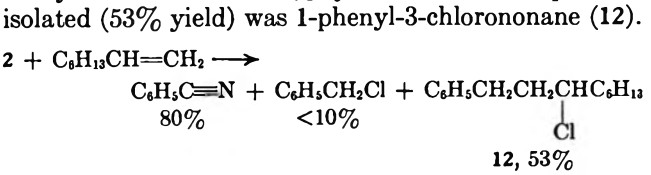
Thermal cleavage of the phenyl α-methylbenzhydryl analog 3 in dilute chlorobenzene solution at 130–131° gave benzonitrile (84%), 1,1-diphenylethylene (95%), and hydrogen chloride (70.5%), which was constantly swept out of solution with a stream of nitrogen. Based on the known thermal instability of 1,1-diphenyl-1-chloroethane (10) toward dehydrochlorination,[19] we propose a decomposition scheme parallel to that of 2; in particular, no 1,1-diphenylethane was produced.



Reactions with 1-Octene.—When N-chlorimine 1 in a refluxing 1:1 mixture of 1-octene and chlorobenzene under nitrogen (internal temperature ~124°) was subjected to slow addition of benzoyl peroxide, loss of active chlorine did occur, but nmr spectra of the crude product failed to reveal significant absorption in the δ 2.5–5.0 region expected for protons α to chlorine or doubly bonded nitrogen[20] in the hoped-for adduct, 11. Some allylic chlorination of the olefin is suspected on the basis of glpc evidence but has not been rigorously confirmed.

$(C_6H_5)_2C{=}NCH_2CHClC_6H_{13}$
11

Slow addition of 2 to a refluxing 1:1 mixture of chlorobenzene and 1-octene under nitrogen gave smooth decomposition to produce benzonitrile in 80% yield but benzyl chloride in <10% yield. The new product isolated (53% yield) was 1-phenyl-3-chlorononane (12).



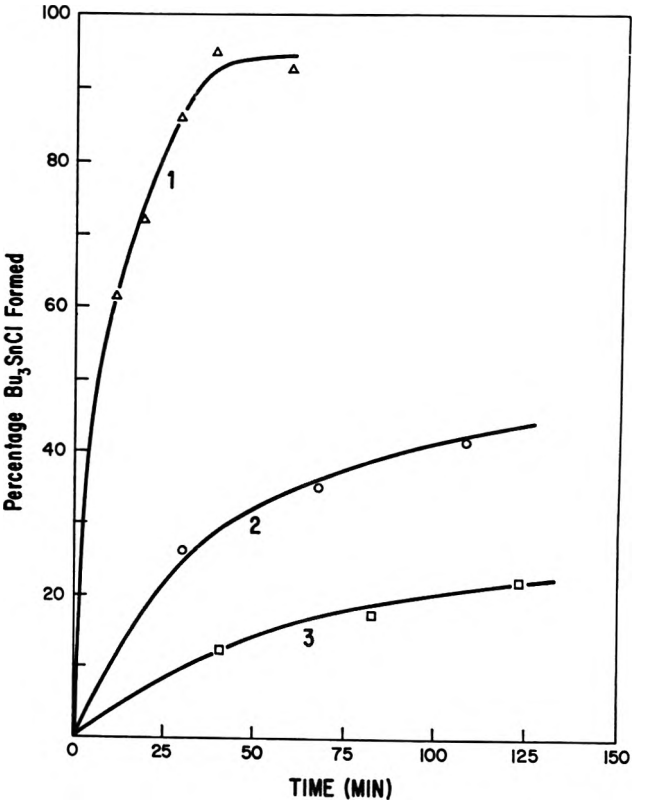
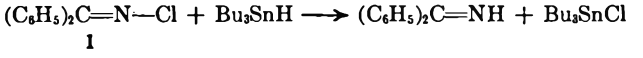


Figure 2.—Typical rate profiles for reaction of diphenyl N-chloroketimine (1) with tri-*n*-butyltin hydride at 55° (each 0.02 *M* in benzene): curve 1 (△), 10 mol % di-*t*-butyl peroxyoxalate added over 30-min period; curve 2 (○), nitrogen atmosphere; curve 3 (□), oxygen atmosphere.

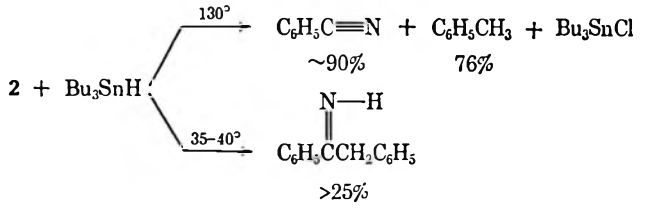
Reductions with Tri-*n*-butyltin Hydride.—Treatment of a 0.02 *M* solution of 1 in benzene at 80° with an equimolar amount of tri-*n* butyltin hydride (Bu_3SnH)[21] led to 100% conversion into tri-*n*-butyltin chloride (Bu_3SnCl) after 2 hr as judged by titration of aliquots with standard base.[22] (Iodometric titration for active chlorine could not be used in the presence of Bu_3SnH since it consumed the iodine liberated in the usual procedure.) Treatment of the residue with hydrogen chloride gave benzophenone imine hydrochloride in 80% yield. This reduction of 1 by Bu_3SnH was studied at 55 ± 1° under a variety of conditions; results obtained by titration for Bu_3SnCl formed are shown in Figure 2. Under nitrogen with 0.02 *M* concentrations of each reagent, reaction was complete in 16–24 hr and



imine hydrochloride was isolated in 90% yield. However, under oxygen, the reaction was initially slower and proceeded to only 50–60% completion after 48 hr. In contrast, slow addition of 10 mol % of di-*t*-butyl peroxyoxalate[23] ($t_{1/2}$ = 10–15 min in benzene at 55°[23]) in benzene solution over a 30-min period led to essentially complete reaction at the end of the addition period. Individual values shown for this run in Figure 2 may be slightly high, since the initiator was shown to consume some base during a typical titration, but the dramatic effect of this radical initiator is unmistakable.

(18) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **113**, 639 (1918).
(19) C. S. Schoepfle and J. D. Ryan, *J. Amer. Chem. Soc.*, **52**, 4021 (1930); **54**, 3687 (1932).
(20) D. Y. Curtin and J. W. Hausser, *ibid.*, **83**, 3474 (1961).
(21) H. G. Kuivila, *Advan. Organometal. Chem.*, **1**, 47 (1964).
(22) D. H. Lorenz, P. Shapiro, A. Stern, and E. I. Becker, *J. Org. Chem.*, **28**, 2332 (1963).
(23) P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *J. Amer. Chem. Soc.*, **82**, 1762 (1960).

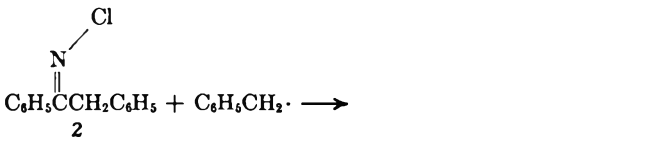
Slow addition of equimolar solutions of **2** and Bu_3SnH at identical rates to refluxing chlorobenzene under nitrogen gave reaction essentially as fast as the reagents were introduced, as judged by glpc analysis for toluene product. At the end of the addition period, titration revealed the appropriate amount of Bu_3SnCl formed and glpc analysis showed benzonitrile (90–100%) and toluene (76%). Reduction could also be carried out at

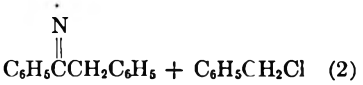


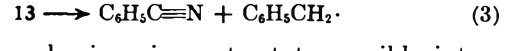
35–40° with photolytic initiation, although much less efficiently; toluene was found in only minor amounts and phenyl benzyl ketimine became a significant product.

Discussion

The thermal cleavage of N-chloroketimine **2** to benzonitrile and benzyl chloride seems best explained by a radical chain decomposition (steps 2 and 3) involving formation and β scission of ketimino radical **13**.



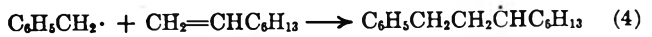


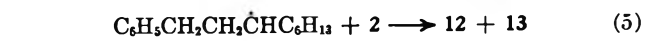


This chain mechanism, in contrast to possible intramolecular rearrangements or heterolytic rearrangements related to the "abnormal Beckmann reaction,"[16] is supported by the initiation and inhibition data depicted in Figure 1 (as well as by the tendency of the reaction to exhibit variable inhibition periods). The isolation of bibenzyl speaks for involvement of benzyl radicals. Since the oxygen-inhibited reaction eventually produced benzonitrile but little benzyl chloride, oxygen apparently traps benzyl radical more effectively than radical **13** under the conditions of our experiment.

The sequence outlined in steps 2 and 3 is analogous to the well-documented[24] decomposition of *t*-alkyl hypochlorites to ketones and alkyl chlorides; in this reaction, cleavage of alkoxy radicals gives the most stable possible departing radical. Similarly, cleavage of **13** proceeds as in step 3 rather than to produce the less stable phenyl radical and phenylacetonitrile. The much greater stability of N-chlorimine **1** can then be related to the absence of a good leaving radical, and the facile decomposition of **3** is as predicted.

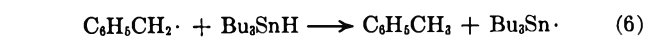
In the presence of a large excess of 1-octene, the benzyl radical is trapped by the olefin before reacting with **2**, so that step 2 is replaced by the combination of steps 4 and 5; thus steps 3–5 constitute the major

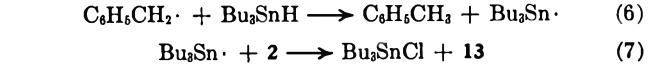




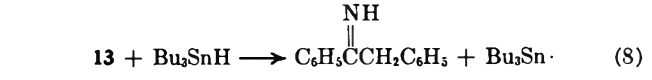
chain. The addition of benzyl radicals to terminal olefins has been observed previously.[25] No products derived from addition of ketimino radical **13** to 1-octene were observed. Even in the diphenyl case where β scission is insignificant, a radical addition of **1** to 1-octene could not be achieved.

The reduction of **2** by Bu_3SnH is also apparently a radical chain reaction[26] analogous to the reduction of alkyl halides (see below for more conclusive evidence for the case of **1**). Since reduction at 130° is much faster than thermal decomposition, the reaction must be more complex than simply secondary reduction of benzyl chloride to toluene, and steps 6 and 7 seem reasonable. Thus, the chain is now steps 6, 7, and 3 with the combination of steps 6 and 7 being less of a





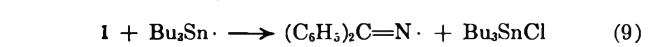
barrier to reaction than step 2. In contrast to the run at 130° where the average concentration of Bu_3SnH was low, the run at 35–40° where the concentration of Bu_3SnH was surely higher gave mainly ketimine, rather than toluene, apparently through step 8. Thus, at low

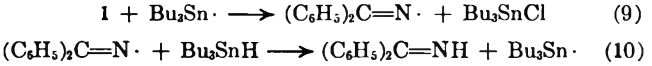


temperatures and high concentrations of chain-transfer agent, bimolecular step 8 is faster than unimolecular step 3, whereas at high temperatures and low concentrations, the reverse is true. Such an effect is reasonable for the sequence proposed.

In summary, then, both radical species proposed in steps 2 and 3 for the thermal cleavage of **2** have been trapped by added reagents: the benzyl radical as adduct **12** and as toluene (as well as by itself to form bibenzyl) and radical **13** as the ketimine.

The reduction of N-chloroketimine **1** with Bu_3SnH was studied as a model reaction for the more complex reduction of **2** discussed above. The occurrence of both marked initiation and moderate inhibition support a radical chain (steps 9 and 10) pathway and demonstrate that trialkyltin radicals can abstract chlorine from nitrogen as well as from carbon. Although radical addition of trialkyltin hydrides to certain >C=N–





bonds has been reported,[27] the good yields of both benzophenone imine and Bu_3SnCl preclude any significant contribution from such a potential secondary reaction.

Experimental Section

All melting and boiling points are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrometer. Nmr spectra were recorded on a Varian A-60 spectrometer in carbon tetrachloride solution unless otherwise specified, and results are expressed in parts per million downfield from internal tetramethylsilane. Glpc analyses were performed on a Micro-Tek

(24) F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.*, **28**, 55 (1963); C. Walling and A. Padwa, *J. Amer. Chem. Soc.*, **85**, 1593 (1963).

(25) R. L. Huang, H. H. Lee, and L. Y. Wong, *J. Chem. Soc.*, 6730 (1965).

(26) L. W. Menapace and H. G. Kuivila, *J. Amer. Chem. Soc.*, **86**, 3047 (1964).

(27) W. P. Neumann and E. Heymann, *Ann.*, **683**, 24 (1965).

2500R instrument equipped with a flame ionization detector. All quantitative results compared to internal standards were based on measured molar response factors determined from known mixtures of authentic materials. Chlorobenzene was distilled from calcium hydride, and benzene from Drierite.

Ketimine Hydrochlorides.[11,28]—To a 2.2 *M* solution of phenylmagnesium chloride in ether was added the appropriate nitrile: benzonitrile, diphenylacetonitrile (Matheson Coleman and Bell), or 2,2-diphenylpropionitrile.[29] After 24–48 hr at reflux, the mixture was treated with excess gaseous ammonia. The solids were removed by filtration and the filtrate was treated with gaseous hydrogen chloride after partial evaporation to remove excess ammonia. The precipitated hydrochlorides were stored in a freezer after drying *in vacuo* over phosphorus pentoxide. Phenyl benzyl ketimine hydrochloride was prepared from benzylmagnesium chloride and benzonitrile in analogous fashion.[11]

N-Chloroketimines.—A stirred suspension of 11.85 g (51 mmol) of phenyl benzyl ketimine hydrochloride in 140 ml of benzene was treated with gaseous ammonia at 0° for 30 min. The solids were removed by filtration and the filtrate was partially evaporated *in vacuo* without heating to remove excess ammonia. The resulting solution of ketimine was treated dropwise with a solution of 6.0 g (55 mmol) of *t*-butyl hypochlorite (Frinton Laboratories) in 15 ml of benzene at 0° and then stirred for 1 hr. The solvent was evaporated *in vacuo* at room temperature to give an oil which crystallized in the freezer. The product was dissolved in chloroform at room temperature and precipitated with two volumes of hexane to give after cooling 6.37 g of phenyl benzyl N-chloroketimine (**2**), mp 78–79° (lit.[11] mp 78°); a second crop (1.25 g) had mp 77.5–78.5°. The nmr spectrum showed a singlet at 4.37 ppm and a multiplet at 7.15–7.75 ppm in the ratio of 1.9:10.1; two protons of the latter multiplet were rather cleanly separated at ~7.65 ppm from the higher field portion. The singlet remained sharp and no new peaks appeared at −60° in deuteriochloroform solution. A 0.02 *M* solution in carbon tetrachloride was heated at reflux for 1 hr, cooled, and evaporated *in vacuo* to a suitable concentration to determine the nmr spectrum; no significant changes occurred in the spectrum. Iodometric titration of the product in a methylene chloride–aqueous acetic acid mixture consistently showed >95% active chlorine.

Anal. Calcd for $C_{14}H_{12}ClN$: C, 73.20; H, 5.27; N, 6.10; Cl, 15.44. Found: C, 73.15; H, 5.28; N, 6.10; Cl, 15.44.

Analogous reaction gave diphenyl N-chloroketimine (**1**), mp 35.5–37° (lit.[6] mp 35–36°), 100% pure by iodometric titration. A 0.02 *M* solution in chlorobenzene was refluxed under nitrogen for 6 hr with no loss of active chlorine and only slight development of a yellow color. Phenyl α-methylbenzhydryl N-chloroketimine (**3**), mp 164–166°, showed the expected nmr singlet at 1.75 ppm and showed 95% active chlorine by iodometric titration.

Anal. Calcd for $C_{21}H_{18}ClN$: C, 78.87; H, 5.63; N, 4.38; Cl, 11.11. Found: C, 78.72; H, 5.85; N, 4.64; Cl, 11.19.

Reactions of Phenyl Benzhydryl Ketimine with Chlorinating Agents.—The crude ketimine hydrochloride (1.80 g, *ca.* 5.8 mmol) was converted into the free ketimine with ammonia in benzene as above and treated with 0.73 g (6.7 mmol) of *t*-butyl hypochlorite for 1 hr at 0°. Evaporation at room temperature and crystallization from chloroform–hexane gave 1.08 g of product A, mp 91–95° (slight residue); normal iodometric titration indicated *ca.* 40% active chlorine. Repetition with 1.50 g (*ca.* 4.9 mmol) of ketimine hydrochloride and 1.0 g (9.2 mmol) of *t*-butyl hypochlorite gave, after crystallization, 0.58 g of a new product B, mp 141–142°, and several lower melting subsequent crops. Normal iodometric titration gave erratic values; replacement of methylene chloride as the cosolvent by ethanol gave values of *ca.* 150% for active chlorine content. A third run with 1.19 g (*ca.* 3.8 mmol) of hydrochloride and 0.54 g (4.0 mmol) of N-chlorosuccinimide was carried out in benzene solution. Over a 2-hr period at 0°, a precipitate was gradually formed. Filtration after partial evaporation gave succinimide (ir identification). Evaporation of the filtrate and crystallization several times from chloroform–hexane gave 200 mg of product, mp 90–94°, which showed 95% active chlorine by iodometric titration in ethanol and which was the same material by infrared analysis as product A above. Nmr spectra of A and B showed aromatic absorption but no singlet ascribable to the benzhydrylic proton.

Anal. Calcd for $C_{20}H_{16}ClN$ (A): C, 78.56; H, 5.24; N, 4.58; Cl, 11.62. Found: C, 76.30; H, 5.26; N, 4.70; Cl, 11.66.

Anal. Calcd for $C_{20}H_{15}Cl_2N$ (B): C, 70.59; H, 4.41; N, 4.11; Cl, 20.88. Found: C, 71.00; H, 4.51; N, 3.82; Cl, 20.79.

Product A (300 mg) was treated with 40 ml of refluxing 6 *N* hydrochloric acid for 3.5 hr. Extraction with ether, drying, and evaporation gave 287 mg of white solid, mp 81–86°. The ir spectrum showed both hydroxyl and carbonyl absorption as expected for phenyl α-hydroxybenzhydryl ketone (**6**) (lit.[30] mp 87–88°) but was quite different from that of the parent ketone. Similar hydrolysis of B gave an oily residue with a similar infrared spectrum. Therefore we assign A as phenyl α-chlorobenzhydryl ketimine (**7**) and B as phenyl α-chlorobenzhydryl N-chloroketimine (**8**).

Refluxing a 0.02 *M* solution of **7** in chlorobenzene under nitrogen led to total loss of active chlorine after 5 hr, but glpc analysis revealed <7% benzonitrile formation (internal standard technique as described below). Parallel treatment of **8** gave 82% benzonitrile.

Silver Ion Catalyzed Rearrangement of Phenyl Benzyl N-Chloroketimine.—Authentic N-phenylphenylacetamide (**4**), mp 114–116° (lit.[31] mp 117°), and N-benzylbenzamide (**5**), mp 104–105.5° (lit.[32] mp 105–106°), were prepared from the corresponding acid chlorides and amines. The benzylic resonances in the nmr spectrum (deuteriochloroform solution) occurred at 3.62 ppm (s) and 4.54 ppm (d, J = 6 cps), respectively. To a solution of 2.00 g (10.3 mmol) of silver tetrafluoroborate in 25 ml of 3:1 dioxane–water (v/v) at 60° was added 1.07 g (4.66 mmol) of N-chloroketimine **2**. The mixture was held at reflux for 4 hr as precipitation occurred. Cooling and filtration gave 0.655 g (98%) of silver chloride. The filtrate was poured into a solution of of 2.5 g of sodium chloride in 100 ml of water, and the newly formed precipitate was recovered by filtration and dried. Digestion of this solid in 50 ml of boiling ligroin and evaporation of the liquid phase gave 0.39 g (43%) of low-melting solid whose ir spectrum was consistent with that of deoxybenzoin. The ligroin-insoluble residue was digested in 50 ml of boiling acetone, and evaporation of the liquid phase gave 0.26 g (26%) of solid, mp 97–105°, whose ir spectrum was consistent with that of amide **4**; crystallization from ethanol raised the melting point to 113–115°. Extraction of the original aqueous filtrate with chloroform and evaporation of the chloroform gave 0.20 g of a mixture whose ir spectrum suggested the presence of both deoxybenzoin and amide **4**. The experiment was repeated with 0.46 g of **4** and proportional quantities of other reagents; all of the organic product was collected in chloroform solution by a combination of extraction of the aqueous layer and digestion of the inorganic precipitates. Drying and evaporation of the chloroform gave 0.42 g of product whose nmr spectrum (deuteriochloroform solution) showed the expected singlets for deoxybenzoin (4.25 ppm) and amide **4** (3.63 ppm) in comparable amounts as well as a singlet at 3.67 ppm assigned to dioxane; no signal could be observed near 4.5 ppm for amide **5**, whereas 5% of the amount of **4** should have been easily detected.

Silver Ion Catalyzed Rearrangement of Phenyl α-Methylbenzhydryl N-Chloroketimine.—The above experiment was repeated with 3.25 g (16.8 mmol) of silver tetrafluoroborate, 1.43 g (4.45 mmol) of N-chloroketimine **3**, and 40 ml of dioxane–water (3:1). The nmr spectrum of the total organic residue (1.17 g) showed no absorption from 0.0–3.5 ppm expected for the methyl groups in rearranged amides, but instead showed (in addition to a small singlet for dioxane) a singlet at 5.47 ppm and aromatic absorption at 7.0–7.7 ppm in the ratio of 1.0:8.5; the position of the singlet corresponded to that of 1,1-diphenylethylene. Glpc analysis revealed benzonitrile (66% compared to *o*-dichlorobenzene as internal standard) and 1,1-diphenylethylene (90.5% compared to diphenylmethane as internal standard) based on retention times and coinjection with authentic samples.

Thermal Decomposition of Phenyl Benzyl N-Chloroketimine (2) at Low Concentration.—An appropriate amount of benzene or chlorobenzene (usually 25 ml) containing a known amount of *o*-dichlorobenzene (*ca.* 0.01 *M*) was heated to reflux; the mixture was flushed with nitrogen. The N-chloroketimine **2** was added

(28) P. L. Pickard and D. J. Vaughan, *J. Amer. Chem. Soc.*, **72**, 876 (1950).

(29) P. L. Pickard and E. F. Engles, *ibid.*, **73**, 864 (1951).

(30) A. Werner, *Ber.*, **39**, 1278 (1906).

(31) A. W. Hofmann, *ibid.*, **13**, 1223 (1880).

(32) E. Beckmann, *ibid.*, **23**, 3331 (1890).

in one portion and refluxing was continued under a positive nitrogen pressure. For runs under oxygen, the solvent was first saturated with oxygen in similar fashion. For runs with slow addition of benzoyl peroxide, the solution of peroxide in 2 ml of chlorobenzene was added at a constant rate from a syringe driven by a variable-speed syringe pump. Aliquots were removed periodically with a syringe through a serum cap and quenched in excess potassium iodide in 40% aqueous acetic acid; liberated iodine was titrated with standard sodium thiosulfate solution. When reaction was complete as judged by total disappearance of active chlorine, glpc analysis was used to determine the yields of benzonitrile and benzyl chloride based on the *o*-dichlorobenzene as internal standard. Results are summarized in Table I; plots of 2 remaining *vs.* time were made to estimate $t_{1/4}$ and $t_{1/4}$ (times for $^1/_4$ and $^1/_2$ reaction) which are listed *only* to indicate the general progress of the reaction and have no exact kinetic significance because the exact nature of the curves varied somewhat from run to run and probably depended on the purity of 2 as well as the exact degree of oxygen exclusion.

A slow-addition procedure was also successful. A solution of 28.9 mg (0.197 mmol) of *o*-dichlorobenzene in 15 ml of chlorobenzene was flushed with nitrogen and brought to reflux. A solution of 221 mg (0.963 mmol) of 2 in 5 ml of chlorobenzene was added in 5 hr at a constant rate from the motor-driven syringe. Iodometric titration showed that at 54% addition, 20% of the added 2 had disappeared; at 100% addition, 50% of 2 had disappeared, so that the concentration at this point was 0.024 *M*. After 16-hr reflux, titration was negative. Glpc analysis showed 100% benzonitrile and 92% benzyl chloride.

Partial decomposition to benzonitrile and benzyl chloride also occurred whenever solutions contaning 2 were injected into the heated glpc inlet.

Thermal Decomposition of Phenyl Benzyl N-Chloroketimine (2) at High Concentration.—A solution of 951 mg (4.14 mmol) of 2 and 96.5 mg of *o*-dichlorobenzene in 4.0 ml of chlorobenzene was flushed with nitrogen and heated under reflux. Almost immediately a flocculent precipitate appeared; iodometric titration after 1.75 hr was negative. After cooling to room temperature, the solid (60.8 mg, 1.14 mmol) was collected by centrifugation; it did not melt below 315° and had an ir spectrum (KBr) consistent with that for ammonium chloride. Additional cooling and concentration of the mother liquor gave 252.5 mg (0.68 mmol) of new solid in several crops melting in the range 205–212°. The ir spectrum[33] identified the product as 2,3,4,5-tetraphenylpyrrole (9) (lit.[24] mp 214–215°). Glpc analysis of the final mother liquor showed 22% benzonitrile and 17% benzyl chloride.

Thermal Decomposition of Phenyl α-Methylbenzhydryl N-Chloroketimine (3).—A solution of 165 mg (0.514 mmol) of N-chloroketimine 3 and 30.7 mg of *o*-dichlorobenzene in 25 ml of chlorobenzene was heated at reflux. A slow stream of nitrogen was fed over the reaction surface, through the condenser, and into a known volume of standard base. Iodometric titration of aliquots indicated complete reaction after 3 hr. Titration of the base trap with standard acid indicated the formation of 0.362 mequiv (70.5%) of volatile acid, presumably hydrogen chloride. Glpc analysis revealed 84% benzonitrile compared to the *o*-dichlorobenzene internal standard (after correction for aliquots taken) and a peak of retention time equal to that of 1,1-diphenylethylene in 95% yield compared to a diphenylmethane internal standard added after reaction; this identity was confirmed by nmr spectroscopy (singlet at 5.47 ppm). No 1,1-diphenylethane was detected either by glpc or nmr analysis.

Thermal Decomposition of Diphenyl N-Chloroketimine (1) in the Presence of 1-Octene.—To a solution of 1.168 g (5.42 mmol) of N-chloroketimine 1 in a mixture of 50 ml of chlorobenzene and 50 ml of 1-octene at reflux under nitrogen was added a solution of 135 mg (0.56 mmol) of benzoyl peroxide in 17 ml of chlorobenzene from a motor-driven syringe over a 5-hr period. At the end of the addition, 58% of active chlorine had disappeared, which increased to 82% overnight. Another 15.5 mg of benzoyl peroxide in 6 ml of chlorobenzene was added in 2 hr. After another 5-hr reflux, the active chlorine content had decreased to zero. Evaporation *in vacuo* gave 1.88 g of residue whose nmr spectrum showed 170 units of absorption intensity in the aromatic region, <4 units between 5.0 and 2.3 ppm, and 116 units between 2.3 and 0.6 ppm. Chromatography over alumina gave a large number of ill-defined fractions.

(33) "The Sadtler Standard Spectra Catalog," Sadtler Research Laboratories, Philadelphia, Pa., compound no. 14152.

Thermal Decomposition of Phenyl Benzyl N-Chloroketimine (2) in the Presece of 1-Octene.—A solution of 24.9 mg of *o*-dichlorobenzene in a mixture of 7.5 ml of chlorobenzene and 7.5 ml of 1-octene was flushed with nitrogen and brought to reflux (solution temperature 124°). A solution of 226 mg (0.98 mmol) of N-chloroketimine 2 in 5 ml of chlorobenzene was added from a motor-driven syringe at a constant rate in 5 hr. After 70% addition, iodometric titration indicated that 54% of the added 2 had disappeared; after 100% addition, 89% had reacted. The solution was held under reflux for 16 additional hr; glpc analysis showed 78% benzonitrile and <10% benzyl chloride. The solution was evaporated at 40° and *ca.* 1 Torr. The residue (236 mg) was dissolved in benzene and passed through a short column of Woelm neutral alumina. Benzene eluted 123 mg (53%) of clear liquid whose ir and nmr spectra coincided with those of 1-phenyl-3-chlorononane (12).

1-Phenyl-3-nonanol.—Condensation of 2-phenylethyl Grignard reagent and heptanal in ether gave, after acidic work-up and distillation, a center cut (63%), bp 95–97° (0.5 mm), n^{24}D 1.4986. The nmr spectrum showed a broadened singlet at 7.18 ppm (C_6H_5), a very broad band at 3.58 ppm ($-CH_2-\underset{\displaystyle H}{\underset{|}{C}}OHCH_2-$), a singlet at 3.10 ppm (OH), a multiplet at 2.70 ppm ($C_6H_5CH_2-CH_2-$), and complex absorption at 1.9–0.8 ppm with a terminal methyl group clearly visible; the relative areas were 5.0:1.05:1.1:1.95:14.9.

3-Chloro-1-phenylnonane (12).—Several attempts to convert the related alcohol into 12 were accompanied by olefin formation; the best attempt follows. To a stirred mixture of 6.12 g (0.028 mol) of the alcohol and 4.48 g (0.056 mol) of pyridine was slowly added 6.22 g (0.052 mol) of thionyl chloride as the temperature gradually rose to 60°. The mixture was heated at 100–110° for 1.5 hr before cooling and quenching with water. The organic material was collected in pentane to give 4.6 g of residue after drying and evaporation. Distillation gave two fractions with indistinguishable ir spectra: 1.48 g, bp 60–68° (0.03 mm), and 1.55 g, bp 68° (0.03 mm). The nmr spectrum showed absorption at 7.17 ppm, a broad band at 3.72 ppm, a multiplet at 1.95 ppm, and complex absorption at 1.8–0.8 ppm; the spectrum was analogous to that of the parent alcohol, as expected.

Anal. Calcd for $C_{15}H_{23}Cl$: C, 75.44; H, 9.71; Cl, 14.85. Found: C, 76.25; H, 9.87; Cl, 14.28.

Reduction of Diphenyl N-Chloroketimine (1) with Tri-*n*-butyltin Hydride (Bu_3SnH).—Quantitative runs were conducted at 0.02 *M* concentrations of each reagent in benzene. A solution of N-chloroketimine 1 in the bulk of the benzene required was flushed with nitrogen and heated to the desired temperature. The Bu_3SnH in a small volume of benzene was then added in one portion. Reaction was followed by titration of aliquots in aqueous ethanol for tri-*n*-butyltin chloride (Bu_3SnCl) formed with standard base.[22] Control experiments showed that neither N-chloroimines nor Bu_3SnH consumed base under these titration conditions. Iodometric titration could not be used to follow N-chloroimine loss, since control experiments showed that the iodine produced was consumed by Bu_3SnH. To determine the yield of diphenyl ketimine formed, selected reaction mixtures were evaporated at room temperature *in vacuo*, taken up in ether, and treated with dry hydrogen chloride to precipitate the ketimine hydrochloride; its ir spectrum was compared to that of authentic material. This procedure could be performed only when titration indicated complete reaction, since N-chloroketimines also can react with hydrogen chloride to give ultimately ketimine hydrochlorides.[10]

At reflux (81°), reduction was complete in 2 hr (100% yield of Bu_3SnCl by titration) and ketimine hydrochloride was obtained in 80% yield after correction for aliquots taken for titration. At 55 ± 1°, reaction proceeded smoothly with a first half-life of *ca.* 1.5 hr, but required standing overnight for complete reaction; ketimine hydrochloride was isolated in 90% yield. Under an oxygen atmosphere, reaction proceeded to only 50–60% conversion after 48 hr. Addition of 10 mol % di-*t*-butyl peroxyoxalate[23] in 1 ml of benzene over a 30-min period to a 50-ml initial reaction mixture led to complete reaction at the end of the addition period; each point in this run may be *ca.* 10% high, since the initiator was shown to consume some base during titration. Typical runs at 55 ± 1° are shown in Figure 2 to demonstrate the effects of oxygen and the peroxyoxalate. At 42 ± 1°, reduction proceeded through a first half-life in *ca.* 4 hr, but then the rate fell off sharply and only 70–75% of the theo-

retical amount of Bu_3SnCl was formed after 24 hr. A run under oxygen proceeded to only *ca.* 15% conversion in 4 hr and *ca.* 35% in 24 hr.

Reduction of Phenyl Benzyl N-Chloroketimine (2) with Bu_3SnH. A. 130–131°.—A solution of 30.3 mg (0.206 mmol) of *o*-dichlorobenzene in 10 ml of chlorobenzene was flushed with nitrogen and heated to reflux. Separate solutions of 227 mg (0.99 mmol) of N-chlorimine 2 in 5 ml of chlorobenzene and 303 mg (1.04 mmol) of Bu_3SnH in 5 ml of chlorobenzene were added under nitrogen at the same rate from motor-driven syringes over a 5-hr period. A cold trap was placed in the system to trap any volatile material which escaped the reflux condenser. Glpc analysis of aliquots indicated that toluene was formed essentially as fast as the reagents were added. At the end of the addition period, titration of an aliquot indicated 1.10 mmol of Bu_3SnCl formed. Glpc analysis revealed 76% toluene and 90–100% benzonitrile formed.

B. 35–40°.—To a solution of 235 mg (1.03 mmol) of N-chloroketimine 2 and 20 μl (0.196 mmol) of chlorobenzene in 15 ml of benzene was added a solution of 308 mg (1.06 mmol) of Bu_3SnH in 5 ml of benzene from a motor-driven syringe over 5 hr under N_2. The solution was irradiated throughout with a 275-W sun lamp at *ca.* 6 in., and the temperature was maintained at 35–40° by cooling with an air stream. Titration of an aliquot after 3-ml addition (0.64 mmol Bu_3SnH added) showed that 0.41 mmol of Bu_3SnCl had formed. At the end of the addition, 0.70 mmol had formed, and, after 1.3 hr additional, 0.75 mmol. Glpc analysis then showed 4% toluene, 8% benzyl chloride (apparently from inlet decomposition of residual 2), and 15% benzonitrile, by comparison to the chlorobenzene internal standard. Addition of dry hydrogen chloride to the residual reaction mixture and chilling overnight gave a solid, mp 215–216°, whose infrared spectrum agreed with that of phenyl benzyl ketimine hydrochloride; the yield corrected for the aliquots removed for titration was 0.57 mmol, *at least* one-half of which must have been derived from ketimine in the reaction mixture rather than residual 2 based on the final titration for Bu_3SnCl.

Registry No.—1, 7699-76-5; 2, 20453-02-5; 3, 20452-77-1; 1-phenyl-3-nonanol, 20452-78-2; 12, 20452 79-3; Bu_3SnH, 688-73-3.

Autoxidation of 1-Octene with *t*-Butyl Hydroperoxide and Chromium(III) Acetylacetonate. I. Kinetics

N. INDICTOR, T. JOCHSBERGER,[1a] AND D. KURNIT[1b]

Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn, New York 11210

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The system chromium(III) acetylacetonate–*t*-butyl hydroperoxide has been used to initiate autoxidation of 1-octene in 1-chlorooctane solvent in the temperature range 0–60°. Emperical kinetic equations are presented based upon spectrophotometrically determined disappearance rates of chromium(III) acetylacetonate, titrimetrically determined *t*-butyl hydroperoxide decomposition rates, and oxygen absorption data. Activation parameters for the kinetic data have been calculated. The data are interpreted in terms of two superimposed chain reactions, one involving peroxide decomposition through chromium complexes, the other involving chain autoxidation of the 1-octene. Products of the autoxidation are compared with azo-initiated olefin autoxidation products.

Recently, metal acetylacetonates have been studied in terms of their ability to promote olefin epoxidation,[2,3] amine oxidation,[4] styrene polymerization,[5] and autoxidation[6] in the presence of hydroperoxide. This paper and subsequent ones[7] describe in some detail the use of chromium(III) acetylacetonate and *t*-butyl hydroperoxide as an autoxidation initiator for 1-octene. Reaction mixtures from the 1-octene autoxidation have been chromatographed and compared with azo-initiated autoxidation.[8] The effects of solvents and free-radical inhibitors on the reaction are described in part II.[7]

Experimental Section

Chemicals.—The chemicals for these experiments have been described previously.[6]

Kinetics.—Oxygen absorption measurements and *t*-butyl hydroperoxide decomposition studies for these experiments are as previously described.[6] The rate of chromium(III) acetylactonate disappearance was measured by observing the disappearance of the absorption peak at 336 mμ (ε 15,500 l./mol-cm).[9] Samples for analysis were taken from the same evacuated tubes as for *t*-butyl hydroperoxide decomposition studies and diluted in chlorobenzene. Measurements were done on a Cary Model 14 or a Perkin-Elmer Model 202 spectrophotometer. The reference cell contained chlorobenzene. It was observed that the presence of *t*-butyl hydroperoxide in chromium(III) acetylacetonate solutions caused deviations in Beer's law plots of absorbance *vs.* concentration. Corrections were made either by including *t*-butyl hydroperoxide in the reference cell or from calibration curves of absorption *vs.* *t*-butyl hydroperoxide concentration.

Rates in all cases were taken from initial portions of the kinetic curves. Rates of autoxidation and *t*-butyl hydroperoxide decomposition showed considerable curvature (lowering) after the initial portions. Chromium(III) acetylacetonate disappearance was linear. The reproducibility of duplicate rate measurements was *ca.* ±5% for chromium(III) acetylacetonate disappearance, *ca.* ±3% for autoxidation, and *ca.* ±6% for *t*-butyl hydroperoxide decomposition.

Product Analysis.—Product analysis was done by vapor phase chromatography on a Perkin-Elmer Model 154 gas chromatograph using a glass 88-in. Carbowax 20M column, helium pressure 10 psi, column temperature 150°, block temperature 74°. Retention times of products from previously described systems were used to correlate products from this work. Retention times of significant compounds are given in Table I for the above column conditions.

Preparation of 3-*t*-Butylperoxy-1-octene, 1-*t*-Butylperoxy-3-octene, and 3-Octenal.—Following the method of Kharasch and Fono[10] 0.033 g of cuprous chloride, 10 ml of 1-octene, and 2 ml of *t*-butyl hydroperoxide were mixed under nitrogen for *ca.* 5 hr at 60–70°. Four products peaks were observed gas chromatographically. Products of long retention time were assigned to the dialkyl peroxides, *t*-butyl alcohol was identified by comparison to an authentic sample, and octenal was assigned the remaining peak.

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TABLE I

GAS CHROMATOGRAPH RETENTION TIMES

Compd	Retention time, min
1,2-Epoxyoctane	7.5
2-Octenal	10.3
1-Octen-3-one	13.5
1- + 3-*t*-butyloctenyl peroxide	19.5, 21.0
1-Octen-3-ol	20.3
Peak I[a]	25.5
Peak II[b]	26.5

[a] Unidentified vpc peak from *in vacuo* reaction of *t*-butyl hydroperoxide, chromium(III) acetylacetonate, and 1-octene. [b] Unidentified vpc peak from autoxidation of 1-octene initiated by chromium(III) acetylacetonate and *t*-butyl hydroperoxide.

Autoxidation of 1-Octene by Azobisisobutyronitrile.—Following the procedure of Mayo,[8] 0.032 g of azobisisobutyronitrile was placed in 20 ml of 1-octene and permitted to absorb oxygen for 16 hr at 65–70°. Oxygen (36 ml; p = 1 atm, corrected for nitrogen evolution) was absorbed. Iodometric titration indicated formation of 0.36 mmol of hydroperoxide. Peak assignments were made on the basis of products reported by Mayo for the autoxidation of 1-hexene under similar conditions.[8]

Autoxidation of 1-Octene by Chromium(III) Acetylacetonate and *t*-Butyl Hydroperoxide.—Solutions (6 M) of 1-octene in 1-chlorooctane were autoxidized in the presence of 0.0016 M chromium(III) acetylacetonate and varying amounts of *t*-butyl hydroperoxide for several days at 30°. The reaction mixture was chromatographed as that from azobisisobutyronitrile-initiated autoxidation. After 4 days, a run at initial *t*-butyl hydroperoxide concentration of 3.3×10^{-4} M showed peroxide titration values of *ca.* 10^{-3} M.

Results and Discussion

The experimentally measured data points are of three kinds: disappearance of uv absorption at 336 mμ[9] attributed to chromium(III) acetylacetonate ($-\Delta[\mathrm{Cr}]/\Delta t$); *t*-butyl hydroperoxide decomposition ($-\Delta[t\text{-BuOOH}]/\Delta t$); and oxygen absorption ($-\Delta \mathrm{O}]_2]/\Delta t$). Table II contains some initial rate data over the concentrations and temperature ranges studied. Table III gives rate "constants" and concentration superscripts of the various rate equations obtained from log–log plots of initial rates *vs.* initial concentrations. Activation parameters, Table IV, were obtained from plots of log $(\mathrm{rate}/[\mathrm{Cr}]^a[t\text{-BuOOH}]^b[\text{1-octene}]^c)_0$ *vs.* T^{-1} using the appropriate superscripts for the indicated concentration ranges.

Chromium(III) Acetylacetonate Disappearance Rates.—The chromium(III) acetylacetonate disappearance data of Tables II, III, and IV suggest a complex multistep process requiring a series of concentrations terms. The kinetics require Cr(III)–*t*-butyl hydroperoxide and Cr(III)–1-octene interaction, the conversion of Cr(III) into Cr(VI), and the production of radical species.

$$\mathrm{Cr(III)} + \nu\, t\text{-BuOOH} \rightleftharpoons \text{complex I} \quad (1)$$

$$\text{complex I} \longrightarrow \mathrm{Cr(III} + \mu) + \mu\, t\text{-BuO}\cdot + \mathrm{OH}^- \quad (2)$$

$$\mathrm{Cr(III} + \mu) + \mathrm{Cr(III)} \longrightarrow \mathrm{Cr(VI)} + \mathrm{Cr}(\mu) \quad (3)$$

$$\mathrm{Cr(III)} + \lambda \mathrm{C_8H_{16}} \rightleftharpoons \text{complex II} \quad (4)$$

$$\text{complex II} + \chi \mathrm{Z} \longrightarrow \mathrm{Cr(III} + \mu) + \mu \mathrm{Z}^- \quad (5)$$

$$-\mathrm{d[Cr]}/dt = (k_1k_2/k_{-1})[\mathrm{Cr(III)}][t\text{-BuOOH}]^\nu + k_3[\mathrm{Cr(III)}][\mathrm{Cr(III} + \mu)] + (k_4k_5/k_{-4})[\mathrm{Cr(III)}][\mathrm{C_8H_{16}}]^\lambda[\mathrm{Z}]^\chi \quad (6)$$

(Z may be a reactive species such as a free radical or oxygen and Z^- represents radical and nonradical products)

The inconstancy of the superscripts and rate "constants" in the empirical expression $(\Delta[\mathrm{Cr}]/dt)_0 = k[\mathrm{Cr}]^a[t\text{-BuOOH}]^b[\text{1-octene}]^c$ are evident in Table III. Values of a >1 imply that the species [Cr(III + μ)] is not a steady-state intermediate but rather some complex function of [Cr(III)] and [*t*-BuOOH]. Values of b under the conditions described in Table II are 0.5 or less, implying that steps 1 and 2 of the above scheme are fast or that the complex I need not be fully formed to react (see section on *t*-butyl hydroperoxide decomposition). The Cr(III)–1-octene complex is significant only at low *t*-butyl hydroperoxide and high 1-octene concentrations.

In the absence of oxygen or *t*-butyl hydroperoxide, there is no detectable change in the uv spectrum of chromium(III) acetylacetonate solutions in 1-octene, although identical solutions absorb oxygen (see Table II). It has been reported[11] that, in diphenyl ether, chromium(III) acetylacetonate does not absorb oxygen at 100°. This may be a solvent effect,[7] since chromium(III) acetylacetonate solutions in 1-chlorooctane absorb oxygen at 100°.[12] Direct reaction between oxygen and chromium(III) acetylacetonate is negligible in the temperature range 0–60°. Because oxygen is absorbed in the presence of 1-octene even in the initial absence of *t*-butyl hydroperoxide in the temperature range 0–60°, a 1-octene–chromium(III) acetylacetonate complex is postulated. Metal–olefin complexes are well known.[13]

The activation energy for chromium(III) acetylacetonate disappearance at low *t*-butyl hydroperoxide concentration (<0.1 M) is greater (see Table IV) than for high *t*-butyl hydroperoxide concentrations. It is also observed that at low *t*-butyl hydroperoxide concentrations the activation energy plots for chromium(III) acetylacetonate disappearance are nonlinear. Such nonlinearity might result from temperature sensitivity to the concentration of complex I, eq 1, or to the variability in structure of complex I with temperature *and* *t*-butyl hydroperoxide concentration. At higher *t*-butyl hydroperoxide concentrations, for example, more ligands might be exchanged. The generally lower activation energies for higher *t*-butyl hydroperoxide concentrations may also result from a solvent effect in which greater polarity of the medium or increased hydrogen bonding facilitates electron transfer.[14] Slightly enhanced chromium(III) acetylacetonate disappearance rates are also observed in polar solvents and in the presence of some inhibitors.[7] The positive $\Delta S^\ddagger$ values are consistent with disordering of the highly compact structure of the acetylacetonate into structures of less restricted motion.

Oxidation states of chromium between III and VI have been frequently postulated, as have reactions of Cr(IV) and Cr(V) with Cr(III) to form Cr(VI).[15] Evidence for Cr(VI) formation in this work comes from the observation that an absorption peak appears at 438 mμ as the reaction proceeds. (Dichromate is

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(15) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1964, p 33 ff.

TABLE II
INITIAL RATES: DISAPPEARANCE OF *t*-BUTYL HYDROPEROXIDE;[a,b] DISAPPEARANCE OF CHROMIUM(III) ACETYLACETONATE;[a,b] OXYGEN ABSORPTION[b,c]

$[Cr(acac)_3]_0$, $\times 10^4$ *M*	$[t\text{-BuOOH}]_0$, *M*	$[1\text{-Octene}]_0$, *M*	Temp, °C	R_{Cr}[d]	R_P[d]	R_O[d]
4.00	0.094	2.56	−1.0[e]	0.0[f]	0.0[f]	2.03
4.00	0.76	0.64	−1.0	0.13	0.0025	n[g]
4.00	0.76	2.56	−1.0	0.31	0.0018	0.40
0.00	0.76	5.97	30		n	0.0[h]
0.762	0.00	2.56	30	0.0[i]		0.17
0.800	0.76	5.97	30	n	n	0.53
0.904	0.76	2.56	30	1.47	0.257	n
4.00	0.00	2.56	30	0.0[i]		0.34
4.00	0.00	4.50	30	0.0[i]		0.85
4.00	0.0045	2.56	30	0.39	0.0[j]	1.29
4.00	0.064	2.56	30	1.42	0.0002	n
4.00	0.094	1.27	30	n	n	2.09
4.00	0.094	2.56	30	n	0.003	2.31
4.00	0.183	0.128	30	n	n	0.90
4.00	0.76	0.00	30	2.52	1.77	0.0[k]
4.00	0.76	0.128	30	2.33	0.533	0.74
4.00	0.76	2.56	30	6.43	0.761	2.25
4.00	1.52	0.128	30	n	1.52	n
8.00	0.00	2.56	30	0.0[i]		0.57
8.00	0.76	2.56	30	13.4	0.967	n
12.00	0.094	2.56	30	n	n	5.85
0.574	0.76	2.56	40	4.27	0.565	1.15[l]
4.00	0.094	2.56	40	47.6	0.006	2.52
4.00	0.76	0.00	40	63.9	2.75	n
4.00	0.76	0.640	40	65.5	1.91	n
4.00	0.76	2.56	40	66.6	2.25	4.84
0.574	0.76	2.56	50	12.1	2.24	n
2.00	0.094	2.56	50	n	n	1.47
4.00	0.094	2.56	50	206	0.049	2.94
4.00	0.76	0.00	50	278	4.97	n
4.00	0.76	0.077	50	n	n	1.09
4.00	0.76	2.56	50	286	5.91	8.61
4.00	0.094	2.56	60	n	0.666	3.10
4.00	0.76	0.64	60	537	8.92	n
4.00	0.76	2.56	60	859	8.29	14.7
8.00	0.00	2.56	60	n		7.50

[a] *In vacuo*. [b] Reactions run in 1-chlorooctane. [c] Oxygen pressure = 1 atm. [d] $R_{Cr} = (-\Delta[Cr(acac)_3]/\Delta t)_0 \times 10^{-6}$ *M*/sec; $R_P = (-\Delta[t\text{-BuOOH}]/\Delta t)_0 \times 10^{-4}$ *M*/sec; $R_O = (-\Delta[O_2]/\Delta t)_0 \times 10^{-6}$ *M*/sec. [e] Autoxidations run at 2°. [f] No detectable change after 15 days. [g] n = no data. [h] No oxygen picked up for 5.5 hr. [i] No detectable change after 18 hr. [j] No detectable change after 71 hr. [k] Negligible oxygen pick-up (< 1 ml) after 7 hr. [l] $[Cr(acac)_3]_0 = 8.0 \times 10^{-5}$ *M*.

known to have an absorption at 440 mμ.)[16] It is also observed that as the reaction proceeds (in 1-chlorooctane in either the presence or absence of oxygen) the initially pale purple solution takes on a yellow-orange color suggestive of chromate or dichromate. In the presence of a few drops of methanol, the characteristic blue color of chromium peroxides[17] is developed instead of the yellow-orange color. A similar blue color is obtained by adding potassium dichromate to a solution of *t*-butyl hydroperoxide and 1-octene in methanol.

The Decomposition of *t*-Butyl Hydroperoxide.—Initial rates, empirical kinetic equations, and activation parameters for *t*-butyl hydroperoxide decomposition *in vacuo* are listed in Tables II, III, and IV.

The activation parameters in Table IV indicate a process consistent with O–O bond rupture at low *t*-butyl hydroperoxide concentrations. The entire effect of the presence of chromium(III) acetylacetonate upon the decomposition process is in the entropy term, implying that the chromium species serves as a favorable site for bond rupture. When *t*-butyl hydroperoxide is present in higher concentrations (>0.1 *M*), the activation enthalpy is *ca.* 20 kcal/mol, consistent with a chain process for decomposition in which some decomposition occurs at chromium sites and some by induced decomposition by radicals generated from the initiation process. Inhibitor studies also support chain decomposition of *t*-butyl hydroperoxide.[7]

For *t*-butyl hydroperoxide concentrations >0.1 *M*, chain decomposition in which most of the *t*-butyl hydroperoxide disappears in the propagation step is consistent with initiation by chromium(III) acetylacetonate disappearance. Assuming steady-state conditions

$$-d[t\text{-BuOOH}]/dt = k_p[t\text{-BuOOH}][R\cdot] \quad (7)$$

R· = *t*-BuO·, *t*-BuOO·, and octenyl radicals

$$-d[t\text{-BuOOH}]/dt \propto (k_p/k_t^{1/2})R_i^{1/2} \quad (8)$$

(16) H. H. Willard, L. L. Merritt, Jr., and J. A. Dean, "Instrumental Methods of Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 1963, p 133.

(17) T. Moeller, "Inorganic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1961, p 514.

TABLE III

EMPIRICAL RATE EQUATIONS

$[Cr]_0$,[a] $\times 10^4$ M	$[t$-BuOOH$]_0$, M	$[1$-Octene$]_0$, M	Temp, °C	$k \times 10^4$	a	b	c
		A. $\left(\frac{-\Delta[Cr]}{\Delta t}\right)_0 = k[Cr]_0^a[t\text{-BuOOH}]_0^b[1\text{-Octene}]_0^c$					
4.0–16.0	0.8	2.56	−1.0	0.0005	1.0	n[b]	n
4.0	0.8	0.6	30	0.067	n	n	0.0
0.8–8.0	0.005–0.8	0.6–2.6	30	0.072	1.0	0.52	1
0.6–4.0	0.1–0.8	0.6–2.6	40	0.282	1.4	0.13	0.0
0.6–4.0	0.1–0.8	0.6–2.6	50	1.12	1.7	0.13	0.0
		B. $\left(\frac{-\Delta[t\text{-BuOOH}]}{\Delta t}\right)_0 = k[Cr]_0^a[t\text{-BuOOH}]_0^b[1\text{-Octene}]_0^c$					
4.0	0.005–0.8	2.6	30	1.59	n	$1 < b < 4$	n
0.9–4.0	0.8–1.6	0.13–2.6	30	50.1	0.49	1.0	0.0
0.6–4.0	0.1–8.0	0–2.6	40	138	0.71	2.9	0.0
0.6–4.0	0.1–8.0	0–2.6	50	407	0.50	2.3	0.0
		C. $\left(\frac{-\Delta[O_2]}{\Delta t}\right)_0 = k[Cr]_0^a[t\text{-BuOOH}]_0^b[1\text{-Octene}]_0^c$					
4.0	0.09–0.8	2.6	2	6.03	n	−0.7	n
4.0–12.0	0.0004–0.02	0.13–4.5	30	40.1	0.85	0.49	0.23
4.0	0.8	0.07–2.6	30	146	n	n	0.93
0.8–8.0	0.1–0.8	2.6	30	41.3	1.1	0.0	0.26
4.0	0.1–4.5	0.13	30	22.5	n	−0.2	n
0.8–8.0	0.0	2.6–6.0	30	0.049	0.45		1.57
4.0	0.02–0.09	2.6	40	42.4	n	0.16	n
0.8–4.0	0.8	2.6	40	97.0	1.0	n	n
4.0	0.8	0.07–0.26	40	214	n	n	0.95
4.0	0.8	0.07–0.26	50	324	n	n	0.76
2.0–4.0	0.1–0.8	2.6	50	180	1.1	0.51	n
4.0	0.1–0.8	2.6	59	326	n	0.77	n

[a] Cr = Chromium(III) acetylacetonate. [b] n = no data.

TABLE IV

ACTIVATION PARAMETERS[a]

$[Cr]_0$,[b] $\times 10^4$ M	$[t$-BuOOH$]_0$, M	$[1$-Octene$]_0$, M	E_{act}, kcal/mol	$\Delta S^{\ddagger}$, cal/deg-mol	$\Delta H^{\ddagger}$, kcal/mol
		A. Disappearance of Cr[b,c]			
4.00	0.76	2.56	26.6 ± 3.5	3.32	26.0
4.00	0.093	2.56	(30–46)[d]	(41.8)[d]	(37.8)[d]
4.00	0.76	0.00	39.3 ± 2.8	45.2	38.7
4.00	0.76	0.64	29.1 ± 5.6	11.1	28.5
		B. Decomposition of t-BuOOH[c]			
4.00	0.76	2.56	19.9 ± 4.1	−5.72	19.3
4.00	0.093	2.56	41.7 ± 8.4	66.5	41.1
4.00	0.76	0.00	10.1 ± 1.7	−36.4	9.5
4.00	0.76	0.64	20.2 ± 4.0	−5.04	19.6
		C. Autoxidation of 1-Octene[e]			
4.00	0.76	2.56	12.1 ± 0.7	−31.8	11.5
4.00	0.093	2.56	1.3 ± 0.1	−67.8	0.66
4.00	0.76	0.256	7.66 ± 0.43	−44.2	7.05
4.00	0.76	0.077	7.5 ± 0.16	−44.2	6.93
4.00	0.00	2.56	18.2 ± 0.3	−11.4	17.3

[a] Temperature range = −1.0–60° for A and B and 2–59° for C. [b] Cr = Chromium(III) acetylacetonate. [c] *In vacuo*, 1-chlorooctane solvent. [d] Nonlinear Arrhenius plot. [e] 1-Chlorooctane solvent, oxygen pressure = 1 atm.

where k_t = termination rate constant and R_i = initiation rate = f([Cr], [t-BuOOH], [1-octene]), *e.g.*, eq 6.

$$E_{obsd} = E_p - 0.5\,E_t + 0.5\,E_i \qquad (9)$$

E_{obsd} = observed activation energy
E_p = activation energy for propagation, eq 7
E_t = activation energy for termination
E_i = activation energy for the initiation process

Calculated values of E_p, assuming that $E_t \cong 0$–2 kcal/mol[18] and E_i is identical with the activation energy for chromium(III) acetylacetonate disappearance give E_p = 6.6–7.6 kcal/mol, in good agreement with literature values of 7.0–7.5 kcal/mol.[19]

In the absence of olefin, the low activation energy for t-butyl hydroperoxide disappearance cannot be consistent with initiation rates from chromium(III) acetylacetonate disappearance unless an unusually large activation energy for termination is postulated. It is more likely that a much lower activation energy, 3–5 kcal/mol, for initiation perhaps involving ligand

(18) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 95.

(19) S. W. Benson, *J. Chem. Phys.*, **40**, 1007 (1960).

exchange[20] occurs before the experimentally observed chromium(III) acetylacetonate disappearance.

The effect of 1-octene on *t*-butyl hydroperoxide rates is generally consistent with the behavior of a weak inhibitor or chain transfer agent. At 30°, the chromium(III) acetylacetonate induced decomposition of *t*-butyl hydroperoxide in 1-chlorooctane is decreased by the presence of 1-octene. This effect is less as temperature rises. At 50°, 1-octene has a small accelerating effect upon the rate. This effect is understandable in terms of differences in activation energy for propagation and termination involving octenyl radicals. Termination is less sensitive, generally, to temperature than hydrogen abstraction processes,[21] and weak inhibitors (or retarders) at low temperatures may show opposite effects at increased temperatures. It has frequently been found that a series of solvent–hydroperoxide or olefin–hydroperoxide terms is required to describe the kinetic behavior of hydroperoxide decomposition data.[21-23] The accelerating effects of these interactions are undoubtedly sensitive to temperature.

Autoxidations.—Initial oxygen absorption rates, empirical kinetic equations, and activation parameters for the autoxidation of 1-octene with chromium(III) acetylacetonate and *t*-butyl hydroperoxide are listed in Tables II, III, and IV. The multiplicity of rate laws and activation parameters again implies a complex multistep process.

A clearly detectable autoxidation is discernible in the absence of *t*-butyl hydroperoxide which shows a markedly higher activation energy than autoxidation in the presence of *t*-butyl hydroperoxide. This process, which probably involves 1-octene–chromium(III) acetylacetonate interactions, would be more important at higher temperatures.

At low hydroperoxide concentration (<0.1 *M*), autoxidation has a very low activation energy and a very low entropy of activation consistent, in the usual processes, eq 9, with low activation energy initiation or high energy termination. Important propagation steps would be

$$C_5H_{11}\underset{\displaystyle O_2\cdot}{\underset{|}{C}}HCH{=}CH_2 + C_5H_{11}CH_2CH{=}CH_2 \longrightarrow C_5H_{11}CH{=}CH_2 + C_5H_{11}\underset{\displaystyle O_2H}{\underset{|}{C}}HCH{=}CH_2 \quad (10)$$

$$t\text{-BuO}\cdot \text{ or } t\text{-BuOO}\cdot + C_5H_{11}CH_2CH{=}CH_2 \longrightarrow t\text{-BuOH or } t\text{-BuOOH} + C_5H_{11}\underset{\displaystyle O_2H}{\underset{|}{C}}HCH{=}CH_2 \quad (11)$$

with significant chain transfer.[15]

$$C_5H_{11}\underset{\displaystyle O_2\cdot}{\underset{|}{C}}HCH{=}CH_2 + t\text{-BuOOH} \longrightarrow C_5H_{11}\underset{\displaystyle O_2H}{\underset{|}{C}}HCH{=}CH_2 + t\text{-BuOO}\cdot \quad (12)$$

If it is assumed that peroxy radical coupling reactions lead to termination ($E_t \cong 10$ kcal/mol)[24] and eq 10–12 are important propagation steps ($E_p \cong 7$ kcal/mol),[19] then the observed activation energy should be about half the activation energy of the initiation process (within *ca.* ± 5 kcal/mol). It may be seen from inspection of Table IV that at low *t*-butyl hydroperoxide concentrations (<0.1 *M*) the initiation process cannot be interpreted either in terms of *t*-butyl hydroperoxide decomposition or chromium(III) acetylacetonate disappearance, but must involve complex formation not kinetically detectable in our system. At *t*-butyl hydroperoxide concentrations >0.1 *M*, activation parameters for autoxidation are obtained consistent with chromium(III) acetylacetonate disappearance rates as a measure of the initiation process.

It is clear from the activation parameters and the complex kinetic equations that neither *t*-butyl hydroperoxide decompositions nor autoxidations in the presence of chromium(III) acetylacetonate obey the relatively simple schemes postulated for these types of reactions.[25-28] Both types of reactions are chain reactions, although the initiation processes do not correspond to chromium(III) acetylacetonate disappearance rates at low (<0.1 *M*) *t*-butyl hydroperoxide concentrations. Table V lists ratios $(\Delta[O_2]/\Delta[Cr])_0$ and $([\Delta[t\text{-BuOOH}]/\Delta[Cr])_0$ from initial rate data. These numbers represent chain lengths for *t*-butyl hydroperoxide concentrations >0.1 *M* and probably indicate a rough estimate of chain length for *t*-butyl hydroperoxide concentrations <0.1 *M*. It is observed that longer chains are achieved at lower initial chromium(III) acetylacetonate concentrations and lower temperatures.

TABLE V

OBSERVED RATE RATIOS OF OXYGEN ABSORPTION AND *t*-BUTYL HYDROPEROXIDE DISAPPEARANCE COMPARED WITH CHROMIUM(III) ACETYLACETONATE DISAPPEARANCE.

$[Cr(acac)_3]_0$, $\times 10^4$ *M*	$[t\text{-BuOOH}]_0$, *M*	$[1\text{-Octene}]_0$, *M*	Temp, °C	R_0/R_{Cr}	R_p/R_{Cr}
4.00	0.76	2.56	−1.0	1300	580
0.904	0.76	2.56	30	350	18000
4.00	0.0047	2.56	30	2700	0[a]
4.00	0.064	2.56	30	n[b]	14
4.00	0.094	2.56	30	1000	130
4.00	0.76	0.128	30	320	23000
4.00	0.76	0.640	30	600	n
4.00	0.76	2.56	30	350	12000
8.00	0.76	2.56	30	340	7200
0.574	0.76	2.56	40	190	13000
4.00	0.094	2.56	40	53	13
4.00	0.76	0.64	40	n	2900
4.00	0.76	2.56	40	73	3400
0.574	0.76	2.56	50	n	19000
4.00	0.094	2.56	50	14	24
4.00	0.76	0.64	50	n	1800
4.00	0.76	2.56	50	30	2100
4.00	0.76	0.64	60	n	1700
4.00	0.76	2.56	60	17	970

[a] No detectable *t*-BuOOH decomposition after 71 hr. However, the rate is probably not zero; a rate of 10^{-9} *M*/sec would be beyond the limits of detection but would result in a value of about one for the chain length. [b] n = no data.

(20) V. S. Matem'yanov and E. T. Denisov, *Zh. Fiz. Khim.*, **41** (3), 687 (1967); *Chem. Abstr.*, **67**, 63496v (1967).
(21) C. Walling and L. Heaton, *J. Amer. Chem. Soc.*, **87**, 48 (1965).
(22) A. V. Tobolsky and L. R. Matlack, *J. Polym. Sci.*, **55**, 49 (1961).
(23) N. Indictor and C. Linder, *ibid.*, *Part-A3*, 3668 (1965).
(24) J. R. Thomas, *J. Amer. Chem. Soc.*, **87**, 3935 (1965).
(25) Reference 19, pp 697 ff, 503 ff.
(26) R. B. Mesrobian and A. V. Tobolsky in "Autoxidation and Antioxidants," W. O. Lunberg, Ed., John Wiley & Sons, Inc., New York, N. Y., 1961, p 119.
(27) W. H. Richardson, *J. Amer. Chem. Soc.*, **87**, 247 1096 (1965); **88**, 975 (1966).
(28) R. Hiatt, *et al.*, *J. Org. Chem.*, **33**, 1416, 1421, 1428, 1430, 1436 (1968).

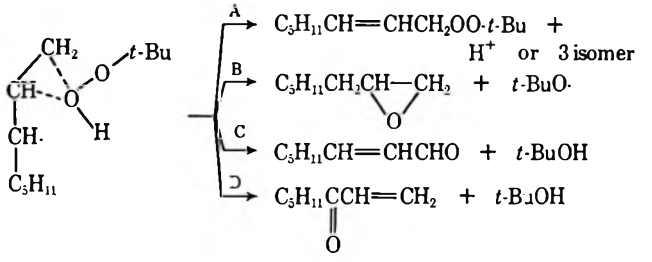
TABLE VI

AUTOXIDATION PRODUCTS

	mmol of product obtained/mmol of O_2 consumed under the following conditions			
	1-Hexene (384 mmol),[a] 8.92×10^{-3} *M* ABC initiator, 90°, 753 min, 40 psc O_2, 18.1 mmol of O_2 consumed	1-Octene (128 mmol), 9.75×10^{-3} *M* AIBN initiator, 70°, 945 min, 15 psc O_2, 1.61 mmol of O_2 consumed	1-Octene (6.4 *M*), 1.6×10^{-3} *M* Cr(acac)$_3$, 0.095 *M* *t*-BuOOH, 30°, 7 days, 15 psc O_2, 0.67 mmol of O_2 consumed	1-Octene (6.4 *M*), 1.6×10^{-3} *M* Cr(acac)$_3$, 0.76 *M* *t*-BuOOH, 30°, 1 day, 15 psc O_2, 2.85 mmol of O_2 consumed
Hydroperoxide[b]	0.258	0.225	...	...
Alcohol[b]	0.033	0.147	...	...
Ketone	0.042	0.138	0.644	0.752
Aldehyde	0.040	0.118	0.040	0.171
Epoxide	0.048	0.042	0.029	0.033
Residue	0.324			0.234
Peak II (Table I)			0.439	0.145

[a] Reference 8. [b] May be mixtures of isomers.

Products. Absence of Oxygen.—When *t*-butyl hydroperoxide, chromium(III) acetylacetonate, and 1-octene were allowed to react for 10 days at 30° in the absence of oxygen, *t*-butyl alcohol, 1,2-epoxyoctane, 2-octenal, 1-octen-3-one, and an unidentified substance of high molecular weight (*ca.* two C_8 units) were detected (peak I, Table I) gas chromatographically. The experiment was repeated with cuprous chloride instead of chromium(III) acetylacetonate for 5–6 hr at 60–70° according to the method of Kharasch and Fono,[10] and the reaction mixture was analyzed under the same gas chromatographic conditions as that from experiment using chromium(III) acetylacetonate. Only 2-octenal was common to both reaction mixtures. Kharasch and Fono suggest the intermediacy of a radical peroxide complex such as that shown. This complex is oxidized mainly to dialkyl peroxide (path A) in the presence of copper, but paths B, C, and D are available when chromium(III) acetylacetonate is



present, apparently to the exclusion of path A, implying that, if this reaction takes place at ligand sites, *t*-butyl hydroperoxide has a greater affinity for chromium than it does for the 1-octene or for the copper. No ketone peak was found in the presence of cuprous chloride, and no dialkyl peroxide peak was found in the presence of chromium(III) acetylacetonate. These experiments established that the chromium(III) acetylacetonate catalyzed reaction is not identical with the cuprous chloride catalyzed reaction.

Products. Presence of Oxygen.—When 1-octene is autoxidized in the presence of chromium(III) acetylacetonate and *t*-butyl hydroperoxide, the main products as determined by gas chromatography are *t*-butyl alcohol, 1-octen-3-one, 1,2-epoxyoctane, an unidentified substance (*ca.* two C_8 units, peak II, Table I), and residue (more than two C_8 units) and octenyl hydro peroxide (by iodometric titration).

Products of the autoxidation of 1-octene chromatographically observed at different initial *t*-butyl hydroperoxide concentrations at 30° are listed in Table VI side by side with product distributions obtained by Mayo, *et al.*,[8] from the azobiscyclohexane-1-carbonitrile initiated autoxidation of 1-hexene at 90° and in this laboratory from the azobisisobutyronitrile autoxidation of 1-octene at 65–70°. Mayo actually converted hydroperoxide formed to alcohol with triphenylphosphine and corrected the chromatographically obtained values.[8] In this laboratory, products were chromatographed directly. All peaks could be accounted for without assigning one to octenyl hydroperoxide. Under our chromatographic conditions, octenyl hydroperoxide was probably converted into ketone, alcohol, and aldehyde, in which case close correspondence is obtained between Mayo's data for 1-hexene and our data for 1-octene. The chromium(III) acetylacetonate–*t*-butyl hydroperoxide initiated runs differ in showing no alcohol and higher yields of 1-octen-3-one, arising partly from octenyl hydroperoxide decomposition and partly from the direct attack of *t*-butyl hydroperoxide upon 1-octene in the presence of chromium(III) acetylacetonate (see preceding section). The absence of alcohol may result from rapid oxidation by a chromium species.[15] When methanol was used as a solvent,[7] enough formaldehyde was produced to make the measured autoxidation rate appear to be negligible.

Registry No.—1-Octene, 111-66-0; *t*-butyl hydroperoxide, 75-91-2; chromium(III) acetylacetonate, 13681-82-8.

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Autoxidation of 1-Octene with *t*-Butyl Hydroperoxide and Chromium(III) Acetylacetonate. II. Solvent Effects and Free-Radical Inhibitors

N. INDICTOR, T. JOCHSBERGER,[1a] and D. KURNIT[1b]

Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn, New York 11210

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The effect of 18 organic solvents has been observed in the autoxidation of 1-octene initiated by *t*-butyl hydroperoxide and chromium(III) acetylacetonate at 30°. *t*-Butyl hydroperoxide decomposition rates were also measured *in vacuo* iodometrically and chromium(III) acetylacetonate disappearance rates were measured spectrophotometrically. *t*-Butyl hydroperoxide and chromium(III) acetylacetonate disappearance rates were relatively insensitive to solvent, but autoxidation rates indicated participation of the solvent in the autoxidation process. The inhibitor effects of phenols, amines, and nitrobenzene has also been observed upon the same reactions. Induction periods for autoxidation, stoichiometric factors for the inhibitors, and oxygen absorption rates during and after inhibition are reported. Initiation rates of autoxidation measured by chromium(III) acetylacetonate disappearance rates are in good agreement with initiation rates obtained from measurements of induction periods.

In the preceding paper[2] the kinetics of 1-octene autoxidation at 0–60° initiated by *t*-butyl hydroperoxide and chromium(III) acetylacetonate was investigated. Both chain autoxidation and chain *t*-butyl hydroperoxide decomposition were observed. In this paper the same type of experimental data are tabulated for runs at 30° in the presence of several organic solvents. The solvents tested showed very little effect upon chromium(III) acetylacetonate disappearance. Most solvents tested showed a small but measurable retarding effect upon *t*-butyl hydroperoxide decomposition *in vacuo* compared to decomposition in 1-chlorooctane. The autoxidation results showed somewhat more complex solvent dependence implying intimate participation of the solvent in the autoxidation process. Some solvents clearly were autoxidized by a chain process. Aromatic solvents not readily autoxidized by a chain process had a retarding effect upon autoxidation rates compared to autoxidations of 1-octene in 1-chlorooctane.

The effects of well-known free-radical inhibitors on these two chain processes is also presented. The inhibitor compounds studied were phenols, amines, and nitrobenzene.[3]

By using measured small quantities of inhibitors and observing induction periods, it is possible to determine stoichiometric factors for inhibitor molecules. The stoichiometric factor, n, is the number of radical chains stopped/molecule of inhibitor and is given by eq 1.[3,4]

$$n = Z/N \tag{1}$$

Z is the number of radicals produced during induction period and is equal to $R_i \times$ induction period; N is the number of molecules of inhibitor originally present and R_i is equal to the rate of production of radicals.

Alternatively it is possible, knowing the stoichiometric factor, to calculate R_i, the rate of the initiation process.

Stoichiometric factors of ~2 obtained for many phenols and anilines[3,4,5] apparently arise from the following termination steps.

$$\mathrm{ROO\cdot} + \mathrm{InH} \xrightarrow{k_{In}} \mathrm{ROOH} + \mathrm{In\cdot} \tag{2}$$

$$\mathrm{ROO\cdot} + \mathrm{In\cdot} \longrightarrow \text{inactive products} \tag{3}$$

Stoichiometric factors greater than 2[3,5,6] would be obtained if the "inactive products" had inhibitor properties or for polyfunctional inhibitors. Stoichiometric factors of less than 2[3,6,7] could be obtained if the species In· were stable (*e.g.*, if the inhibitor molecule were itself a free radical) or if competition between the inhibitor steps and the chain-propagating step[3] (4) is significant.

$$\mathrm{ROO\cdot} + \mathrm{RH} \xrightarrow{k_p} \mathrm{ROOH} + \mathrm{R\cdot} \tag{4}$$

Experimental Section

Chemicals.—Solvents and inhibitors were generally taken from freshly opened bottles and purified by standard procedures.[8]

Butylated hydroxyanisole (a mixture of 2- and 3-*t*-butyl-4-hydroxyanisole, Sigma Chemical Corporation) and DL-α-Tocopherol (Nutritional Biochemical Corporation) were taken from freshly opened bottles and used without purification.

Kinetics.—All kinetics runs were performed as previously described.[2,9] Oxygen absorption runs were permitted to run well past inhibition periods. In all autoxidation runs described, well-defined inhibition periods could be observed, but oxygen absorption rates after the inhibition period did not reach the rate obtained in uninhibited runs, implying that products of the reaction behaved as weak inhibitors or retarders, possibly in the manner of the aromatic solvents herein described.

Results and Discussion

A. Solvent Effects.—Table I sets forth initial chromium(III) acetylacetonate disappearance rates, *t*-butyl hydroperoxide decomposition rates *in vacuo*, and autoxidation rates at 30°.

Chromium(III) Acetylacetonate Disappearance Rates.—The data of Table I show less than a twofold change in chromium(III) acetylacetonate disappearance rates among the solvents listed. Although it has been shown that chromium(III) acetylacetonate disappearance rates are not always a measure of initiation rate,[2] the concentration of reactants chosen generally gave activation parameters[2] and inhibited autoxidation rates (see below) consistent with the chromium(III)

(1) (a) From the Ph.D. Thesis of T. J., City University of New York, 1968; (b) NSF undergraduate research participant.

(2) N. Indictor, T. Jochsberger, and D. Kurnit, *J. Org. Chem.*, 2855 (1969).

(3) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 430 ff.

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(7) See ref 3, p 432.

(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath & Co., Boston, Mass., 1957.

(9) N. Indictor and T. Jochsberger, *J. Org. Chem.*, **31**, 4271 (1966).

TABLE I

SOLVENT EFFECTS ON THE RATE OF AUTOXIDATION OF 1-OCTENE AND THE RATE OF *t*-BUTYL HYDROPEROXIDE AND CHROMIUM(III) ACETYLACETONATE DISAPPEARANCE[a] (30°)

Solvent	Solvent Concn,[b] *M*	$(-\Delta[O_2]/\Delta t)_0$ × 10^6 *M*/sec	$(-\Delta[t\text{-BuOOH}]/\Delta t)_0$ × 10^4 *M*/sec	$(-\Delta[Cr]/\Delta t)_0$ × 10^9 *M*/sec
1-Octene	5.97	3.12	n[e]	n
1-Chlorooctane[c]	6.75	0.0	1.77	n
1-Chlorooctane	3.06	2.25	0.76	6.46
n-Heptane	2.73	2.40	1.01	8.24
sym-Tetrachloroethane	3.81	2.08	0.68	n
Carbon tetrachloride	4.15	3.08	0.51	n
Benzene[d]	6.31	0.0	n	n
Benzene	4.51	n	0.91	7.22
Benzene	0.68	1.38	n	n
Benzene	1.36	0.95	n	n
Naphthalene	0.57	0.71	n	n
Naphthalene	0.37	n	0.30	n
Phenyl ether	3.28	0.82	n	n
Phenyl ether	2.52	n	0.31	n
Chlorobenzene	3.90	0.36	0.88	n
Cumene	2.88	n	0.32	7.61
Cumene	1.44	2.56	n	n
Tetralin	2.94	n	0.41	n
Tetralin	1.47	1.42	n	n
Pyridine	4.98	0.50	1.15	5.92
t-Butanol	5.56	0.23	n	n
t-Butanol	4.28	0.19	0.83	10.4
Ethanol	6.84	0.24	n	n
Methanol	9.96	0.0	0.56	8.85, 9.92[f]
Acetic acid	5.25	3.30	n	n
Acetic acid	7.00	n	0.27	9.00
Acetic acid	9.10	7.09	n	n
Ethyl acetate	3.07	0.71	n	n
Ethyl acetate	4.08	n	0.35	n
N,N-Dimethylformamide	4.96	n	0.66	8.00
N,N-Dimethylformamide	3.71	2.11	n	n
p-Dioxane	4.71	0.27	0.59	n

[a] *In vacuo*. [b] All runs cited contain 4.00×10^{-4} *M* $Cr(acac)_3$, 0.76 *M* *t*-BuOOH (except where noted), 2.56 *M* 1-octene (except in first two cases), and chlorooctane diluent. [c] No 1-octene present. [d] *t*-BuOOH concentration 0.37 *M*. [e] n = no data. [f] Oxygen not excluded from this run.

acetylacetonate disappearance rates as a measure of chain initiation rate. The insensitiveness of these data to solvents may be interpreted as an indication that the actual chain initiation rates of *t*-butyl hydroperoxide decomposition and 1-octene autoxidation are not sensitive to solvent change.

t-Butyl Hydroperoxide Decomposition Rates.—Table I shows decomposition rates of *t*-butyl hydroperoxide *in vacuo* at 30°. Relative to 1-chlorooctane, all solvents

$$t\text{-BuO}\cdot \text{ or } t\text{-BuOO}\cdot + RX \rightarrow R\cdot \qquad (5)$$

capable of chain-transfer reactions[10] (carbon tetrachloride, cumene, tetralin, methanol, acetic acid, ethyl acetate, dioxane, as well as phenyl ether and naphthalene) show a small but measurable rate retardation of the chromium(III) acetylacetonate catalyzed decomposition of *t*-butyl hydroperoxide.

Presumably the transferred solvent radical is less reactive at 30° toward *t*-butyl hydroperoxide than are *t*-butoxy or *t*-butylperoxy radicals. It has been shown in the preceding paper[2] that 1-octene itself behaves as a chain-transfer agent which retards decomposition at lower temperatures (0–40°) but induces decomposition at elevated temperatures (>50°). Benzene and chlorobenzene appear to have essentially no effect upon *t*-butyl hydroperoxide decomposition rates. The retarding effect of phenyl ether and naphthalene may be a viscosity effect[11] (these solutions were visibly more viscous than others), although this possibility was not demonstrated. The rate-enhancing effect of pyridine was probably from solvent attack producing nonradical product (pyridine N-oxide).[12] It is interesting that pyridine in catalytic quantities behaved as an inhibitor both for *t*-butyl hydroperoxide decomposition and 1-octene autoxidation in the presence of chromium(III) acetylacetonate. (See Table III.)

Many workers have demonstrated solvent–hydroperoxide interactions in describing hydroperoxide decomposition.[13–19] These interactions are probably temperature dependent and of greater significance at elevated temperatures (>60°). In this work, the solvent–hydroperoxide interactions are much less significant (only *ca.* seven-fold change in decomposition rate was noted among different solvents), either because the temperature does not favor them or because solvent–hydroperoxide interactions are insignificant compared

(10) See ref 3, p 150.

(11) A. Factor, C. Russell, and T. Traylor, *J. Amer. Chem. Soc.*, **87**, 3692 (1965).

(12) M. Sheng and J. Zajacek, *J. Org. Chem.*, **33**, 538 (1968).

(13) C. Walling and L. Heaton, *J. Amer. Chem. Soc.*, **87**, 38, 48 (1965).

(14) A. V. Tobolsky and L. R. Matlack, *J. Polym. Sci.*, **55**, 49 (1961).

(15) V. Stannett and R. Mesrobian, *J. Amer. Chem. Soc.*, **72**, 4125 (1950).

(16) N. Indictor and C. Linder, *J. Polym. Sci., Part A-1*, **5**, 1101 (1967).

(17) W. H. Richardson, *J. Amer. Chem. Soc.*, **88**, 975 (1966).

(18) R. Hiatt, *et al.*, *J. Org. Chem.*, **33**, 1416, 1421, 1428, 1430, 1436 (1968).

(19) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **45**, 793 (1967).

with chromium–hydroperoxide interactions. No correlations could be drawn between the effect of solvents on the uncatalyzed decomposition of *t*-butyl hydroperoxide at 73.5°[15] and this work at 30° in the presence of chromium(III) acetylacetonate.

Autoxidation Rates. Aromatic Solvents.—Although the effect of aromatic solvents on chromium(III) acetylacetonate disappearance rates and *t*-butyl hydroperoxide decomposition rates is small, a marked effect is noted on 1-octene autoxidation rates (Table I). Small amounts of benzene in 1-chlorooctane lower the oxygen absorption rate of 2.6 *M* solutions of 1-octene, and in 6 *M* benzene the system showed no oxygen absorption for 72 hr. Similar systems containing diphenyl ether, chlorobenzene, and naphthalene showed decreased rates compared to autoxidations of 1-octene in 1-chlorooctane solvent. Even compounds known to autoxidize readily, such as tetralin and cumene,[20] showed surprisingly low autoxidation rates when compared in separate runs (see Table II) to 1-octene. At

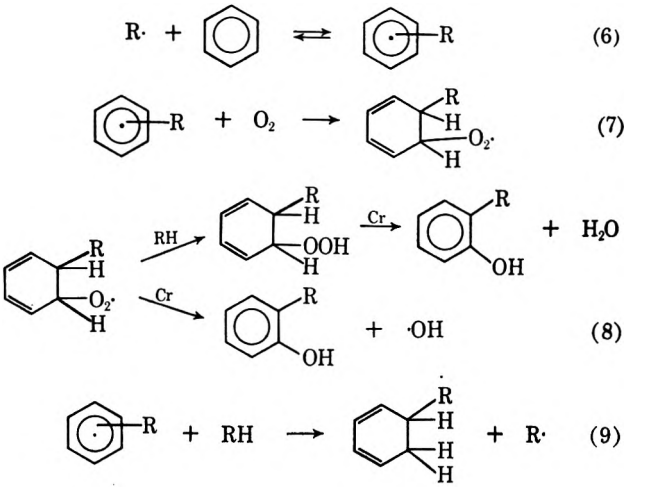
TABLE II
AUTOXIDATIONS WITH CHROMIUM(III) ACETYLACETONATE[a] AND *t*-BUTYL HYDROPEROXIDE[b] AT 30° IN 1-CHLOROOCTANE

Compd	Concn, *M*	$-(d[O_2]/dt)_0 \times 10^6$
1-Octene	1.27	2.09
Cumene	1.44	1.88
Tetralin	1.47	2.03
Acetic acid	12.20	2.08
N,N-Dimethylformamide	8.68	1.27

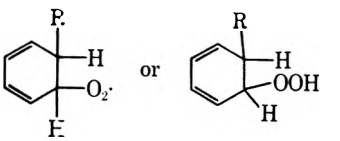
[a] 4.00×10^{-4}. [b] 0.74 *M*.

30° the photochemically induced autoxidations of tetralin, cumene, and 1-octene showed rate ratios of 37:24:1,[19] whereas all three substances autoxidized at about the same rates with chromium(III) acetylacetonate–*t*-butyl hydroperoxide initiator.

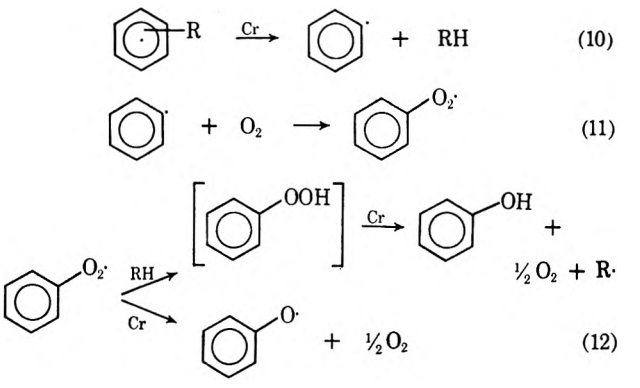
The absence of a large solvent effect in either the chromium(III) acetylacetonate or the *t*-butyl hydroperoxide disappearance rates suggests that the presence of oxygen is important for the retarding effect of aromatic compounds in the autoxidation. Since the presence of aromatic compounds does not apparently affect azo, peroxide, or photochemically initiated autoxidation in a major way,[20] chromium(III) acetylacetone must also be important for the observed retarding effect of aromatic compounds in autoxidation. Richardson[17] has observed a small effect of oxygen on the copper-induced decomposition of *t*-butyl hydroperoxide in chlorobenzene. Several workers[21,22] have demonstrated that aromatic compounds may be converted to phenolic compounds in the presence of peroxides and metals. Hiatt[18] has suggested that phenol may be formed in the AIBN-induced decomposition of *t*-butyl hydroperoxide in benzene in the presence of oxygen. Ingold has observed that some autoxidations are retarded when carried out in aromatic solvents and has suggested phenol formation as the cause.[23] A plausible sequence *via* a radical–aromatic complex[24] followed by attack by oxygen and a chromium species is shown in eq 6–9.



Under most autoxidation conditions[20] (at higher temperature), the dissociated form of the complex (eq 6) would probably be favored. Also at elevated temperatures, the decomposition of the peroxy species



would not necessarily produce radical chain inhibitors. Another path to phenol might involve hydrogen atom abstraction from the aromatic ring (normally a highly exothermic process)[25] facilitated by the presence of chromium (eq 10–12).



Autoxidation Rates. Oxygen-Containing Solvents.—Table I shows that, although the chromium(III) acetylacetonate and *t*-butyl hydroperoxide disappearance rates are only slightly sensitive to changes in solvent, the oxygen absorption rates in aliphatic alcohols, ethyl acetate, and dioxane are discernibly less than and those in acetic acid and N,N-dimethylformamide equal to or greater than oxygen absorption rates of 1-octene in chlorooctane. This effect is most simply interpreted as a coautoxidation of 1-octene and solvent. That these compounds absorb oxygen separately in

(20) See ref 3, Chapter 9.
(21) P. Kovacic and M. Kurz, *J. Amer. Chem. Soc.*, **88**, 2068 (1966); **89**, 4960 (1967).
(22) D. I. Metelitsa and E. T. Denisov, *Neftekhimiya*, **1** (1), 65 (1967); *Chem. Abstr.*, **67**, 21271n.
(23) K. U. Ingold, *Chem. Rev.*, **61**, 563 (1961).
(24) E. S. Huyser in "Advances in Free Radical Chemistry," G. H. Williams, Ed., Logos Press Ltd., London, 1965, p 77 ff.
(25) T. L. Cotrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworths and Co. Ltd, London, 1958.

the presence of chromium(III) acetylacetonate and *t*-butyl hydroperoxide at 30° has been verified in this laboratory[26] (see also Table II). The zero rate reported for methanol undoubtedly arises from gaseous autoxidation products. The 2,4-dinitrophenylhydrazone derivative of formaldehyde was isolated from the gaseous entrapment of a reaction mixture. The retarding effect of *t*-butyl alcohol is interesting in that it is the major product of *t*-butyl hydroperoxide decomposition in the presence of chromium(III) acetylacetonate.[23,27] It must play a role in lowering the autoxidation rate as the reaction proceeds. A falling off from the initial autoxidation rates is invariably observed in chromium(III) acetylacetonate–*t*-butyl hydroperoxide initiated systems. Other workers[11,28] have observed similar rate retardations in the presence of *t*-butyl alcohol.

Product studies of several of the chromium(III) acetylacetonate–*t*-butyl hydroperoxide initiated autoxidations of solvents mentioned in this study are under investigation in this laboratory.

B. Free-Radical Inhibitors.—Table III lists chromium(III) acetylacetonate disappearance rates at 30° in the presence of 2.56 *M* 1-octene, 0.74 *M* *t*-butyl hydroperoxide, and small measured amounts of several known free-radical inhibitors. The rates obtained varied by less than a factor of two compared with the rate measured in the absence of inhibitor. The implication of this result is that the inhibitor species have little or no effect upon the initiation process. A similar result was obtained for the effect of solvents on chromium(III) acetylacetonate disappearance rates (Table I).

Table III also lists *t*-butyl hydroperoxide decomposition rates *in vacuo* under the same reaction conditions used for chromium(III) acetylacetonate disappearance rates. The reduced rates in the presence of inhibitors may be interpreted as a suppression of induced or chain *t*-butyl hydroperoxide decomposition. Apparently the induced decomposition under the conditions described in Table III may account for as much as 90% of the *t*-butyl hydroperoxide decomposition.

Induction periods for the inhibited autoxidation of 1-octene initiated by chromium(III) acetylacetonate–*t*-butyl hydroperoxide at 30° are presented in Table III. Autoxidation rates measured during and after the induction periods are also presented in Table III.

Stoichiometric factors, n, are presented in Table III calculated from eq 1 using R_i values obtained from chromium(III) acetylacetonate disappearance rates. Stoichiometric factors of *ca.* 2 for the phenols and aniline inhibitors present a consistent picture in this system compared with other phenol and aniline inhibited autoxidations,[3-7] and imply an initiation step involving a one-electron change (eq 13).

$$\text{Cr(III)} + t\text{-BuOOH} \longrightarrow \text{Cr(IV)} + t\text{-BuO}\cdot + \text{OH}^- \quad (13)$$

Phenolic Inhibitors.—The usual manner of describing inhibitor efficiency is by evaluation of the inhibitor constant[3,4] k_p/nk_{In} from initial inhibited autoxidation

$$-\mathrm{d}[O_2]/\mathrm{d}t = R_i k_p[RH]/nk_{In}[InH] \quad (14)$$

rates; k_p and k_{In} are defined in eq 2 and 4. Values of k_p/nk_{In} are listed in Table III. Assuming a value of k_p *ca.* 1 l./mol sec[19] (from rotating sector experiments at 30°), the values of k_{In} for the attack by peroxy radical obtained from 1-octene on the phenolic inhibitors are *ca.* 10^3 l./mol sec. The hindered phenol, 2,6-dioctadecylphenol, gave k_{In} *ca.* one order of magnitude higher. The data are in reasonable agreement with other studies of inhibitor efficiencies based on tetralin and 9,10-dehydroanthracene[5,29] autoxidation and suggest that allylic peroxy radicals are only slightly less selective than benzylic peroxy radicals toward phenols.

The general equations given by Mahoney,[29] as elegantly demonstrated for phenol-inhibited autoxidations of 9,10-dehydroanthracene initiated by tetraphenylbutane, are the following where RH refers to substrate and AH refers to phenolic inhibitor.

$$\text{initiation} \xrightarrow{k_1}$$

$$\mathrm{R}\cdot + \mathrm{O_2} \xrightarrow{k_2} \mathrm{ROO}\cdot$$

$$\mathrm{ROO}\cdot + \mathrm{RH} \xrightarrow{k_3} \mathrm{ROOH} + \mathrm{R}\cdot$$

$$2\mathrm{ROO}\cdot \xrightarrow{k_4} \mathrm{O_2} + \text{termination}$$

$$\mathrm{ROO}\cdot + \mathrm{AH} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \mathrm{ROOH} + \mathrm{A}\cdot$$

$$\mathrm{A}\cdot + \mathrm{ROO}\cdot \xrightarrow{k_6} \text{inert products}$$

$$2\mathrm{A}\cdot \xrightarrow{k_7} \text{inert products}$$

$$<\mathrm{A}\cdot + \mathrm{RH} \xrightarrow{k_8} \mathrm{AH} + \mathrm{R}\cdot$$

When a second weaker inhibitor is present, such as a hindered phenol, the following additional steps were postulated[29] where BH refers to the weaker inhibitor.

$$\mathrm{A}\cdot + \mathrm{BH} \underset{k_{-9}}{\overset{k_9}{\rightleftharpoons}} \mathrm{AH} + \mathrm{B}\cdot$$

$$\mathrm{ROO}\cdot + \mathrm{BH} \xrightarrow{k_5'} \mathrm{ROOH} + \mathrm{B}\cdot$$

$$\mathrm{A}\cdot + \mathrm{B}\cdot \xrightarrow{k_{10}} \text{inert products}$$

$$\mathrm{ROO}\cdot + \mathrm{B}\cdot \xrightarrow{k_{11}} \text{inert products}$$

Mahoney simplified these equations[29] by pointing out two kinetically distinguishable situations based on the relative importance of steps 3 and 5.[30] For $k_5[AH]/k_3[RH] < 1$, eq 15 applies where $q = 1$ if termination

$$-\mathrm{d}[O_2]/\mathrm{d}t = R_i k_3[RH]/\{qk_5[AH] + qk_5'[BH]\} \quad (15)$$

is by step 10; q = 2 if termination is by step 11. For $k_5[AH]/k_3[RH] > 1$, eq 16 applies.

$$-\mathrm{d}[O_2]/\mathrm{d}t = (k_3/k_7^2)[RH]R_i^{1/2}[1 + \{k_9k_{10}[BH]/k_7k_{-9}[AH]\}]^{-1/2} \quad (16)$$

The chromium(III) acetylacetonate–*t*-butyl hydroperoxide initiated autoxidation of 1-octene inhibited by phenol may be regarded as analogous to the doubly inhibited system described by Mahoney in which the weakly inhibiting substance, BH, is the initially present *t*-butyl hydroperoxide. That eq 16 may obtain for phenol is indicated by an increased initial autoxidation rate at higher phenol concentration.

(26) Unpublished data, D. Miller, T. Jochsberger, and N. Indictor.
(27) N. Indictor and W. Brill, *J. Org. Chem.*, **30**, 2074 (1935).
(28) H. Berger and A. Bickel, *Trans. Faraday Soc.*, **57**, 1325 (1961).
(29) L. R. Mahoney, *J. Amer. Chem. Soc.*, **89**, 1895 (1967); **89**, 5619 (1967); **87**, 1089 (1965).
(30) These equations are slightly modified to account for the absence of a step in the initiation process which absorbs oxygen.

TABLE III

THE EFFECT OF FREE-RADICAL INHIBITORS ON THE RATE OF AUTOXIDATION[a] OF 1-OCTENE AND THE RATE OF DISAPPEARANCE[b] OF CHROMIUM(III) ACETYLACETONATE AND *t*-BUTYL HYDROPEROXIDE (30° IN 1-CHLOROOCTANE)

Inhibitor	Inhibitor concn, $M \times 10^4$	Induction period,[c] sec $\times 10^{-3}$	R_{Oi}[d]	R_O[e]	n[f]	$k_p/nk_{In} \times 10^4$	R_{Cr}[g]	R_P[h]
Nitrobenzene	1.63	5.2	0.165	1.08	0.77	4.4	2.43	5.89
Aniline	1.08	8.5	0.500	1.94	2.14	7.8	2.72	4.03
Ethylenediamine	1.83	3.0	0.130	0.851	0.34	4.5	2.06	7.10
Pyridine	2.03	4.0	0.073	2.11	0.28	4.0	1.43	5.21
α-Tocopherol	1.12	6.8	0.500	1.85	1.65	8.0	2.72	2.07
BHA[i]	1.28	8.3	0.408	1.59	2.32	5.7	3.58	4.24
DOP[j]	0.75	5.0	0.113	1.22	2.86	0.8	4.29	8.95
Phenol	0.44	3.5	0.114	1.01	2.99	5.3	3.72	1.59
Phenol	1.74	8.7	0.491	1.52	2.00	8.3	4.00	2.26
None	...	...	9.00[k]	2.44[l]	...	...	2.68	13.7

[a] Oxygen pressure = 1 atm, [1-octene] = 2.56 M, [Cr(acac)$_3$] = 1.6×10^{-3} M, [*t*-BuOOH] = 0.76 M. [b] *In vacuo*, [1-octene] = 2.56 M, [Cr(acac)$_3$] = 1.6×10^{-3} M, [*t*-BuOOH] = 0.76 M. [c] For autoxidation. [d] Rate of oxygen uptake during induction period $\times 10^6$ M/sec. [e] Rate of oxygen uptake after induction period $\times 10^6$ M/sec. [f] Stoichiometric factors. [g] R_{Cr} = rate of Cr(acac)$_3$ disappearance $\times 10^8$ M/sec. [h] R_P = rate of *t*-BuOOH disappearance $\times 10^5$ M/sec. [i] Mixture of 2- and 3-*t*-butyl-4-hydroxyanisole. [j] 2,6-Di-octadecylphenol. [k] Rate for first 1000 sec. [l] Rate after 5000 sec.

Additional reactions which undoubtedly further complicate the kinetics of our system would include

$$t\text{-BuOO}\cdot + \text{RH} \xrightarrow{k_5'} t\text{-BuOOH} + \text{R}\cdot$$

$$t\text{-BuOO}\cdot + \text{ROOH} \xrightarrow{k_{-5}'} t\text{-BuOOH} + \text{RO}_2\cdot$$

It is clear from the data of Table III that inhibitor is involved in the *t*-butyl hydroperoxide decomposition chains, but it is also clear from the stoichiometric factors in Table III that the effectiveness of the phenols in autoxidation inhibition is not reduced by the simultaneous involvement in *t*-butyl hydroperoxide decomposition. The implication of this observation is that propagation steps in peroxide decomposition in this system lead to autoxidation.

Nitrogen-Containing Compounds.—Inhibition of free-radical reactions by amines is well known.[3,4] The mechanism for inhibition by primary and secondary amines almost certainly involves radical abstraction of the N hydrogen.[3,4] The complexing of amines with chromium species is a well-established phenomenon.[31] In the present work it was noted that aniline, ethylenediamine, and pyridine inhibit both autoxidation and *t*-butyl hydroperoxide decomposition chains. Almost no effect is observed on the rate of chromium(III) acetylacetonate disappearance, implying that ligand exchange (if any) at low amine concentrations does not affect the initiation process.

A stoichiometric factor of *ca.* 2 was obtained for aniline, similar to phenols, but pyridine and ethylenediamine gave values less than 0.5, typical of the behavior of weak inhibitors or chain-transfer agents.[3]

Although pyridine inhibits *t*-butyl hydroperoxide decomposition at low concentrations (*ca.* 10^{-4} M) when it is used as a solvent (*ca.* 5 M), it actually enhanced the *t*-butyl hydroperoxide decomposition rate (see Table I). Sheng and Zajacek have recently shown that pyridine reacts slowly with *t*-butyl hydroperoxide in the presence of chromium(III) acetylacetonate (and other metal acetylacetonates) to form pyridine N-oxide. At low pyridine concentrations, this reaction is apparently insignificant.

It has been observed that nitrobenzene acts as an inhibitor toward both the *t*-butyl hydroperoxide decomposition and the autoxidation chains. Nitro compounds have been shown to be effective inhibitors in free-radical polymerizations,[7] but not in cumene or dihydroanthracene[5,29] autoxidations. We should like to suggest that nitro compounds may react with alkoxy radicals but may be inert toward alkyl peroxy radicals and, to the extent that an autoxidizing system contains alkoxy radicals, nitrobenzene will behave as an inhibitor.

Registry No.—Chromium(III) acetylacetonate, 13681-82-8; 1-octene, 111-66-0; *t*-butyl hydroperoxide, 75-91-2.

Acknowledgment.—Equipment grants from the City University of New York and NSFURP support are gratefully acknowledged.

(31) J. Kleinberg, Wm. J. Argersinger, Jr., and E. Groswold, "Inorganic Chemistry," D. C. Heath & Co., Boston, Mass., 1960, p 526.

Unsaturated Heterocyclic Systems. LII.[1] A General Synthetic Entry to Derivatives of 1H-Azepine

LEO A. PAQUETTE, DONALD E. KUHLA,[2a] JAMES H. BARRETT, AND ROBERT J. HALUSKA[2b]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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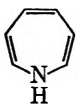
A general synthesis of 1H-azepines has been realized, which consists in the electrophilic addition of iodine isocyanate to easily accessible 1,4-dihydrobenzene derivatives. Cyclization of the resulting iodoisocyanates or their derived carbamates with various bases gives rise to unsaturated aziridines which can be brominated–dehydrobrominated to produce the desired 1H-azepines. This preparative route has been found to be versatile and to allow the ready introduction of alkyl groups on the central ring as well as a variety of substituents on nitrogen. The effect of annelation at the 2,7 positions of a 1H-azepine has been studied. The presence of a tetramethylene bridge is not sufficient to constrain the molecule into the tautomeric azanorcaradiene form; however, a trimethylene bridge serves well in this capacity. The various spectral properties of these cyclic 8π-electron heterocycles are correlated. The preparation of iron carbonyl complexes of these azepines and their fluxional nmr behavior are described.

Hückel molecular orbital calculations predict that 1H-azepine (1) will exhibit marked polyene character.[3]

The absence of a driving force for delocalization in this $4n-\pi$ system suggests decreased π-electron stability relative to open-chain congeners. This antiaromaticity[4] in 1H-azepines will be of importance only if the molecule is planar. Recent X-ray studies of the N-*p*-bromobenzenesulfonyl derivative of **1** have confirmed that the molecule clearly exists in a boat conformation with substantial sp^2 character for the nitrogen atom.[5]



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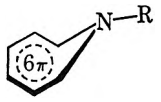
There remains the question of the precise structural makeup and conformation of 1H-azepines as the transition states demanded by their chemical reactions are approached. For example, the azahomoaromatic formulation **2** or the tautomeric azanorcaradiene form **3**[6] can be considered.



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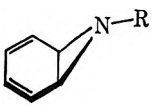

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We have explored in some detail a number of ground- and excited-state properties of these interesting molecules, and in the present paper, we describe a versatile and generally applicable synthesis of 1H-azepines.[7] Subsequent papers are concerned with their thermochemical behavior,[8] selective photoisomerization,[9] and certain cycloadditive transformations.[10]

Although 1H-azepine (1) remains unknown, its N-carbethoxy derivative was first prepared in the early 1960s by photolysis[11,12] or pyrolysis[13] of ethyl azidoformate in benzene solution. This ring enlargement is formulated as proceeding *via* an aziridinobenzene intermediate, and the reactive intermediate is now recognized to be singlet carbethoxynitrene.[14] Although this reaction has served well for the synthesis of unsubstituted 1H-azepines, the over-all process suffers from two serious drawbacks. With substituted aromatics such as toluene, bromobenzene, and anisole, a mixture of isomeric 1H-azepines is formed which, in general, defies preparative scale vpc separation.[15] Further, although N-carbalkoxy and N-cyano nitrenes[16] do provide useful yields of the respective azepines upon reaction with benzene, other nitrenes are not effective in this regard.[17] In view of these serious limitations and because of the need in this study for a variety of specifically substituted 1H-azepines, our efforts were concentrated on a few new synthesis of 1H-azepines which would allow for the positionally selective introduction of one or more substituents at the three different ring positions and functional groups other than carbalkoxy and cyano at the nitrogen center.

The synthetic scheme began with the monoaddition of iodine isocyanate[18-20] to 1,4-dihydrobenzene derivatives, which are readily available by means of the Birch reduction of appropriate aromatic compounds. For

(1) For previous paper in this series, see L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Amer. Chem. Soc.*, **91**, 3616 (1969).

(2) (a) National Institutes of Health Predoctoral Fellow, 1965–1968; (b) National Institutes of Health Predoctoral Fellow, 1966–present.

(3) R. W. Schmid, *Helv. Chim. Acta*, **45**, 1982 (1962).

(4) R. Breslow, J. Brown, and J. Gajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967).

(5) I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Barrett, and R. J. Haluska, *ibid.*, **90**, 5023 (1968).

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(7) A preliminary account of a portion of this work has appeared: L. A. Paquette and D. E. Kuhla, *Tetrahedron Lett.*, 4517 (1967).

(8) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.*, **34**, 2879 (1969).

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(12) (a) W. Lwowski, T. J. Maricich, and T. W. Mattingly, Jr., *J. Amer. Chem. Soc.*, **85**, 1200 (1963); (b) W. Lwowski and T. J. Maricich, *ibid.*, **87**, 3630 (1965).

(13) R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964).

(14) W. Lwowski and R. L. Johnson, *Tetrahedron Lett.*, 891 (1967).

(15) (a) L. A. Paquette and J. H. Barrett, unpublished observations; (b) K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Lett.*, 1733 (1964); (c) J. E. Baldwin and R. A. Smith, *J. Amer. Chem. Soc.*, **87**, 4819 (1965); (d) I. C. Paul, J. E. Baldwin, and R. A. Smith, *ibid.*, **88**, 3653 (1966); (e) R. A. Smith, J. E. Baldwin, and I. C. Paul, *J. Chem. Soc., B*, 112 (1967).

(16) F. D. Marsh and H. E. Simmons, *J. Amer. Chem. Soc.*, **87**, 3529 (1965).

(17) (a) R. A. Abramovitch, J. Roy, and V. Uma, *Can. J. Chem.*, **43**, 3407 (1965); (b) See, however, R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968).

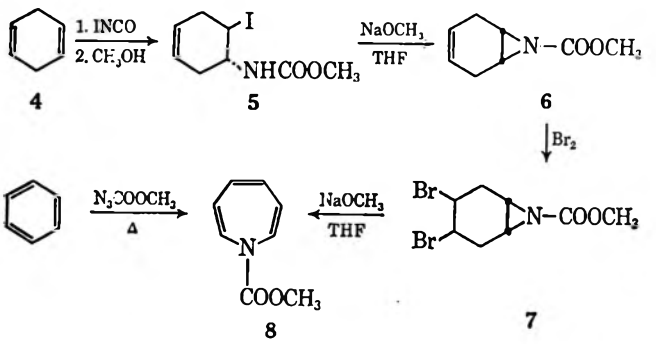
(18) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967), and earlier papers in this series.

(19) (a) C. G. Gebelein and D. Swern, *ibid.*, **33**, 2758 (1968); (b) B. E. Grimwood and D. Swern, *ibid.*, **32**, 3665 (1967); and previous papers from this laboratory.

(20) (a) G. Drefahl and K. Ponsold, *J. Prakt. Chem.*, **23**, 136 (1964); (b) R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 244 (1961); (c) G. Drefahl and K. Ponsold, *Chem. Ber.*, **93**, 519 (1960).

example, treatment of 1,4-dihydrobenzene (**4**) with this pseudohalogen, and finally with refluxing methanol, produced the crystalline *trans*-iodocarbamate **5** in 54% yield (Scheme I). Cyclization of **5** with powdered so-

SCHEME I

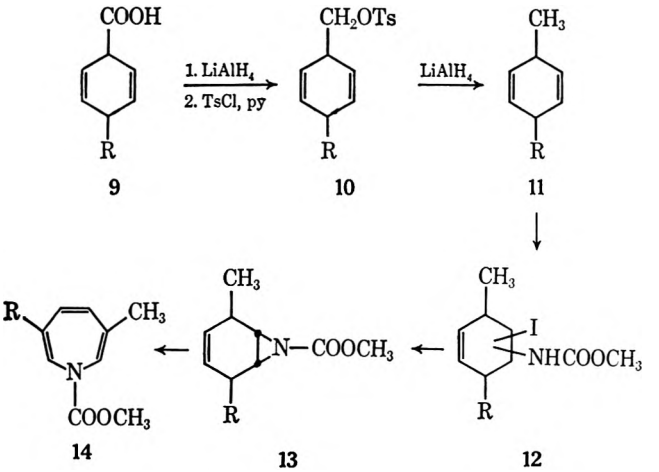


4 5 6 8 7

dium methoxide in dry tetrahydrofuran afforded aziridine **6**. Bromination of **6** in methylene chloride solution at −70° and exposure of the crude dibromide (**7**) thus formed to powdered methoxide in refluxing tetrahydrofuran solution for 2 hr led to N-carbomethoxyazepine (**8**). The structure of **8** followed from its spectral parameters and was confirmed by independent synthesis from benzene and methyl azidoformate.

1,4-Dihydrotoluene (**11a**) and 1,4-dihydro-*p*-xylene (**11b**) were accessible by virtue of the directing capability of a carboxyl group on the course of alkali metal–ammonia reductions.[21,22] Thus, 1,4-dihydrobenzoic acid (**9a**) and 1,4-dihydro-*p*-toluic acid (**9b**) were converted using the method of Nelson,[23] into the desired hydrocarbons (Scheme II). Sequential addition of

SCHEME II

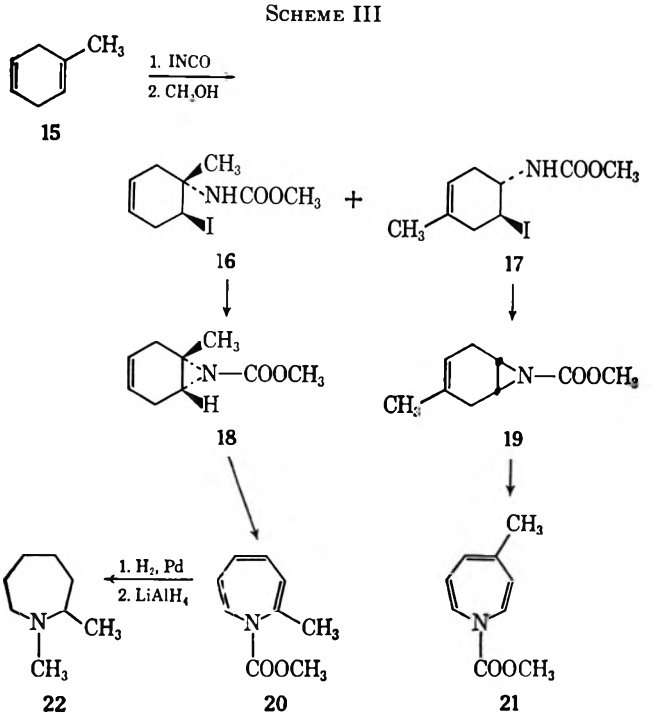


a series: R = H; b series: R = CH_3

iodine isocyanate and methanol to **11a** and **11b** gave rise to iodocarbamates **12a** (substitution pattern unknown) and **12b**, which, after cyclization, bromination, and dehydrobromination, were transformed into 1-carbomethoxy-3-methylazepine (**14a**) and 1-carbomethoxy-3,6-dimethylazepine (**14b**), respectively.

The effect of alkyl substitution on the vinyl carbons of the 1,4-cyclohexadiene structure was next considdered. Exposure of a tetrahydrofuran solution of 2,5-dihydrotoluene (**15**) to iodine isocyanate under the standard heterogeneous conditions (silver cyanate and iodine), with subsequent methanolysis, resulted in the formation of a mixture of crystalline carbamates **16** and **17** in yields of 54% and 10%, respectively (Scheme III). The predominance of **16** over **17** was expected

SCHEME III



from the stabilities of the two possible iodonium ions. It has been shown that variously substituted olefins react with iodine isocyanate at significantly differing rates.[19,24] A typical relative reactivity order is 2,3-dimethyl-2-butene, 38; 2-methyl-1-pentene, 12.5; *trans*-3-hexene, 5.7; cyclohexene, 1.0; and 1-hexene, 0.5—in good agreement with the normal electrophilic reactivity patterns exhibited by such hydrocarbons. As will soon become evident, however, the reactivity of iodine isocyanate is markedly affected by steric influences.

The iodocarbamate mixture was separated by chromatography. The availability of **16** and **17** on a preparative scale permitted independent transformation of each urethane to the 2-methyl (**20**) and 4-methyl (**21**) derivatives of 1-carbomethoxyazepine, respectively. As in the previous examples, the azepines were isolated free of contamination by positional isomers. Hydrogenation of **20** followed by reduction with lithium aluminum hydride gave 2,N-dimethylhexamethylenimine (**22**), confirming the gross structure of the substance.

A similar reaction of 2,3-dimethyl-1,4-dihydrobenzene (**23**) gave an oil, from which two compounds were isolated after column chromatography. The first product, isolated in 10% yield, was the iodocarbamate **24**. This colorless solid showed infrared absorption at 3425

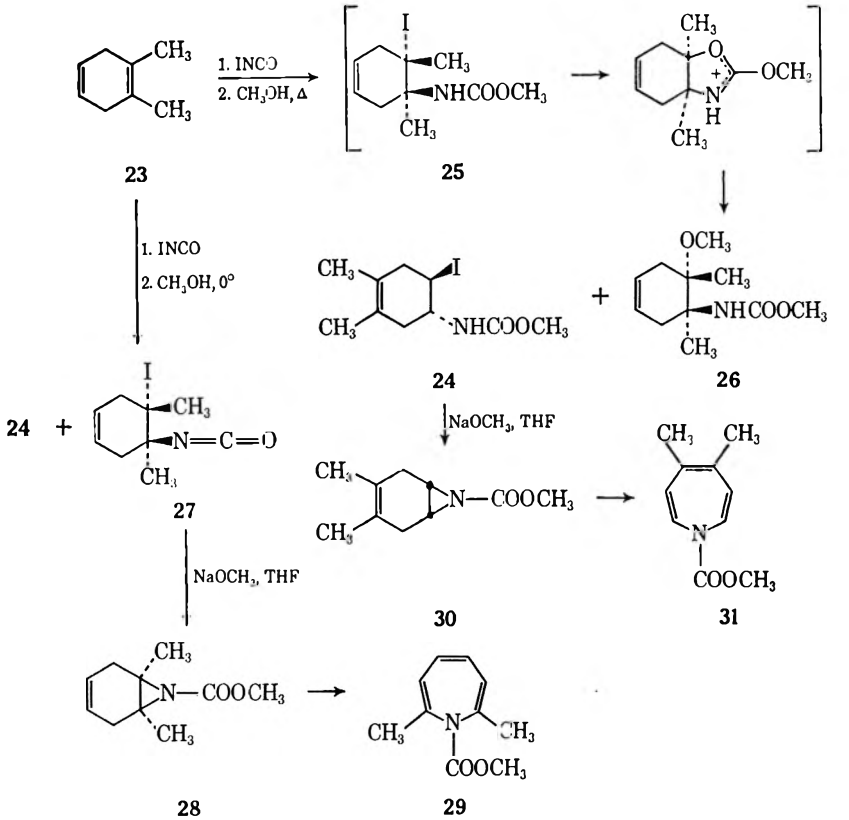
(21) Products derived from benzene derivatives bearing electron-donating substituents are 1-substituted 2,5-dihydrobenzenes, while those derived from aromatics having electron-withdrawing substituents are 1-substituted 1,4-dihydrobenzenes: (a) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 64–71; (b) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); (c) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958).

(22) M. E. Kuehne and B. F. Lambert, *Org. Syn.*, **43**, 22 (1963).

(23) N. A. Nelson, J. H. Fassnacht, and J. U. Piper, *J. Amer. Chem. Soc.*, **83**, 206 (1961).

(24) C. G. Gebelein and D. Swern, *Chem. Ind.* (London), 1462 (1965).

SCHEME IV



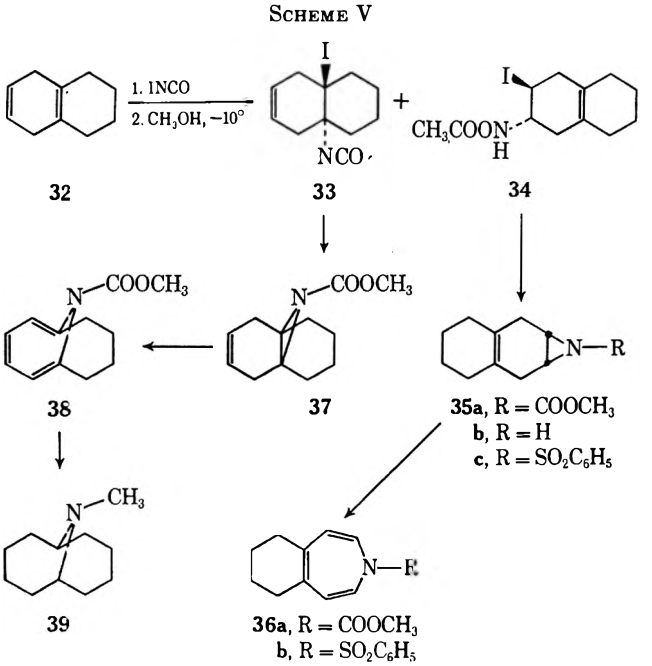
and 1725 cm^{-1} and an nmr spectrum fully compatible with the proposed structure. The major product (39% yield), a colorless oil, was shown by nmr to be **26**. The *trans* disposition of the urethan and methoxyl substituents has been assigned on the basis of the earlier observations that *trans*-2-halo-N-acylamines are converted to *cis*-oxazolines upon gentle heating[25] and that *trans*-β-halocarbamates afford *cis*-2-oxazolidones when pyrolyzed at 120–200°.[18,26] Thus, the initially produced *trans*-iodocarbamate **25** is presumably solvolyzed with anchimeric assistance from the carbamate group and subsequent backside attack of methanol at that site (Scheme IV).

The formation of **26** could be completely suppressed by treatment of the mixture of intermediate iodoisocyanates with methanol at 0°, which led to a 10% yield of **24** and a 63% yield of a pungent, waxy solid shown to be **27**. Clearly, under these reaction conditions, the less hindered isocyanate remains subject to the addition of methanol, whereas the isomeric tertiary isocyanate is virtually unreactive. Also, since the isocyanate function is a poor neighboring group, the proximate iodo substituent in **27** does not undergo assisted solvolysis.

When treated with 1 equiv of powdered sodium methoxide in tetrahydrofuran solution, **27** was converted quantitatively in a vigorously exothermic reaction to the carbomethoxy aziridine **28**. Bromination–dehydrobromination of **28** gave the 2,7-dimethyl-substituted azepine **29** in quantitative yield. The further transformation of **24** in the standard manner afforded the isomeric 4,5-dimethyl congener **31** without difficulty.

In view of these promising results, we turned our efforts to the synthesis of annelated 1H-azepine derivatives. As in the case of **23**, reaction of 1,4-dihydrotetralin (**32**) with ethereal iodine isocyanate and then methanol at −10° produced a mixture of iodoisocyanate **33** and iodocarbamate **34** (Scheme V). In contrast to the previous example, however, the two addition compounds were produced in yields of 16% and 69%, respectively. Thus, although the substitution patterns of the double bonds in **23** and **32** are virtually identical, the usual kinetically favored addition of the pseudohalogen to the more highly substituted π bond

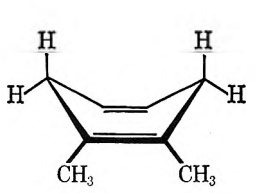
SCHEME V



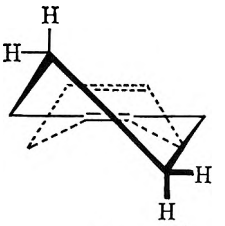
(25) S. Winstein and R. Boschan, *J. Amer. Chem. Soc.*, **72**, 4669 (1950).
(26) E. Katchalski and D. B. Ishai, *J. Org. Chem.*, **15**, 1067 (1950).

(seen, for example, in **23**) is disfavored in **32** by a factor greater than 10.

The wide divergence in reactivity is a result of the differing steric environments of the tetrasubstituted olefin linkages. In the case of **23**, the molecule can be considered to be nearly flat[27] with some small deviation of the ring into a boat conformation (models of molecules such as **23c** suggest a very small energy barrier to boat–boat interconversion).[28] Steric inhibition to the approach of the bulky iodonium ion is expected to be minimal. By comparison, the tetramethylene bridge in **32** must adopt a half-chair conformation,[29] with the result that the π bond is effectively shielded on both sides (see **32c**). Support for these conclusions comes



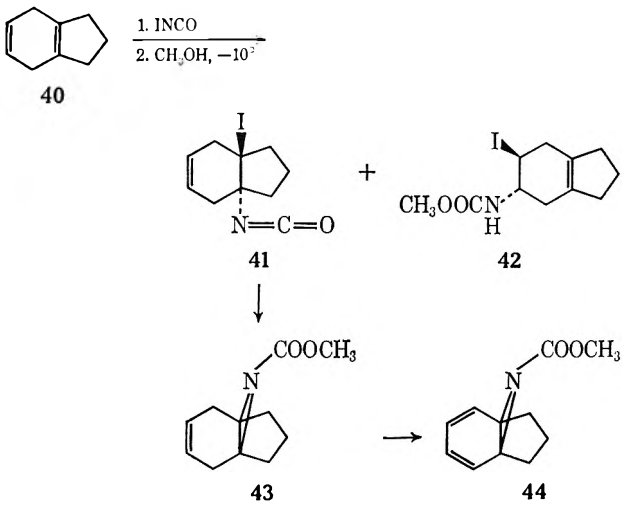
23c



32c

from a study of the reaction of 1,4-dihydroindane (**40**) with iodine isocyanate. Dreiding models of **40** indicate an almost planar conformation with little, if any, steric hindrance. Indeed, in this example the normal reactivity pattern does reemerge, with 32% iodoisocyanate **41** and 7% iodocarbamate **42** being produced (Scheme VI).

SCHEME VI

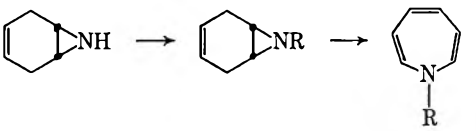


When iodoisocyanate **33** was subjected to similar methoxide treatment, aziridine **37** was isolated in excellent (92%) yield. As in the previous example, **37** was found to be uncontaminated with other possible by-products. By sequential treatment of **37** with bromine and sodium methoxide, there was produced a colorless solid (**38**) which was found to be uniform and to exist solely as the 1H-azepine tautomer. The structure of **38** was assigned on the basis of ultraviolet and nmr spectroscopy and by a three-step conversion to the known 11-methyl-11-azabicyclo-[4.4.1]undecane (**39**).[30,31]

The effect of diminishing the extent of annelation in azepine **38** from four to three methylene units was realized with the preparation of **44**, which exists as the aziridine tautomer (see above). This substance is of particular interest because it represents the only azanorcaradiene known to the present time, and for the fact that **44** displays a chemistry which differs appreciably from that of the closely related 1H-azepines.[8b,10] The result of bridging the azepine ring at the 2 and 7 positions with a methylene chain having a sufficiently small number of members is therefore to force the formation of an iminobenzene (**44**). This result parallels the earlier observations recorded for the corresponding bridged norcaradiene,[32] benzene oxide,[33] and 7-azabicyclo[4.2.0]octa-2,4,7-triene congeners.[34] In contrast, although azepine **38** is appreciably strained, the azanorcaradiene tautomer cannot be detected spectroscopically (nmr) over a wide temperature range.[35] This property is shared by the related cycloheptatriene analog,[32] but is at variance with the characteristics of the oxygen[33] and –N=C(OR)– bridged compounds.[34]

The azepine obtained from iodocarbamate **34** proved to be a heavy viscous oil which was not satisfactorily purified by distillation and chromatography (column and vapor phase). Saponification and decarboxylation of **35a** did, however, give rise to aziridine **35b**, which was conveniently transformed to the crystalline N-benzenesulfonylazepine **36b**.

The method of nitrogen functionalization has proven to be quite versatile and has permitted the synthesis of such 1H-azepines as **47a–47d**. With the successful



45 **46** **47**

a, R = SO_2CH_3; **b**, R = $SO_2C_6H_5$
c, R = p-$SO_2C_6H_4Br$; **d**, R = $PO(C_6H_5)_2$

preparation of these compounds, it becomes clear that ready access to a large number of nitrogen-substituted azepines is now available without concern for the reactivity, or unreactivity, of the derived nitrene.

Ultraviolet Spectra.—In general, the ultraviolet spectra of 1H-azepine derivatives consist of three major bands comprising a low-intensity maximum of variable position in the 285–330-mμ region, a medium-

(27) From an investigation of the Raman and infrared spectra of 1,4-cyclohexadiene, Gerding and Haak [*Rec. Trav. Chim.*, **68**, 293 (1949)] concluded that the molecule is nearly flat. See also the recent nmr studies of E. W. Garbisch, Jr., and M. G. Griffith, *J. Amer. Chem. Soc.*, **90**, 3590 (1968).

(28) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 125; (b) W. D. Kumler, R. Boikess, P. Bruck, and S. Winstein, *J. Amer. Chem. Soc.*, **86**, 3126 (1964).

(29) Reference 28a, p 109.

(30) A. C. Cope, R. J. Cotter, and G. G. Roller, *J. Amer. Chem. Soc.*, **77**, 3590 (1955).

(31) It is important to emphasize that chemical transformations of a molecule such as **38** will not necessarily differentiate between azepine and aziridine valence tautomers, but merely provide confirmation of the gross structure.

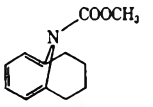
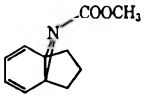
(32) E. Vogel, W. Wiedemann, H. Kiefer, and W. F. Harrison, *Tetrahedron Lett.*, 673 (1963).

(33) E. Vogel and H. Günther, *Angew. Chem. Intern. Ed. Engl.*, **6**, 385 (1967).

(34) L. A. Paquette and J. C. Philips, *J. Amer. Chem. Soc.*, **90**, 3898 (1968).

(35) As discussed in a later paper,[8b] **38** is subject to an irreversible thermal reaction above 150°.

TABLE I
ULTRAVIOLET MAXIMA OF 1H-AZEPINES

Compd	Color	N substituent	Ring substituent(s)	λ_{max}, mμ (ε) *n*-Hexane	λ_{max}, mμ (ε) 95% ethanol
8	Dark orange	$-COOCH_3$		210.5 (23,075), 238 sh (3,145), 330 (570)	207.5 (22,000), 242 sh (2,740), 318 (675)
14a	Yellow-orange	$-COOCH_3$	3-CH_3	212 (23,560), 238 sh (3,030), 321 (640)	212 (23,780), 238 sh (2,425), 309 (745)
14b	Pale yellow	$-COOCH_3$	3,6-$(CH_3)_2$	214.5 (22,780), 242 sh (2,695), 316 (525)	214.5 (22,820), 244 sh (2,240), 301 (674)
20	Very pale yellow	$-COOCH_3$	2-CH_3	211.5 (21,870), 302 (1,015)	209.5 (23,900), 291 (1,615)
21	Dark orange	$-COOCH_3$	4-CH_3	210.5 (22,740), 239 sh (3,210), 323 (675)	207 (24,980), 241 sh (4,720), 309 (975)
29	White	$-COOCH_3$	2,7-$(CH_3)_2$	215 (19,600), 230 sh (3,830), 285 (2,110)	208 (21,00), 275.5 (2,510)
31	Very pale yellow	$-COOCH_3$	4,5-$(CH_3)_2$	247 (5,480), 313 (1,120)	208 (22,600), 251 (4,980) 306 (1,180)
36b	Pale yellow	$-SO_2C_6H_5$	4,5-$(CH_2)_4$	*a*	205 (20,000), 274 (3,265) 350 (350)
47a	Yellow	$-SO_2CH_3$		*a*	205 (17,200), 307 (760)
47b	Pale yellow	$-SO_2C_6H_5$		*a*	205 (22,200), 266 (3,000)
47c	Yellow	*p*-$SO_2C_6H_4Br$		*a*	233 (13,200), 268 sh (3,800)
47d	Yellow	$-PO(C_6H_5)_2$		*a*	238 (9,860), 261 (2,130), 267 (2,220), 273 (1,750), 310 sh (590)
38	White			213 (18,965), 258 (2,690)	209 (20,650), 252 (3,130)
44	White			246 (2,980), 255 (2,870)	242 (2,410) 258 (2,850)

[a] Not soluble.

intensity band at 240–247 mμ, and strong end absorption (Table I). The medium-intensity band is customarily seen as a shoulder, although in certain examples it is not discernible above the intense base absorption. The long-wavelength band is solvent dependent and undergoes an hypsochromic shift when the polarity of the solvent is increased. Not unexpectedly, the position of the various bands is quite subject to the nature of the substituent on nitrogen. Somewhat less anticipated was the observation that the location of the long-wavelength band is notably dependent upon substitution of the ring with alkyl groups, particularly at the 2 and 7 positions. When this band is seen to reach a maximum at 305–330 mμ, the absorption extends to about 400–430 mμ and gives such azepines their yellow to orange color. In contrast, no tailing into the visible region is seen when this band is blue shifted to below 300 mμ, and such azepines, *e.g.*, **29**, are colorless in appearance. The blue shift is even more marked in the annelated azepine **38**, which is also a white solid. It may be concluded, therefore, that the electronic transition energy of this azepine chromophore is quite sensitive to distortions in molecular geometry and is probably associated with the interaction of the nitrogen electron pair with the carbocyclic π system. The greater the steric hindrance about the substituted nitrogen atom, the more the particular 1H-azepine is constrained into the boat conformation, and the less favorable is the electronic interaction. The bridged azepine **38** is, of course, markedly constrained in this fashion.

Significantly, the ultraviolet spectra of **44** differ substantially from those of 1H-azepines. The substance exhibits spectra which are solvent independent and which are characteristic of the 1,3-cyclohexadiene chromophore. Perhaps the most suitable reference substance for **44** is 8,9-indanoxide, which in isooctane displays λ_{max} 258 mμ (ε 4900).[33,36]

Nmr Spectra.—The nmr spectra of a representative number of 1H-azepines are illustrated in Figure 1. In azepines substituted only on nitrogen, it is to be expected that the differing electron density at the three types of ring carbon atoms will profoundly affect the ring proton chemical shifts. Schmid's molecular orbital calculations[3] have indicated that the β carbon bears the highest charge density; on this basis, the β protons are expected to be more shielded than the remaining vinyl protons.[37] That such is the actual situation is clearly demonstrated in Figure 1A. The protons α to the nitrogen atom are located in the center of the multiplet; the over-all pattern is seen to be a doublet which is skewed in the direction of the β-proton absorption. The slight broadening observed is most likely caused by long range coupling effects with the γ protons which appear at lowest field.

Symmetrical dialkyl substitution of the ring results in simplification of the nmr spectrum. As can be seen

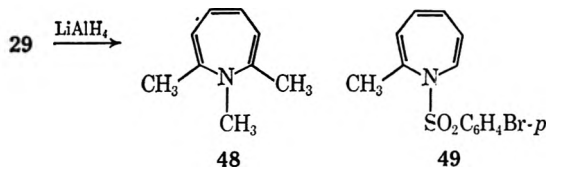
(36) For a survey of additional bridged cyclohexadienes, see G. Maier *Angew. Chem. Intern. Ed. Engl.*, **6**, 402 (1967).

(37) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 256.

in Figure 1B, methyl substituents in the 4,5 positions reduce the spectrum to a doublet of doublets (J = 7.5 Hz). Replacement of hydrogen by methyl groups at the 3 and 6 positions causes the most dramatic spectral alteration, the α- and γ-proton pairs appearing as singlet absorptions. The greater line broadening apparent in the singlet due to the α protons is congruent with allylic coupling to the methyl groups not available to the γ positions because of the fixed nature of the π bonds.

In the 2,7-dimethyl isomer, the β protons appear as a broadened multiplet. The situation is much the same in the annelated azepine **38**. Perhaps the most remarkable feature of these spectra (Figures 1D and 1E) is the marked downfield shift of the β protons. Since the nitrogen atom in ring-unsubstituted 1H-azepines is sp^2 hybridized, there is substantial interaction of the nonbonded nitrogen electrons with the carbonyl group and with the triene π system. For maximum overlap with the carbonyl function, the carbon and oxygen atoms must lie in the plane defined by C_2, C_7, and N. The steric effect of substituents at C_2 and C_7 reduces this overlap, leading to a change in hybridization of the nitrogen atom from sp^2 toward sp^3 and therefore a downfield shift of the β protons.

The strong dependence of the chemical shifts of the vinyl protons, and in particular the β protons, upon the nature of the nitrogen substituent is further seen when comparing the spectrum of **8** (Figure 1A) with those of N-methylazepine ($\delta_{TMS}^{CCl_4}$ 4.5–5.0),[38] 1,2,7-trimethylazepine (**48**) [$\delta_{TMS}^{CDCl_3}$ 5.05 (β protons) and 5.70 (γ protons)], **47c** ($\delta_{TMS}^{CDCl_3}$ 5.74–5.87), **49** ($\delta_{TMS}^{CDCl_3}$ 5.75–6.15), and **36b** doublets, J = 7.5 Hz, centered at [$\delta_{TMS}^{CDCl_3}$ 5.62 (β) and 5.95 (γ)].



48 49

Especially noteworthy is the fact that all of the nmr spectra of these 1H-azepines proved to be invariant over a substantial temperature range (−90° to 130°). This lack of change with temperature points to the absence of valence tautomerism of the 1H-azepine–benzenimine type.

The nmr spectrum of **44** (Figure 1F) clearly differs from those of the azepines, and those of a number of 1,3-cyclohexadienes.[39]

Mass Spectra.—The overwhelmingly favored electron impact fragmentation of ring unsubstituted 1H-azepines occurs between the ring nitrogen atom and the 1 substituent to give the corresponding azatropylium cation **51** (base peak, m/e 92).[40] Although the azepinium molecular ion **50** is always seen, its intensity is variable within the series, presumably because of a propensity for conversion to cation **51** in certain derivatives (see Table II). Another feature of the spectra is

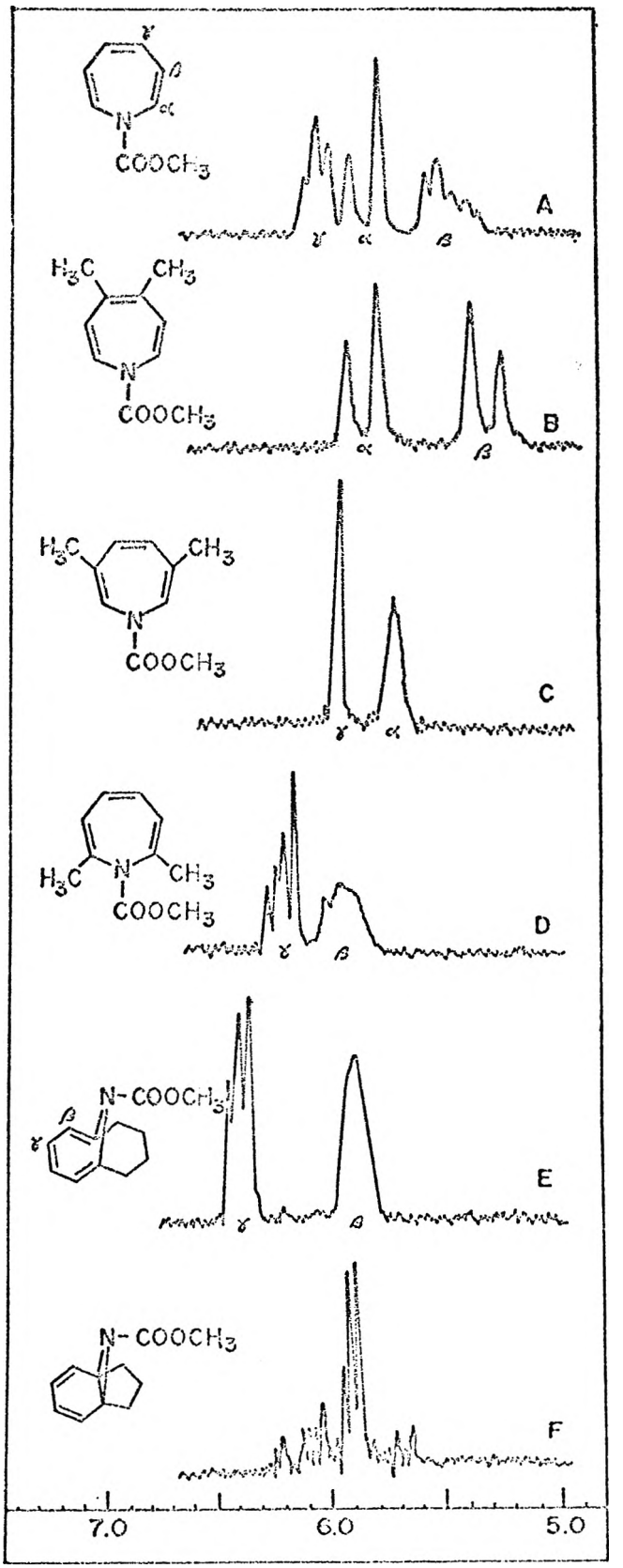


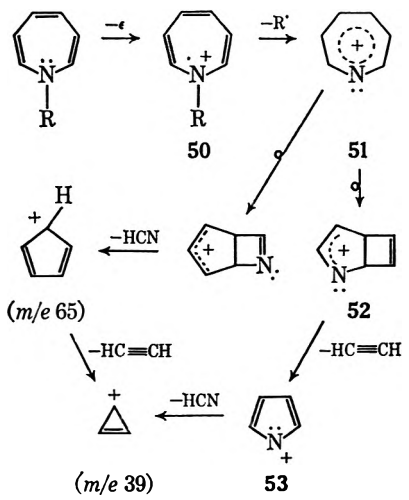
Figure 1.—60-MHz nmr spectra of representative 1H-azepines in deuteriochloroform (δ units).

due mainly to loss of the elements of HCN from **51**; the particle thus formed, which is presumably the cyclopentadienyl cation, decomposes further by the loss of acetylene to yield the cyclopropenium cation. Alternate bond reorganization in **51** can also lead to **52**, from which the elements of acetylene can be expelled to pro-

(38) K. Hafner and J. Mondt, *Angew. Chem.*, **78**, 822 (1966).

(39) H. Günther and H.-H. Hinrichs, *Ann.*, **706**, 1 (1967); *Tetrahedron Lett.*, 787 (1965).

(40) The lone exception to this generalization noted in this study is found in the case of **47d**, where the diphenylphosphinoxy group appears to control the course of the fragmentation.



duce **53**. However, this mode of cleavage does not seem to be of general importance. The mass spectral fragmentation of 1H-azepines parallels the behavior of anilines under such conditions, since the latter compound fragment by way of intermediate azepinium ions.[41]

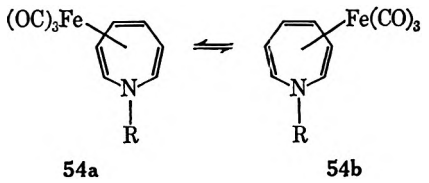
TABLE II
MASS SPECTRAL DATA FOR VARIOUS FRAGMENT IONS OF SELECTED 1H-AZEPINES

Compd	m/e (% relative abundance)
8	39 (25), 59 (11), 65 (73), 92 (100), 93 (10), 119 (15), 151 (63)
14a	39 (15), 44 (28), 51 (18), 77 (17), 78 (30), 91 (18), 104 (44), 105 (23), 106 (38), 132 (30), 133 (100), 165 (41)
14b	39 (23), 77 (38), 91 (41), 93 (33), 105 (20), 118 (32), 119 (25), 120 (100), 132 (41), 146 (25), 147 (84), 179 (93)
20	39 (15), 51 (14), 65 (14), 77 (18), 78 (30), 91 (15), 104 (50), 105 (25), 106 (55), 132 (30), 133 (100), 165 (140)
21	40 (45), 44 (70), 51 (20), 77 (25), 78 (20), 104 (20), 106 (30), 132 (40), 133 (100), 165 (50)
29	51 (11), 56 (12), 77 (30), 78 (11), 79 (36), 91 (10), 120 (100), 179 (35)
31	39 (20), 41 (13), 51 (15), 76 (29), 91 (27), 93 (23), 118 (16), 120 (100), 132 (57), 147 (72), 179 (96)
36a	39 (36), 41 (30), 43 (50), 44 (72), 51 (20), 55 (21), 57 (23), 65 (25), 67 (32), 77 (29), 78 (30), 79 (26), 91 (82), 93 (100), 94 (35), 104 (80), 128 (25), 132 (70), 150 (19), 205 (25)
36b	77 (19), 91 (19), 146 (100), 287 (58)
38	91 (19), 117 (15), 132 (48), 146 (100), 173 (34), 205 (44)
44	117 (68), 130 (21), 132 (100), 159 (42), 191 (42)
47a	39 (20), 65 (70), 78 (15), 92 (100), 93 (18), 171 (15)
47b	39 (15), 65 (38), 92 (100), 233 (15)
47d	51 (14), 65 (17), 77 (26), 92 (25), 201 (100), 243 (48)
49	39 (25), 65 (37), 77 (35), 106 (100), 327 (5)

The mass spectra of 1-carbomethoxy-1H-azepines bearing the one or more alkyl groups at the 2, 3, or 4 positions show that loss of methanol is also a very significant process. Although of considerable mechanistic interest, these observations have not been studied to an extent sufficient to warrant mechanistic speculation.

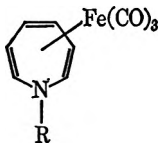
(41) K. L. Rinehart, Jr., A. C. Buchholz, and G. E. VanLear, *J. Amer. Chem. Soc.*, **90**, 1073 (1968); A. V. Robertson, M. Marx, and C. Djerassi, *Chem. Commun.*, 414 (1968).

Iron Tricarbonyl Complexes.—A number of π-bonded olefin complexes of transition metals are known in which the free ligand has π electrons to offer in excess of the electronic requirements of the metal.[42] Several of these π-type complexes are now recognized to be subject to degenerate valence tautomerism by virtue of the capability of the metal atom to move from one diene or triene unit to the next. The best known species of this type are the cyclooctatetraene-derived metal carbonyls. Iron tricarbonyl complexes of 1H-azepines were considered by us to be possible new examples of such fluxional molecules, since the metal could take up two alternative coordination positions on the seven-membered heterocyclic ring as shown in **54a** and **54b**.



54a **54b**

Brief treatment of N-carbomethoxyazepine (**8**) with iron enneacarbonyl in warm hexane produced in 69% yield the air stable, highly crystalline iron tricarbonyl complex **55a**. Similar reaction of the N-carbophenoxy and N-methanesulfonyl (**47a**) analogs gave rise to **55b** and **55c**, respectively. Fischer and Rühle[43] have found that irradiation of N-carbethoxyazepine and iron pentacarbonyl in tetrahydrofuran solution gave the derived $Fe(CO)_3$ complex. We have applied their procedure



55a, R = $COOCH_3$
b, R = $COOC_6H_5$
c, R = SO_2CH_3
d, R = $COOC(CH_3)_3$
e, R = $COOCH_2C_6H_5$

to the synthesis of **55a**, **55d**, and **55e**, and conclude that the iron enneacarbonyl method is simpler and leads to cleaner products. Both procedures failed in attempts to prepare iron tricarbonyl derivatives of alkyl-substituted azepines. Intractable black gums or highly colored green solutions (from which a quantity of azepine could generally be recovered) were obtained.

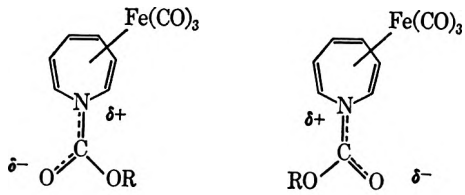
The proton nmr spectra of the various iron tricarbonyl complexes were dramatically temperature dependent. This characteristic was also recognized independently by Günther and Wenzl,[44] who have reported the details of an equally thorough study with N-carbethoxyazepineiron tricarbonyl. Since our results and conclusions do not differ from those of the above

(42) For leading references, see (a) J. E. Mahler, D. A. K. Jones, and R. Pettit, *ibid.*, **86**, 3589 (1964); (b) G. F. Emerson, J. E. Mahler, R. Pettit, and R. Collins, *ibid.*, **86**, 3590 (1964); (c) C. E. Keller, G. F. Emerson, and R. Pettit, *ibid.*, **87**, 1388 (1965); (d) C. G. Kreiter, A. Maasbol, F. A. L. Anet, H. D. Kaesz, and S. Winstein, *ibid.*, **88**, 3444 (1966); (e) F. A. Cotton, J. W. Faller, and A. Musco, *ibid.*, **88**, 4506 (1966); (f) F. A. Cotton, A. Davison, and J. W. Faller, *ibid.*, **88**, 4507 (1966); (g) F. A. L. Anet, H. D. Kaesz, A. Maasbol, and S. Winstein, *ibid.*, **89**, 2489 (1967); (h) F. A. L. Anet, *ibid.*, **89**, 2491 (1967); (i) R. Grubbs, R. Breslow, R. Herber, and S. J. Lippard, *ibid.*, **89**, 6864 (1967); (j) F. A. Cotton and A. Musco, *ibid.*, **90**, 1444 (1968); (k) R. B. King, *J. Organometal. Chem.*, **8**, 129 (1967).

(43) E. O. Fischer and H. Rühle, *Z. Anorg. Allg. Chem.*, **341**, 137 (1965).

(44) H. Günther and R. Wenzl, *Tetrahedron Lett.*, 4155 (1967).

workers, we will only summarize the pertinent points of our study.[45] At room temperature, the onset of the equilibrium **54a** ⇋ **54b** has already begun, as seen by the broad coalesced peaks which characterize the spectra. In the vicinity of 65–85°, the movement of the iron tricarbonyl residue about the two possible positions becomes sufficiently rapid that a symmetrical spectrum of the AA′XX′YY′ type results. At 0°, there is a well-defined spectrum indicative of the fixed structure **54a** (or alternatively **54b**). In the N-carbalkoxy derivatives, further lowering of the probe temperature (to −30° and −60°) is seen to cause new line broadening, coalescence, and finally the appearance of additional signals. Such observations can be best attributed to the "freezing out" of the normally rapid rotation of the carbalkoxy function about the C–N bond (see **56a** and **56b**); when this rotational process is sufficiently retarded, the chemical shifts of the α, α', β, β', γ, and γ' protons will understandably be different and unique and will give rise to the observed spectra. As anticipated, this last consideration does not apply to the N-methanesulfonyl derivative **55c**.



56a **56b**

Thus, the 1H-azepineiron tricarbonyls represent new examples in the rapidly expanding number of fluxional π-bonded organometallic molecules.

Experimental Section[46]

Methyl N-(*trans*-2-Iodo-4-cyclohexene)carbamate (5).—To a cooled (−20°) stirred slurry consisting of 25.0 g (0.312 mol) of 1,4-dihydrobenzene (**4**), 60.0 g (0.40 mol) of freshly prepared silver cyanate,[47] and 600 ml of anhydrous tetrahydrofuran was added 76.0 g (0.30 mol) of iodine. The reaction mixture became dark brown, but developed a canary-yellow hue after stirring for 4 hr at this temperature. The reaction mixture was allowed to warm to room temperature, at which point the inorganic salts were removed by filtration and the filtrate was concentrated to about 75–100 ml *in vacuo*. Anhydrous methanol (600 ml) was added and the orange solution was refluxed for 1.5 hr. The methanol was evaporated under reduced pressure and the residue was dissolved in 400 ml of ether and washed with a water solution (200 ml) of sodium sulfite (5 g). The layers were separated and the aqueous phase was extracted with two additional 100-ml portions of ether. The combined organic layers were dried and evaporated and the resulting yellow gummy solid was recrystallized from methylene chloride–hexane. There was obtained 45.2 g (53.6%) of **5** as a fluffy white solid, mp 99.5–100.5° (lit. mp 93–95°,[18] 100–101°[19b]); ir $\nu_{max}^{CCl_4}$ 3365, 3268 (N–H), and 1733 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.28–5.85 (br m, 2 H, vinyl protons), *ca.* 5.3 (br, 1 H, N-H), 3.73–4.58 (m, 2 H, CHI and CHN), 3.66 (s, 3 H, —OCH_3), 1.81–3.05 (m, 4 H, allylic protons).

Anal. Calcd for $C_8H_{12}INO_2$: C, 34.18; H, 4.30; N, 4.98. Found: C, 34.11; H, 4.36; N, 4.78.

N-Methylcarbamoyl-1,2-iminocyclohex-4-ene (6).—A mixture of 18.2 g (0.065 mol) of **5** and 3.52 g (0.065 mol) of freshly prepared powdered sodium methoxide in 100 ml of anhydrous tetrahydrofuran was refluxed with rapid stirring for 1 hr. The solvent was removed *in vacuo*, and the residue was dissolved in 300 ml of ether. The ether solution was washed carefully with water, dried, and evaporated. Distillation of the residue afforded 7.85 g (79.1%) of **6** as a colorless liquid, bp 63–65° (0.1–0.2 mm), $n^{25}D$ 1.4902; ir $\nu_{max}^{CCl_4}$ 1720 cm^{-1} (>C=O); nmr $\delta_{TMS}^{CCl_4}$ 5.08–5.30 (br s, 2 H, vinyl protons), 3.59 (s, 3 H, —OCH_3), 2.39–2.71 (m, 2 H, CHN), 2.11–2.43 (br d, 4 H, allylic protons).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 63.09; H, 7.47; N, 9.08.

N-Carbomethoxyazepine (8). A. Bromination–Dehydrobromination of 6.—Bromine (3.2 g, 0.02 mol) in methylene chloride (15 ml) was added dropwise to a solution of 3.34 g (0.02 mol) of **6** in 20 ml of the same solvent cooled to −78°. After completion of the addition, the solution was allowed to warm to room temperature and the solvent was removed *in vacuo*. Recrystallization of the remaining solid from ether–pentane gave 3.12 g (76.4%) of **7** as white crystals, mp 69–70.5°; ir $\nu_{max}^{CCl_4}$ 1727 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 3.79–4.34 (m, 2 H, CHBr), 3.59 (s, 3 H, —OCH_3), 2.03–3.06 (complex series of bands, 6 H, CHN and methylene protons).

Anal. Calcd for $C_8H_{11}Br_2NO_2$: C, 30.70; H, 3.54; N, 4.48. Found: C, 30.70; H, 3.68; N, 4.30.

A solution of 3.0 g (9.6 mmol) of **7** in 100 ml of anhydrous tetrahydrofuran was treated with 1.04 g (0.0192 mol) of powdered sodium methoxide and the mixture was refluxed for 2 hr. Work-up in a manner paralleling that employed for **6** gave 970 mg (66.9%) of **8** (99% purity) as an orange liquid, bp 59–61° (0.2 mm), $n^{25}D$ 1.5379; ir $\nu_{max}^{CCl_4}$ 1735 cm^{-1} (C=O); identical in all respects with the sample prepared by method B.

B. Carbomethoxynitrene–Benzene Method.—A solution of 15.0 g (0.14 mol) of methyl azidoformate in 400 ml of benzene was placed in a sealed tube which was heated at 135° for 5 hr. The benzene was subsequently evaporated under reduced pressure. From seven such reactions, there was obtained 173 g of crude product. Chromatography of this material on 250 g of Florisil and elution with ether until the yellow eluate no longer appeared, followed by fractional distillation of this eluate, afforded 52 g (33%) of **8**, bp 62–63° (0.05 mm), $n^{25}D$ 1.5367.

Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.23; H, 5.79; N, 9.13.

1,4-Dihydrotoluene (11a).—To a rapidly stirred slurry of 3.94 g (0.103 mol) of lithium aluminum hydride in 300 ml of anhydrous ether was added dropwise a solution of 53.5 g (0.203 mol) of **10a**[23] in 150 ml of ether. The mixture was refluxed overnight, cooled in an ice bath, treated sequentially with 4 ml of water, 4 ml of 30% sodium hydroxide solution, and 12 ml of water, and filtered. The residue was washed well with ether, and the combined filtrate and washings were fractionally distilled through a vacuum-jacketed, 100-cm glass helix packed column and a fraction boiling at 95–105° was collected. Redistillation of this material through a spinning-band column yielded 11.76 g (61.2%) of **11a**, bp 102.5–103.0°.

Anal. Calcd for C_7H_{10}: C, 89.29; H, 10.71. Found: C, 89.16; H, 10.64.

Methyl (*trans*-2-Iodo-6-methyl-4-cyclohexene)carbamate (12a and Isomers).—From 4.08 g (0.0435 mol) of **11a**, 15.0 g (0.1 mol) of freshly prepared silver cyanate, and 11.0 g (0.0435 mol) of iodine in 150 ml of tetrahydrofuran (0°, 4 hr), there was obtained 11.2 g (87.4%) of **12a** as a viscous pale brown oil that was used without further purification.

N-Methylcarbamoyl-1,2-imino-3-methylcyclohex-4-ene (13a).—A stirred solution of 12.8 g (0.0435 mol) of **12a** in 150 ml of anhydrous tetrahydrofuran was treated with 2.35 g (0.0435 mol) of freshly prepared sodium methoxide in one portion. The mixture was refluxed for 1 hr and worked up as above to give 4.13 g (56.5%) of a colorless liquid, bp 61–68° (0.2 mm). Because the liquid consists of two isomers, both of which will lead to **14a**, no further purification was undertaken.

3-Methyl-N-carbomethoxyazepine (14a).—Bromination of 4.06 g (0.0242 mol) of **13a** produced 7.93 g (100%) of a viscous yellow oil which was dehydrobrominated with 2.62 g (0.0484 mol) of fresh sodium methoxide in 200 ml of anhydrous tetrahydrofuran as described earlier. Distillation afforded 1.61 g (40.2%) of orange liquid, bp 62–65° (0.15–0.25 mm), of 90% purity. Pre-

(45) Much of this variable temperature nmr study was done in cooperation with Professor F. A. L. Anet of UCLA to whom we are indebted.

(46) Melting points are corrected and boiling points are uncorrected. The microanalyses were performed by the Microanalytical Laboratory, Herlev, Denmark. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrometer fitted with a sodium chloride prism. Ultraviolet spectra were recorded with a Cary Model 14 spectrometer. The nmr spectra were determined with Varian A-60 or A-60A spectrometers purchased with funds made available through the National Science Foundation. The mass spectra were measured with an AEI MS-9 mass spectrometer at an ionizing energy of 70 eV.

(47) L. Birkenbach and M. Lindhard, *Chem. Ber.*, **62B**, 2261 (1929); **63B**, 2528, 2544 (1930); **64B**, 961, 1076 (1931).

parative scale gas chromatography[48] (121°) provided the analytical sample; ir $\nu_{max}^{CCl_4}$ 1725 (C=O), 1665, and 1630 cm^{-1} (C=C); nmr $\delta_{TMS}^{CCl_4}$ 5.81–6.15 (m, 3 H, β and γ protons), 5.33–5.77 (m, 2 H, α protons), 3.69 (s, 3 H, —OCH_3), and 1.67 (d, J = 1.5 Hz, 3 H, —CH_3).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.50; H, 6.66; N, 8.46.

1,4-Dihydro-*p*-toluic Acid (9b).—To a stirred solution consisting of 75.0 g (0.55 mol) of *p*-toluic acid, 750 ml of absolute methanol, and approximately 2.5 l. of liquid ammonia was added in small pieces 68.0 g (2.96 g-atoms) of sodium metal, allowing the blue color to disappear before further addition. After consumption of the sodium, ammonium chloride (322.5 g, 5.92 mol) was cautiously added. Stirring was continued for 3 hr and the ammonia was then allowed to evaporate overnight. Water (1500 ml) was carefully added to the residue under a stream of nitrogen. The aqueous solution was poured onto 1 kg of ice and acidified with 10% hydrochloric acid. The product was extracted into ether (four 400-ml portions); the combined organic layers were dried and evaporated. The resulting light brown solid was distilled in a Claisen flask and recrystallized from ether–petroleum ether to give 66.1 g (87.0%) of white crystalline solid, mp 105–107°; ir $\nu_{max}^{CCl_4}$ 1710 cm^{-1} (—COOH).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.75; H, 7.34.

1,4-Dihydro-*p*-xylene (11b).—A 4.8-g sample of **9b** was reduced with lithium aluminum hydride according to the procedure of Nelson[23] to give 3.92 g (91.0%) of 4-methyl-1,4-dihydrobenzyl alcohol as a colorless liquid, bp 70–72° (0.3 mm), ir $\nu_{max}^{CCl_4}$ 3310 cm^{-1} (—OH).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.50; H, 9.94.

A 54.04-g (0.194-mol) sample of the derived tosylate was reduced with 3.80 g (0.10 mol) of lithium aluminum hydride as described earlier. Careful work-up and distillation afforded 10.32 g (49.2%) of **11b** as a colorless liquid, bp 119–122°.

Anal. Calcd for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.62; H, 11.37.

Methyl (*trans*-2-Iodo-3,6-dimethyl-4-cyclohexene)carbamate (12b).—From 3.5 g (0.0324 mol) of **11b**, there was obtained 4.13 g (40.5%) of **12b** as a white solid, mp 146–147.5° (from ether); ir $\nu_{max}^{CCl_4}$ 3360 (NH) and 1735 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 5.29–5.71 (m, 2 H, vinyl protons), *ca.* 5.2 (br, 1 H, NH), 4.47–4.83 (m, 1 H, CHI), 3.40–4.29 (m, 1 H, CHN), 3.70 (s, 3 H, OCH_3), 1.98–3.01 (m, 2 H, $CHCH_3$), and 0.99–1.37 (m, 6 H, methyl groups).

Anal. Calcd for $C_{10}H_{16}INO_2$: C, 38.84; H, 5.22; N, 4.53. Found: C, 38.42; H, 5.33; N, 4.49.

N-Methylcarbamoyl-1,2-imino-3,6-dimethylcyclohex-4-ene (13b).—From 5.70 g of **12b**, there was produced 2.68 g (79.7%) of a colorless liquid, bp 63–65° (0.05–0.1 mm), shown by vpc to consist of a mixture of two isomers present in approximately equal amounts. A center cut from a redistillation, bp 64° (0.07 mm), was submitted for analysis; ir $\nu_{max}^{CCl_4}$ 1729 cm^{-1}; nmr $\delta_{TMS}^{CCl_4}$ 5.09–5.41 (m, 2 H, vinyl protons), 3.64 (s, 3 H, —OCH_3), 0.95–2.79 (m, 10 H, CHN and aliphatic protons).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.45; H, 8.44; N, 7.52.

3,6-Dimethyl-N-carbomethoxyazepine (14b).—Bromination of **13b** was readily achieved by means of the generalized procedure. The resulting viscous yellow oil (26.0 g, 0.0762 mol) was dehydrobrominated as before to give 6.71 g (49.1%) of **14b** as a light yellow liquid, bp 80–85° (0.1 mm). Vpc analysis indicated the material to be of 90% purity. Preparative scale vpc[48] (130°) yielded pure **14b** as a pale yellow solid, mp 29–31°; ir $\nu_{max}^{CCl_4}$ 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.07; H, 6.94; N, 7.83.

Methyl (*trans*-1-Methyl-2-iodo-4-cyclohexene)carbamate (16) and Methyl (*trans*-2-Iodo-4-methyl-4-cyclohexene)carbamate (17).—From 40.0 g (0.44 mol) of 2,5-dihydrotoluene (**15**),[49] 60.0 g (0.40 mol) of freshly prepared silver cyanate, and 101.6 g (0.40 mol) of iodine in 800 ml of anhydrous ether (−10°, 2 hr; 25°, 1 hr), there was obtained 30.6 g of white solid, mp 109–113°, and 32.4 g of residual brown oil after one recrystallization from ether–hexane. Chromatography of the oil on Florisil afforded an additional 1.2 g of solid, mp 108–112°, and 11.5 g of a second product, mp 80–83°.

Recrystallization of the first solid (27% yield) from ether gave white crystals of **16**, mp 115–116°; ir ν_{max} 3320 (N-H) and 1705 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 4.77–5.83 (m, 4 H, vinyl protons, CHI and CHN), 3.65 (s, 3 H, —OCH_3), 2.34–3.18 (m, 4 H, allylic protons), and 1.37 (s, 3 H, —CH_3).

Anal. Calcd for $C_9H_{14}INO_2$: C, 36.63; H, 4.78; N, 4.75. Found: C, 36.76; H, 4.76; N, 4.68.

Recrystallization of the second solid (9.8% yield) from hexane gave fluffy white crystals of **17**, mp 82–84°; ir $\nu_{max}^{CCl_4}$ 3320 (N-H) and 1715 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 4.77–5.45 (m, 2 H, vinyl proton and N-H), 3.68–4.59 (m, 2 H, CHI and CHN), 3.65 (s, 3 H, —OCH_3), 1.77–3.07 (m, 4 H, allylic protons), and 1.54–1.73 (s, 3 H, —CH_3).

Anal. Calcd for $C_9H_{14}INO_2$: C, 36.63; H, 4.78; N, 4.75. Found: C, 36.83; H, 4.97; N, 4.86.

N-Methylcarbamoyl-1,2-imino-1-methylcyclohex-4-ene (18).—From 6.0 g (0.0204 mol) of **16**, there was obtained 3.02 g (88.9%) of **18** as a colorless liquid, bp 52–55° (0.15 mm); ir ν_{max} 1718 cm^{-1} (C=O); nmr $\delta_{TMS}^{CCl_4}$ 5.26–5.42 (d, J = 3.0 Hz, vinyl protons), 3.59 (s, 3 H, —OCH_3), 1.88–2.85 (m, 5 H, allylic protons and CHN), and 1.28 (s, 3 H, —CH_3).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.68; H, 8.00; N, 8.21.

2-Methyl-N-carbomethoxyazepine (20).—Bromination of **18** in the predescribed manner led to the formation of a pale yellow oil in quantitative yield. Dehydrobromination of 11.38 g (0.0348 mol) of this crude dibromide in the predescribed fashion afforded 2.81 g (48.7%) of **20** as a light yellow liquid, bp 62–64° (0.10 mm), $n^{25}D$ 1.5264; ir $\nu_{max}^{CCl_4}$ 1720 cm^{-1} (C=O); nmr $\delta_{TMS}^{CCl_4}$ 5.62–6.27 (m, 5 H, vinyl protons), 3.65 (s, 3 H, —OCH_3), and 2.05 (s, 3 H, —CH_3).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.22; H, 6.70; N, 8.42.

2,N-Dimethylhexamethylenimine (22).—A solution containing 1.0 g (6.05 mmol) of **10** in 50 ml of methanol was hydrogenated over 10% palladium on carbon at 50 psig. Reduction of the resulting colorless liquid (1.02 g) with 1.0 g of lithium aluminum hydride in 25 ml of tetrahydrofuran and customary alkaline work-up gave an amine which was treated directly with ethanolic picric acid. Recrystallization of the derived picrate from 95% ethanol afforded flat, light yellow prisms, mp 232–233°, identical with a known sample of **22** picrate (lit.[50] mp 233°).

N-Methylcarbamoyl-1,2-imino-4-methylcyclohex-4-ene (19).—When the generalized procedure was applied to 9.0 g (0.0306 mol) of **17**, there was isolated 4.49 g (87.8%) of **19** as a colorless liquid, bp 53–54° (0.05–0.1 mm), $n^{25}D$ 1.4867; ir $\nu_{max}^{CCl_4}$ 1725 cm^{-1} (C=O); $\delta_{TMS}^{CCl_4}$ 4.91–5.22 (m, 1 H, vinyl proton), 3.60 (s, 3 H, —OCH_3), 2.61 (br s, 2 H, CHN), 1.98–2.60 (m, 4 H, allylic protons), and 1.50 (d, J = <1.0 Hz, —CH_3).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.65; H, 7.90; N, 8.43.

4-Methyl-N-carbomethoxyazepine (21).—Bromination–dehydrobromination of **19** (3.6 g, 0.0216 mol) led to the isolation of 1.97 g (55.6%) of **21** as an orange liquid, bp 62–65° (0.20 mm), $n^{25}D$ 1.5338; ir $\nu_{max}^{CCl_4}$ 1730 cm^{-1} (C=O); nmr $\delta_{TMS}^{CCl_4}$ 5.13–5.92 (m, 5 H, vinyl protons), 3.72 (s, 3 H, —OCH_3), 1.77 (s, 3 H, —CH_3).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.68; H, 7.00; N, 8.30.

Reaction of 2,3-Dimethyl-1,4-dihydrobenzene (23) with Iodine Isocyanate. A. Standard Conditions.—A mixture of 11.0 g (0.10 mol) of **23**,[49] 30.0 g (0.20 mol) of silver cyanate, and 25.4 g (0.10 mol) of iodine in 300 ml of anhydrous tetrahydrofuran was stirred vigorously for 2 hr at −20°. The reaction mixture was filtered and the solids were washed well with 100 ml of the same solvent. To the combined filtrate and washings was added 300 ml of absolute methanol and 3 drops of a dilute lithium methoxide solution (25 mg of lithium in 50 ml of methanol). After standing at room temperature in the dark for 24 hr, the solution was evaporated under reduced pressure and the resulting oil was chromatographed on 60 g of Florisil. Elution with hexane gave an oil which after distillation afforded 8.3 g (39%) of colorless oil identified as **26**, bp 110° (0.10 mm); ir $\nu_{max}^{CCl_4}$ 3390 (N-H) and 1710 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.60 (m, 2 H, vinyl protons), 5.38 (br, 1 H, N-H), 3.60 and 3.26 (s, 6 H, —OCH_3), 2.17–2.86 (m, 4 H, allylic protons), and 1.30 and 1.18 (s, 6 H, —CH_3).

(48) A 5 ft × 0.25 in aluminum column packed with 20% SF96 on Chromosorb W was employed.

(49) (a) W. Hückel and V. Wörffel, *Chem. Ber.*, **88**, 338 (1955); (b) L. A. Paquette and J. H. Barrett, *Org. Syn.*, in press.

(50) G. R. Clemo, R. Raper, and H. J. Vipond, *J. Chem. Soc.*, 2095 (1949).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57 Found: C, 61.45; H, 8.87; N, 6.33.

Elution with ether–hexane (1:9) afforded 2.1 g (7%) of **24**, white crystals, mp 78–79°; ir $\nu_{max}^{CHCl_3}$ 3425 (N–H) and 1725 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.5 (br, 1 H, N–H), 4.3–5.6 (m, 2 H, CHI and CHN), 3.62 (s, 3 H, —OCH_3), 2.2–3.0 (m, 4 H, allylic protons), and 1.58 (s, 6 H, —CH_3).

Anal. Calcd for $C_{10}H_{16}INO_2$: C, 38.85; H, 5.22; N, 4.53. Found: C, 38.68; H, 5.28; N, 4.50.

B. Controlled Conditions.—A mixture of 26.4 g (0.20 mol) of **23** (82% purity, contaminant being o-xylene), 60 g (0.40 mol) of silver cyanate, and 50.7 g (0.20 mol) of iodine in 600 ml of tetrahydrofuran was allowed to react in the above manner. The clear filtrate was concentrated to *ca.* 20% of its original volume and to this solution (precooled to 0°) was added 800 ml of cold absolute methanol. After being stored at 0° for 24 hr, the solution was concentrated under reduced pressure below 10°. Chromatography of the residue on 100 g of Florisil gave, upon elution with hexane, 22.3 g (40.3%) of iodoisocyanate **27**, mp 84–86° [after sublimation at 60° (0.4 mm)]; ir $\nu_{max}^{CCl_4}$ 2250 cm^{-1} (N=C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.58 (m, 2 H, vinyl protons), 2.52–2.84 (m, 4 H, allylic protons), 2.05 and 1.60 (s, 6 H, —CH_3).

Anal. Calcd for $C_9H_{12}INO_2$: C, 39.01; H, 4.37; N, 5.05. Found: C, 39.46; H, 4.42; N, 5.06.

Continued elution with hexane–ether (7:3) gave 5.88 g (9.9%) of **24**, mp 78–79°.

N-Methylcarbamoyl-1,2-imino-1,2-dimethylcyclohex-4-ene (28).—To a rapidly stirred slurry of 6.0 g (0.11 mol) of sodium methoxide in 100 ml of anhydrous tetrahydrofuran was added 27.7 g (0.10 mol) of solid **27** in portions over a 2-min period. The reaction was exothermic and the mixture began to reflux spontaneously. Heating was continued for 30 min, after which time the mixture was filtered and the filtrate was concentrated. The crude aziridine was extracted from the remaining salts with hot hexane. Distillation gave 17.2 g (95%) of **28**, bp 60° (0.7 mm), $n^{24.5}D$ 1.4794; ir $\nu_{max}^{CCl_4}$ 1725 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.35 (m, 2 H, vinyl protons), 3.56 (s, 3 H, —OCH_3), 2.45 (m, 4 H, allylic protons), and 1.31 (s, 6 H, —CH_3).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.74. Found: C, 66.49; H, 8.43; N, 7.75.

2,7-Dimethyl-N-carbomethoxyazepine (29).—Bromination of 1.81 g (0.01 mol) of **28** led to the formation of 3.4 g (100%) of the corresponding dibromide, mp 109–111° (from ether); ir $\nu_{max}^{CCl_4}$ 1720 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 4.16 (m, 2 H, CHBr), 3.68 (s, 3 H, —OCH_3), 1.85–3.13 (m, 4 H, —CH_2), and 1.29 and 1.32 (s, 6 H, —CH_3).

Anal. Calcd for $C_{10}H_{15}Br_2NO_2$: C, 35.21; H, 4.43; N, 4.11. Found: C, 35.25; H, 4.49; N, 4.03.

Dehydrobromination of 11.9 g (0.035 mol) of this dibromide gave 6.25 g (100%) of **29**, white solid, mp 53–54° (from hexane); ir $\nu_{max}^{CCl_4}$ 1725 (C=O) and 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.10; H, 7.38; N, 7.78.

N-Methylcarbamoyl-1,2-imino-3,4-dimethylcyclohex-4-ene (30).—To a slurry of 1.20 g (0.03 mol) of sodium hydride (60% mineral oil dispersion) in 20 ml of anhydrous tetrahydrofuran was added at 0° with rapid stirring a solution of 9.27 g (0.03 mol) of **24** in 20 ml of the same solvent. The mixture came rapidly to reflux, and after 30 min, water (50 ml) was added. The solution was extracted with ether and the combined ether extracts were dried, filtered, and evaporated. Distillation of the residue yielded 5.0 g (92%) of **30**, bp 62° (0.04 mm), $n^{24}D$ 1.4957; ir $\nu_{max}^{CCl_4}$ 1715 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 3.55 (s, 3 H, —OCH_3), 2.65 (s, 2 H, CHN), 2.33 (br s, 4 H, allylic protons), and 1.53 (s, 6 H, —CH_3).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.30; H, 8.43; N, 7.56.

4,5-Dimethyl-N-carbomethoxyazepine (31).—Bromination of 4.1 g (22.6 mmol) of **30** gave 7.7 g (100%) of the derived dibromide, mp 100–102° (from ether); ir $\nu_{max}^{CCl_4}$ 1725 (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 3.62 (s, 3 H, —OCH_3), 3.45–3.85 (m, 6 H, aziridine and methylene protons), 1.95 (s, 6 H, —CH_3).

Anal. Calcd for $C_{10}H_{15}Br_2NO_2$: C, 35.21; H, 4.43; N, 4.10. Found: C, 35.49; H, 4.51; N, 4.05.

Dehydrobromination of this dibromide (6.6 g, 27.4 mmol) in the predescribed manner afforded 2.85 g (63%) of **31**, mp 60–61° (from hexane at 0°); ir $\nu_{max}^{CCl_4}$ 1727 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.70; H, 7.34; N, 7.90.

Reaction of 5,8-Dihydrotetralin (32) with Iodine Isocyanate.—A mixture of 53.68 g (0.40 mol) of **32**,[49a] 112.5 g (0.75 mol) of silver cyanate, and 101.6 g (0.40 mol) of iodine in 600 ml of anhydrous tetrahydrofuran was stirred at −20° for 5 hr. The inorganic salts were separated by filtration and the tetrahydrofuran was removed *in vacuo* at room temperature. The light brown residue was taken up in 600 ml of cold anhydrous methanol and the solution was stored at 0° for 48 hr. The pale yellow solid precipitate of **34** (49.0 g) was filtered and the filtrate was concentrated at <25°. The residue was dissolved in methylene chloride, washed with cold aqueous sodium sulfite solution, dried, and evaporated. The semicrystalline mass was filtered to afford an additional 21.5 g of **34**. The remaining oil (41.0 g) was chromatographed on 250 g of Florisil; elution with hexane gave 7.6 g of recovered **32** and 16.8 g (16.2%) of iodoisocyanate **33**. Elution with hexane–ether (9:1) yielded an additional 8.2 g of **34**. The combined fractions of iodocarbamate **34** (78.7 g, 68.6%) were recrystallized from methylene chloride–ether to give a fluffy white solid, mp 148–149°; ir $\nu_{max}^{CHCl_3}$ 3345 (N–H) and 1740 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.0 (br, 1 H, N–H), 3.75–4.38 (m, 2 H, CHI and CHN), 3.65 (s, 3 H, —OCH_3), 1.39–2.82 (m, 12 H, methylene protons).

Anal. Calcd for $C_{12}H_{18}INO_2$: C, 43.00; H, 5.42; N, 4.17. Found: C, 42.89; H, 5.40; N, 4.38.

Iodoisocyanate **33** ($\nu_{max}^{CHCl_3}$ 2260 cm^{-1}) was not further purified and was used directly in the ensuing step.

N-Methylcarbamyl-2,3-imino-1,2,3,4-tetrahydrotetralin (35a).—Cyclization of 16.75 g (0.05 mol) of **34** with sodium methoxide in tetrahydrofuran according to the predescribed conditions yielded 9.13 g (88.3%) of **35a** as a colorless solid [after distillation at 101–105° (0.3 mm)], mp 38–40° from ether–hexane; ir $\nu_{max}^{CCl_4}$ 1720 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 3.55 (s, 3 H, —OCH_3), 2.60, 2.28, and 1.31–1.95 (complex m, 2 H, 4 H, and 8 H, respectively, due to CHN, allylic protons, and methylene groups).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.70; H, 8.42; N, 6.64.

4,5-Butylene-N-carbomethoxyazepine (36a).—The generalized bromination procedure was applied to 2.0 g (9.7 mmol) of **35a** and yielded 2.96 g (83.6%) of dibromide, white solid, mp 102–104° (from ether–hexane); ir $\nu_{max}^{CCl_4}$ 1727 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 3.74 (s, 3 H, —OCH_3), 2.51–2.96 (m, 6 H, —CH_2CHN), and 1.46–2.24 (m, 8 H, remaining methylene groups).

Anal. Calcd for $C_{12}H_{17}Br_2NO_2$: C, 39.26; H, 4.67; N, 3.82. Found: C, 39.35; H, 4.74; N, 3.73.

Dehydrobromination of 10.0 g (0.027 mol) of the above dibromide gave rise to 2.39 g (42.9%) of a viscous orange oil after elution of the crude product through a column of Florisil. This oil could not be distilled without decomposition. Thin layer chromatography indicated the presence of two minor impurities which were not removed on repeated column chromatography.

2,3-Imino-1,2,3,4-tetrahydrotetralin (35b).—A solution of 10.0 g (0.03 mol) of **34** in a mixture of 150 ml of methanol and aqueous potassium hydroxide (15 g in 30 ml of H_2O) was refluxed with stirring for 5 hr. The solvent was removed *in vacuo* and the residue was treated with 300 ml of ether and 300 ml of water. The layers were separated and the aqueous layer was further extracted with ether. The combined organic layers were dried, filtered, and evaporated to give 2.38 g (53.4%) of an unstable waxy, white solid, mp 120–124.5° (from ether–hexane).

N-Benzenesulfonyl-2,3-imino-1,2,3,4-tetrahydrotetralin (35c).—A stirred solution of 1.10 g (7.4 mmol) of **35b** and 0.78 g (7.4 mmol) of triethylamine in 35 ml of benzene was cooled in ice while 1.31 g (7.4 mmol) of benzenesulfonyl chloride in 20 ml of benzene was added dropwise. Removal of the solvent and crystallization of the oil from ether–hexane gave 1.91 g (89.6%) of white, colorless plates, mp 102.5–104°; ir $\nu_{max}^{CCl_4}$ 1330 and 1165 cm^{-1} (SO_2N).

Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84. Found: C, 66.28; H, 6.62; N, 4.87.

4,5-Butylene-N-benzenesulfonylazepine (36b).—Bromination of 2.15 g of **35c** afforded 2.35 g (70.5%) of white crystalline dibromide, mp 135.5–136°.

Anal. Calcd for $C_{16}H_{19}Br_2NO_2S$: C, 42.78; H, 4.26; N, 3.12. Found: C, 42.82; H, 4.28; N, 3.18.

To a cold (0°) stirred slurry of 0.96 g (8.5 mmol) of potassium *t*-butoxide in 75 ml of anhydrous tetrahydrofuran was added dropwise a solution of 1.90 g (4.2 mmol) of the dibromide in 75 ml of the same solvent. Stirring was continued for 2 hr at this temperature and the solvent was evaporated *in vacuo*. The residue was treated with ether (400 ml) and water (300 ml) and

the organic phase was worked up in the usual manner. There was obtained 790 mg of **36b** as light yellow plates, mp 105–107° (from ether–pentane); ir $\nu_{max}^{CHCl_3}$ 1355 and 1175 cm^{-1} (SO_2N).

Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; S, 11.16. Found: C, 66.99; H, 5.99; S, 11.09.

11-Carbomethoxy-11-azatricyclo[4.4.1.0^{1,6}]undec-3-ene (37).—A solution of 16.8 g (0.056 mol) of **33** in 150 ml of anhydrous tetrahydrofuran was treated with 3.0 g (0.056 mol) of powdered sodium methoxide in one portion. The reaction mixture was seen to reflux gently. After stirring for 30 min, the solvent was evaporated, water and ether were added, and the customary work-up was followed. Distillation afforded 10.6 g (92.2%) of **37** as a colorless liquid, bp 75–77° (0.03–0.05 mm); ir $\nu_{max}^{CCl_4}$ 1712 cm^{-1} (C=O); nmr $\delta_{TMS}^{CCl_4}$ 5.25–5.39 (m, 2 H, vinyl protons), 3.49 (s, 3 H, —OCH_3), 1.13–2.69 (m, 12 H, methylene protons).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.67; H, 8.37; N, 6.63.

11-Carbomethoxy-11-azabicyclo[4.4.1]undeca-1,3,5-triene (38).—Bromination of 4.3 g (0.021 mol) of **37** yielded 5.26 g (69.1%) of colorless crystalline dibromide, mp 85.5–87° (from ether–pentane); ir $\nu_{max}^{CCl_4}$ 1712 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{17}Br_2NO_2$: C, 39.26; H, 4.67; N, 3.82. Found: C, 39.30; H, 4.68; N, 3.77.

Reaction of 6.60 g (0.018 mol) of this dibromide with an equivalent quantity of sodium methoxide in tetrahydrofuran in the above manner gave 3.07 g (83.3%) of **38** as large colorless plates from ether–pentane, mp 57.5–59°; ir $\nu_{max}^{CCl_4}$ 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.33; H, 7.45; N, 6.82.

11-Methyl-11-azabicyclo[4.4.1]undecane (39).—A solution of 500 mg (2.46 mmol) of **38** in 50 ml of dry tetrahydrofuran was hydrogenated over 10% palladium on charcoal at 60 psig. The incompletely hydrogenated product was added dropwise to a stirred slurry of 500 mg (13.2 mmol) of lithium aluminum hydride in 35 ml of the same solvent, and the reaction mixture was refluxed for 18 hr. After the standard alkaline work-up, the resulting light yellow oil was rehydrogenated under the same conditions. Vpc analysis of hydrogenated product indicated the material to be 90% pure. A sample was purified by preparative scale vpc and converted to its picrate in the usual manner, mp 250–252° (sample introduced at 246°), identical with an authentic sample.[51]

Reaction of 4,7-Dihydroindan (40) with Iodine Isocyanate.—Reaction of 40.0 g (0.33 mol) of **40**[52] with 90.0 g (0.60 mol) of silver cyanate and 84.5 g (0.30 mol) of iodine in 500 ml of dry tetrahydrofuran at −20° for 5 hr and subsequent reaction with methanol in the cold as described for **32** gave a mobile, light orange oil which was chromatographed directly on 300 g of Florisil. Elution with hexane gave 34.0 g of a light yellow oil which proved to be a mixture of unreacted **40** and iodoisocyanate **41**. This oil was employed directly without further purification.

Elution with hexane–ether (9:1) yielded 5.80 g (7.0%) of iodocarbamate **42** as white crystals from ether–hexane, mp 120–121°; ir $\nu_{max}^{CHCl_3}$ 3345 (N-H) and 1730 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.18 (br, 1 H, NH), 3.86–4.63 (m, 2 H, CHI and CHN), 3.66 (s, 3 H, —OCH_3), 1.50–2.97 (m, 10 H, allylic and methylene protons).

Anal. Calcd for $C_{11}H_{16}INO_2$: C, 41.14; H, 5.02; N, 4.36. Found: C, 41.20; H, 4.98; N, 4.33.

10-Carbomethoxy-10-azatricyclo[4.3.1.0^{1,6}]dec-3-ene (43).—The crude sample of **41** which was isolated above was treated with 5.4 g (0.1 mol) of powdered sodium methoxide in 200 ml of dry tetrahydrofuran. The customary work-up gave 8.8 g of recovered **40**, bp 30–35° (0.1 mm) and 14.07 g of **43** as a colorless liquid, bp 85–86° (0.05 mm); ir $\nu_{max}^{CCl_4}$ 1718 cm^{-1} (C=O); nmr $\delta_{TMS}^{CCl_4}$ 5.30–5.44 (m, 2 H, vinyl protons), 3.51 (s, 3 H, —OCH_3), and 1.08–3.05 (m, 10 H, methylene groups). The quantity of **43** isolated indicates that iodoisocyanate **41** was produced in the previous reaction in at least 32% yield.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.70; H, 7.96; N, 7.22.

10-Carbomethoxy-10-azatricyclo[4.3.1.0^{1,6}]deca-2,4-diene (44).—The generalized bromination procedure was employed to convert 2.30 g (0.012 mol) of **43** into its dibromide (3.48 g, 83.0%), mp 101.5–103° (from ether–pentane); ir $\nu_{max}^{CCl_4}$ 1727 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}Br_2NO_2$: C, 37.42; H, 4.28; N, 3.97. Found: C, 37.41; H, 4.29; N, 3.93.

Dehydrobromination of 3.30 g (9.35 mmol) of this dibromide afforded 1.21 g (67.6%) of a yellowish liquid, bp 68–69° (0.03–0.06 mm). Vpc analysis indicated two products to be present. Preparative scale separation[53] of the two components at 135° gave **44** (major product) as a white waxy solid, mp 42–44°; ir $\nu_{max}^{CCl_4}$ 1655 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.86; H, 6.77; N, 7.25.

The second component was obtained as a light yellow solid, mp 61–63°, shown to be 2,3-propylene-N-carbomethoxyazepine.[8b]

1,2-Iminocyclohex-4-ene (45). A. Saponification of 5.—To a stirred refluxing solution of 40 g of 85% potassium hydroxide in 200 ml of water was added 20.0 g (0.071 mol) of **5**. Reflux was maintained for 1 hr, during which time the insoluble iodocarbamate dissolved. After cooling, the organic material was extracted into ether and the combined ether layers were dried, filtered, and evaporated. Distillation of the residue gave 5.91 g (87.5%) of **45** as a clear colorless liquid, bp 60.5–61° (14 mm), n^{24}D 1.5024; ir $\nu_{max}^{CCl_4}$ 3260 (NH) and 1645 cm^{-1} (C=O). This amine formed a picrate, mp 146–147° dec (from ethanol).

Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 44.45; H, 3.73; N, 17.28. Found: C, 44.32; H, 3.84; N, 17.38.

The N-methanesulfonyl derivative (**46a**) was obtained in 91.7% yield as a clear, colorless, viscous liquid, bp 107–113° (0.3 mm); ir $\nu_{max}^{CHCl_3}$ 1660 (C=C), 1310, and 1150 cm^{-1} (SO_2N); nmr $\delta_{TMS}^{CDCl_3}$ 5.47 (br s, 2 H, vinyl protons), 2.97 (s, 5 H, overlapping —CH_3 and CHN), and 2.42 (br s, 4 H, allylic protons).

Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.40; S, 18.51. Found: C, 48.34; H, 6.63; S, 18.57.

The N-benzenesulfonyl derivative (**46b**) was obtained in 96.4% yield as lustrous white plates, mp 86–87° (from tetrahydrofuran–pentane); ir $\nu_{max}^{CHCl_3}$ 1670, 1590 (C=C), 1325, and 1165 cm^{-1} (SO_2N).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; S, 13.63. Found: C, 60.98; H, 5.80; S, 13.51.

The N-(*p*-bromobenzenesulfonyl) derivative (**46c**) was obtained in 73% yield as lustrous white plates, mp 106.5–107.5° (from tetrahydrofuran–hexane); ir $\nu_{max}^{CHCl_3}$ 1660, 1580 (C=C), 1330, and 1165 cm^{-1} (SO_2N).

Anal. Calcd for $C_{12}H_{12}BrNO_2S$: C, 45.85; H, 3.81; S, 10.21. Found: C, 45.99; H, 3.81; S, 10.24.

The N-diphenylphosphinoxy derivative (**46d**) was obtained in quantitative yield[54] as lustrous white plates, mp 119–120.5° (from ether); ir $\nu_{max}^{CS_2}$ 1655, 1590 (C=C), 1205 cm^{-1} (P=O).

Anal. Calcd for $C_{18}H_{18}NOP$: C, 73.21; H, 6.14; N, 4.74. Found: C, 73.20; H, 6.37; N, 4.64.

B. Direct from Iodoisocyanate.—A mixture of 4.64 g (0.058 mol) of 1,4-dihydrobenzene (**4**), 17.2 g (0.115 mol) of silver cyanate, and 14.5 g (0.057 mol) of iodine in 200 ml of tetrahydrofuran was stirred at 0° for 1 hr. The precipitated silver salts were removed by filtration and the filtrate was stirred for 9 hr with a solution of 20 g of potassium hydroxide in 100 ml of water. The same work-up as above afforded 2.76 g (51% over-all) of **45**.

N-Methanesulfonylazepine (47a).—The dibromide of **46a** was obtained in 83.8% yield as small yellow needles, mp 126.5–127.5° (from tetrahydrofuran–pentane); ir $\nu_{max}^{CHCl_3}$ 1330 and 1155 cm^{-1} (SO_2N).

Anal. Calcd for $C_7H_{11}Br_2NO_2S$: C, 25.24; H, 3.33; N, 9.63. Found: C, 25.59; H, 3.55; N, 9.85.

Dehydrobromination (KO-*t*-Bu) of 9.8 g (0.0294 mol) of this dibromide gave **47a** in 47.4% yield as lustrous yellow needles, mp 91.5–92.5° (from ether–hexane); ir $\nu_{max}^{CHCl_3}$ 1640, 1620 (C=C), 1350, and 1165 cm^{-1} (SO_2N); nmr $\delta_{TMS}^{CDCl_3}$ 6.20 (m, 2 H), 5.76 (m, 4 H), and 2.89 (s, 3 H).

Anal. Calcd for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18. Found: C, 49.06; H, 5.50; N, 8.08.

N-Benzenesulfonylazepine (47b).—The dibromide of **46b** was obtained in 71.2% yield as small yellow needles, mp 123–124° (from tetrahydrofuran–pentane); ir $\nu_{max}^{CHCl_3}$ 1325 and 1170 cm^{-1} (SO_2N).

Anal. Calcd for $C_{12}H_{13}Br_2NO_2S$: C, 36.47; H, 3.32; S, 8.12. Found: C, 36.62; H, 3.35; S, 8.16.

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(52) E. Giovannini and H. Wegmuller, *Helv. Chim. Acta*, **41**, 933 (1958).

(53) A 3 ft × 0.25 in. aluminum column packed with 20% SF-96 on Chromosorb W was employed.

(54) The procedure of E. H. Amonoo-Neizer, S. K. Ray, R. A. Shaw, and B. C. Smith [*J. Chem. Soc.*, 4296 (1965)] was employed in this instance. We wish to thank the Stauffer Chemical Co. for a generous sample of the diphenylphosphinous chloride used in this work.

Dehydrobromination (KO-*t*-Bu) of 6.8 g (0.0172 mol) of this dibromide gave **47b** in 52.4% yield as yellow plates, mp 132–133° (from tetrahydrofuran–pentane); ir $\nu_{max}^{CHCl_3}$ 1645, 1625 (C=C), 1360, and 1175 cm^{-1} (SO_2N); nmr $\delta_{TMS}^{CDCl_3}$ 7.62 (m, 5 H, aromatic protons) and 5.76 (m, 6 H, vinyl protons).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.82; H, 4.65; N, 6.08.

N-(*p*-Bromobenzenesulfonyl)azepine (47c).—The dibromide of **46c** was obtained in quantitative yield as lustrous yellow crystals, mp 165–167° (from tetrahydrofuran–hexane); ir $\nu_{max}^{CHCl_3}$ 1330 and 1165 cm^{-1} (SO_2N).

Anal. Calcd for $C_{12}H_{12}Br_3NO_2S$: C, 30.40; H, 2.55; S, 6.76. Found: C, 30.67; H, 2.64; S, 6.90.

Dehydrobromination (KO-*t*-Bu) of 20 g (0.042 mol) of this dibromide gave **47c** in 67.9% yield as large yellow crystals, mp 132.5–134° (from tetrahydrofuran); ir $\nu_{max}^{CHCl_3}$ 1645, 1625 (C=C), 1365, and 1170 cm^{-1} (SO_2N); nmr $\delta_{max}^{CDCl_3}$ 7.59 (m, 4 H, aromatic protons), 5.74 (d, 2 H), and 5.87 (m, 4 H, vinyl protons).

Anal. Calcd for $C_{12}H_{10}BrNO_2S$: C, 46.16; H, 3.23; N, 4.49. Found: C, 46.30; H, 3.33; N, 4.55.

N-Diphenylphosphinoxyazepine (47d).—The dibromide of **46d** was obtained in 99.2% yield as yellow needles, mp 192–192.5° (from tetrahydrofuran); ir $\nu_{max}^{CS_2}$ 1205 cm^{-1} (P=O).

Anal. Calcd for $C_8H_{18}Br_2NOP$: C, 47.50; H, 3.99; N, 3.08. Found: C, 47.62; H, 4.13; N, 3.11.

To a stirred refluxing solution of 3.49 g (8.66 mmol) of this dibromide in 150 ml of anhydrous tetrahydrofuran was added dropwise a solution of 3.26 g (26.3 mmol) of 1,5-diazabicyclo-[4.3.0]non-5-ene in 10 ml of the same solvent. The reaction mixture was refluxed for 4 hr, cooled in ice, and hydrolyzed by addition of 150 ml of water and stirring at room temperature for 30 min. Careful extraction with ether and subsequent processing of the combined organic layers in the usual fashion gave 2.16 g (85%) of **47d** as large yellow crystals, mp 151.5–153° (from tetrahydrofuran–ether, 1:4); ir $\nu_{max}^{CS_2}$ 1640, 1610 (C=O), and 1220 cm^{-1} (P=O); nmr $\delta_{TMS}^{CDCl_3}$ 8.13–7.64 (m, 4 H, aromatic protons), 7.37 (m, 6 H, aromatic protons), 6.20 (m, 2 H, vinyl protons), and 5.48 (m, 4 H, vinyl protons).

Anal. Calcd for $C_{18}H_{16}NOP$: C, 73.71; H, 5.50; N, 4.78. Found: C, 73.64; H, 5.46; N, 4.82.

1,2,7-Trimethylazepine (48).—A solution of 1.79 g (0.01 mol) of **29** in 10 ml of anhydrous tetrahydrofuran was added dropwise during 10 min to a stirred slurry of 0.38 g (0.01 mol) of lithium aluminum hydride in 25 ml of the same solvent. The reaction mixture was refluxed for 15 hr under nitrogen and was cooled to 0°. To the cold mixture was added carefully 0.4 g of water, 0.4 g of 30% sodium hydroxide solution, and 1.2 g of water in that order. Anhydrous magnesium sulfate (2.0 g) was added and the solids were filtered and rinsed thoroughly. The combined filtrate and washings were evaporated and the residual liquid was subjected to bulb-to-bulb distillation at 20°. A dilute solution of **48** in tetrahydrofuran could be stored for several weeks at 0°; however, pure **48** was seen to decompose rapidly; ir $\nu_{max}^{CCl_4}$ 1655 cm^{-1} (C=C–N); uv $\lambda_{max}^{isooctane}$ 215 (ε 15,400) and 257 mμ (ε 1650); nmr $\delta_{TMS}^{CS_2}$ 5.72 (m, 2 H, γ ring protons), 5.07 (m, 2 H, β ring protons), 2.58 (s, 3 H, NCH_3), and 1.73 (s, 6 H, C–CH_3).

2-Methyl-N-(*p*-bromobenzenesulfonyl)azepine (49).—To a refluxing solution of 40 g of potassium hydroxide in 200 ml of water was added 20.0 g (0.068 mol) of iodocarbamate **16**. Heating was continued for 30 min, during which time the solid dissolved. After cooling, the organic product was extracted with ether and the oil thus obtained was transferred under high vacuum to give 5.32 g (72%) of colorless 1-methyl-1,2-iminocyclohex-4-ene, ir ν_{max}^{neat} 3300 cm^{-1} (N–H).

The N-(*p*-bromobenzenesulfonyl) derivative was obtained in quantitative yield as colorless crystals, mp 128–129.5° (from tetrahydrofuran); ir $\nu_{max}^{CHCl_3}$ 1320 and 1165 cm^{-1} (SO_2N); nmr $\delta_{TMS}^{CDCl_3}$ 7.68 (q, 4 H, aromatic protons), 5.37 (br d, 2 H, vinyl protons), 3.19 (br, 1 H, CHN), 2.2–2.5 (m, 4 H, allylic protons), and 1.79 (s, 3 H, –CH_3).

Anal. Calcd for $C_{13}H_{14}BrNO_2S$: C, 47.57; H, 4.30; N, 4.27; S, 9.77. Found: C, 47.81; H, 4.38; N, 4.26; S, 9.75.

The derived dibromide was obtained in 61% yield as a powdery white solid, mp 125.5–127.5° (from tetrahydrofuran); ir $\nu_{max}^{CHCl_3}$ 1325 and 1165 cm^{-1} (SO_2N).

Anal. Calcd for $C_{13}H_{14}Br_3NO_2S$: C, 31.99; H, 2.89; S, 6.57. Found: C, 32.49; H, 3.01; S, 6.65.

Dehydrobromination of the dibromide (5.46 g, 11.2 mmol) was achieved by the use of 1,5-diazabicyclo[4.3.0]non-5-ene (4.18 g, 33.7 mmol) in 150 ml of tetrahydrofuran as described above. There was produced 1.73 g (47.4%) of **49** as a white powder, mp 94.5–95.5° (from ether–hexane); ir $\nu_{max}^{CHCl_3}$ 1645, 1625 (C=C), 1385, 1165, and 1150 cm^{-1} (SO_2N); nmr $\delta_{max}^{CDCl_3}$ 7.80 (d, 4 H, aromatic protons), 5.75–6.35 (m, 5 H, vinyl protons), and 2.29 (s, 3 H, –CH_3); uv λ_{max}^{EtOH} 234 (ε 13,000) and 269 sh mμ (ε 3580).

Anal. Calcd for $C_{13}H_{12}BrNO_2S$: C, 47.86; H, 3.71; N, 4.29. Found: C, 48.00; H, 3.83; N, 4.18.

N-Carbomethoxyazepineiron Tricarbonyl (55a). A. Irradiation with Iron Pentacarbonyl.—A solution of 4.53 g (0.03 mol) of **8** and 7.84 g (0.04 mol) of iron pentacarbonyl in 300 ml of anhydrous tetrahydrofuran was irradiated with a 200-W Hanovia lamp in a quartz immersion well for 36 hr. The solvent was evaporated and the residual solid was dissolved in hexane and filtered through a 1.5-in. pad of Woelm grade II neutral alumina (30 g). The filtrate was evaporated and the resulting solid was crystallized from hexane to give 5.84 g (70.5%) of **55a** as yellow prisms, mp 115–115.5° (from hexane); ir ν_{max}^{Nujol} 2070, 1190 (Fe-CO) 1750, 1730 (C=O), and 1655 cm^{-1} (C=C); uv λ_{max}^{EtOH} 250 (ε 17,670) and 297 sh mμ (ε 5390); nmr $\delta_{TMS}^{CDCl_3}$ 6.3, 5.0, 4.6 (broad peaks, temperature dependent, 6 H, vinyl protons) and 3.85 (s, 3 H, –OCH_3).

Anal. Calcd for $C_{11}H_9FeNO_6$: C, 45.39; H, 3.12; N, 4.81. Found: C, 45.44; H, 3.22; N, 4.82.

B. Heating with Iron Enneacarbonyl.—A mixture of 750 mg (5.0 mmol) of **8** and 1.82 g (5.0 mmol) of iron enneacarbonyl[55] in 30 ml of hexane was refluxed with stirring under nitrogen for 20 min. After cooling, the solution was filtered through Celite to remove a small amount of insoluble dark residue. The solvent was evaporated and the resulting solid was recrystallized from hexane to give 1.0 g (69%) of **55a**, mp 116–116.5°.

N-Carbophenoxyazepineiron Tricarbonyl (55b).—A solution of 81.5 g (0.5 mol) of phenyl azidoformate in 2800 ml of benzene was heated in a 6-l. autoclave at 130° for 2 hr. The benzene was removed *in vacuo* and the residual oil was chromatographed on 200 g of Florisil. Elution with ether–hexane (1:1) and ether gave 30.1 g (27.1%) of N-carbophenoxyazepine as pale yellow crystals, mp 67–68° (from hexane–ether); ir $\nu_{max}^{CCl_4}$ 1730 (C=O), 1653, and 1621 cm^{-1} (C=C); nmr $\delta_{TMS}^{CDCl_3}$ 7.2–8.5 (m, 5 H, aromatic protons), and 5.35–6.2 (m, 6 H, vinyl protons).

A 1.05-g (5.0 mmol) sample of 1-carbophenoxyazepine was treated with 1.82 g (5.0 mmol) of iron enneacarbonyl in the manner described above. There was obtained 850 mg (48.2%) of **55b** as yellow prisms, mp 108–109° dec (from hexane); ir $\nu_{max}^{CCl_4}$ 2060, 2000 (FeCO), and 1740 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 7.2 (m, 5 H, phenyl protons), 6.6, 6.1, 5.1, 4.6, and 3.5 (broad peaks, temperature dependent, 6 H, vinyl protons).

Anal. Calcd for $C_{16}H_{11}FeNO_5$: C, 54.42; H, 3.14; N, 3.96. Found: C, 54.37; H, 3.20; N, 3.93.

N-Methanesulfonylazepineiron Tricarbonyl (55c).—To a stirred solution of 967 mg (5.65 mmol) of **47a** in 40 ml of tetrahydrofuran at room temperature was added 2.04 g (5.61 mmol) of iron enneacarbonyl. After stirring for 75 min, all of the metal carbonyl had dissolved and the dark reaction mixture was filtered through Celite. The filtrate was evaporated and the residue was crystallized from hexane to give 1.20 g (69%) of **55c** as lustrous orange-yellow prisms, mp 94.5–96° (from hexane); ir $\nu_{max}^{CHCl_3}$ 2070, 1990 (Fe-CO), 1635 (C=C), 1350, and 1170 cm^{-1} (SO_2N); uv λ_{max}^{EtOH} 232 mμ (ε 14,600); nmr $\delta_{TMS}^{CDCl_3}$ 3.5–6.5 (broad humps, temperature dependent, 6 H, vinyl protons), and 2.92 (s, 3 H, –CH_3).

Anal. Calcd for $C_{10}H_9FeNO_5S$: C, 38.61; H, 2.92. Found: C, 38.74; H, 3.01.

N-Carbo-*t*-butoxyazepineiron Tricarbonyl (55d).—A solution of 14 g (0.1 mol) of *t*-butylazidoformate[56] in 400 ml of benzene was heated in a sealed tube at 145° for 4.5 hr. The solvent was evaporated and the residues from four such runs (65.1 g) were combined. Addition of ether to the crude product resulted in the crystallization of 29.0 g of 5,5-dimethyl-2-oxazolidone, mp 80.5–81.5°.[57] The remaining oil was chromatographed on Florisil. Elution with ether and distillation gave 9.4 g (12.5%) of N-carbo-*t*-butoxyazepine as a red-orange liquid, bp 72–73° (0.05 mm), $n^{25}D$ 1.5073; uv λ_{max}^{EtOH} 209 (ε 22,500), 240 sh (ε 3270), and 317 mμ (ε 638); $\lambda_{max}^{isooctane}$ 206 (ε 22,900) 238 sh (ε 3520), and 330 mμ (ε 520); ir $\nu_{max}^{CCl_4}$ 1665, 1625 (C=C), and 1712 cm^{-1}

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(C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.2–6.1 (m, 6 H, vinyl protons) and 1.49 [s, 9 H, —C(CH$_3$)$_3$].

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.19; H, 7.85; N, 6.96.

This azepine was also prepared in the following manner. The iodoisocyanate resulting from the reaction of 8.0 g (1.10 mol) of 1,4-dihydrobenzene with 40 g (0.20 mol) of silver cyanate and 25.4 g (0.10 mol) of iodine in 30 ml of tetrahydrofuran was treated with 11.2 g (0.10 mol) of powdered potassium *t*-butoxide. The mixture was shaken vigorously for 5 min, filtered, and evaporated. Distillation of the residue gave 16.95 g (87%) of N-*t*-butylcarbamoyl-1,2-iminocyclohex-4-ene, bp 81° (0.6 mm); ir $\nu_{max}^{CCl_4}$ 1725 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 5.40 (br m, 2 H, vinyl protons), 2.61 (br m, 2 H, CHN), 2.44 (m, 4 H, allylic protons), and 1.44 [s, 9 H, —C(CH$_3$)$_3$].

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.67; H, 8.81; N, 7.01.

An 8.65-g (0.044 mol) sample of this aziridine was brominated in the customary fashion to give 15.1 g (100%) of crude dibromide as a yellow oil. Dehydrobromination of this material gave 7.93 g (93%) of N-carbo-*t*-butoxyazepine, bp 71–73° (0.05 mm), identical with the material prepared above.

A solution of 4.60 g (0.0238 mol) of this azepine and 5.5 g (0.028 mol) of iron pentacarbonyl in 350 ml of tetrahydrofuran was irradiated as above for 24 hr. Evaporation of the solvent gave a black oil which was filtered through 50 g of Woelm basic alumina. Crystallization of the resulting orange oil from hexane gave 3.12 g (39.4%) of **55d** as yellow prisms, mp 70–70.5°; ir ν_{max}^{Nujol} 2070, 1990 (FeCO), 1750 (C=O), and 1650 cm^{-1} (C=C); uv λ_{max}^{EtOH} 249.5 (ϵ 18,770) and 298 sh mμ (ϵ 5825); nmr $\delta_{max}^{CCl_4}$ 4.5–6.4 (broad humps, temperature dependent, 6 H, vinyl protons) and 1.48 [s, 9 H, —C(CH$_3$)$_3$].

Anal. Calcd for $C_{14}H_{15}FeNO_5$: C, 50.47; H, 4.54; N, 4.21. Found: C, 50.57; H, 4.68; N, 4.24.

N-Carbobenzyloxyazepineiron Tricarbonyl (55e).—A solution of 5.5 g (0.031 mol) of benzyl azidoformate in 400 ml of benzene was heated at 135–140° for 6 hr in a sealed vessel.[58] The solvent was removed *in vacuo* and the residue was chromatographed on 130 g of Florisil. Elution with ether–hexane (1:19) gave 1.7 g (24%) of N-carbobenzyloxyazepine as an orange oil, n^{29}D 1.5762.

Irradiation of a solution containing 10.9 g (0.048 mol) of this azepine and 9.8 g (0.050 mol) of iron pentacarbonyl in 300 ml of tetrahydrofuran gave 17.45 g (99%) of crude crystalline product mp 112–116°. Three recrystallizations from hexane gave pure **55e** as yellow-orange needles, mp 127–128°; ir ν_{max}^{Nujol} 2065, 2000 (FeCO), 1750 (C=O), and 1650 cm^{-1} (C=C); nmr $\delta_{TMS}^{CCl_4}$ 7.35 (s, 5 H, aromatic protons), 6.0–6.5 and 4.2–4.8 (broad absorption, temperature dependent, 6 H, vinyl protons), and 5.17 (s, 2 H, ArCH$_2$—).

Anal. Calcd for $C_{17}H_{13}FeNO_5$: C, 55.61; H, 3.57; N, 3.82. Found: C, 55.23; H, 3.57; N, 3.81.

(58) This experiment was performed by Mr. Tedd Dawson.

Registry No.—**5,** 20646-79-1; **6,** 20646-80-4; **7,** 20646-81-5; **8,** 17870-94-9; **9b,** 20646-36-0; **11a,** 2050-31-9; 1,4-dihydro-*p*-xylene **11b,** 20646-38-2; **13a,** 20646-82-6; **13b,** 20646-83-7; **14a,** 14194-60-6; **14b,** 20646-39-3; **16,** 20646-84-8; **17,** 20646-85-9; **18,** 20646-86-0; **19,** 20646-87-1; **20,** 14194-59-3; **21,** 20646-42-8; **24,** 20647-01-2; **26,** 20646-88-2; **27,** 20646-89-3; **28,** 20646-90-6; **28** (dibromide), 20646-91-7; **29,** 20646-43-9; **30,** 20646-92-8; **30** (dibromide), 20646-93-9; **31,** 20646-44-0; **34,** 20646-94-0; **35a,** 20646-95-1; **35a,** (dibromide), 20646-96-2; **35b,** 20646-97-3; **35c,** 20646-98-4; **35c** (dibromide), 20646-99-5; **36b,** 20646-45-1; **37,** 20646-51-9; **37** (dibromide), 20708-16-1; **38,** 20646-46-2; **42,** 20647-00-1; **43,** 20646-47-3; **43** (dibromide), 20646-48-4; **44,** 20646-52-0; **45,** 20647-02-3; **45** (picrate), 20647-03-4; **46a,** 20647-04-5; **46a** (dibromide), 20647-05-6; **46b,** 20647-06-7; **46b** (dibromide), 20647-07-8; **46c,** 20647-08-9; **46c** (dibromide), 20647-09-0; **46d,** 20647-10-3; **46d** (dibromide), 20674-11-4; **47a,** 20646-53-1; **47b,** 20646-54-2; **47c,** 20646-55-3; **47d,** 20646-56-4; **48,** 20646-57-5; **49,** 20646-58-6; **55a,** 12359-60-3; **55b,** 12359-62-5; **55c,** 12359-59-0; **55d,** 12359-61-4; **55e,** 12359-63-6; 1-methyl-1,2-iminocyclohex-4-ene, 20647-15-8; 1-methyl-1,2-iminocyclohex-4-ene [N-(*p*-bromobenzenesulfonyl) derivative], 20647-12-5; 1-methyl-1,2-iminocyclohex-4-ene [N-(*p*-bromobenzenesulfonyl) derivative, dibromide], 20647-13-6; N-carbophenoxyazepine, 18697-60-4; N-carbo-*t*-butoxyazepine, 20646-60-0; N-*t*-butylcarbamoyl-1,2-iminocyclohex-4-ene, 20647-14-7; 4-methyl-1,4-dihydrobenzyl alcohol, 20646-50-8.

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Unsaturated Heterocyclic Systems. LIII. Thermochemical Reactions of 1H-Azepine Derivatives. II. Aromatization and Sigmatropic Migrations Involving Nitrogen[1]

LEO A. PAQUETTE, DONALD E. KUHLA,[2] AND JAMES H. BARRETT

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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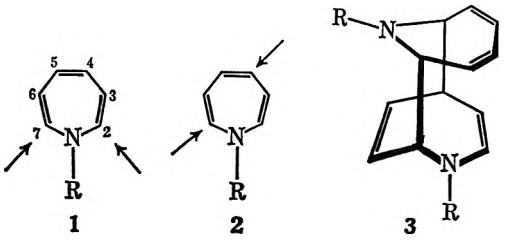
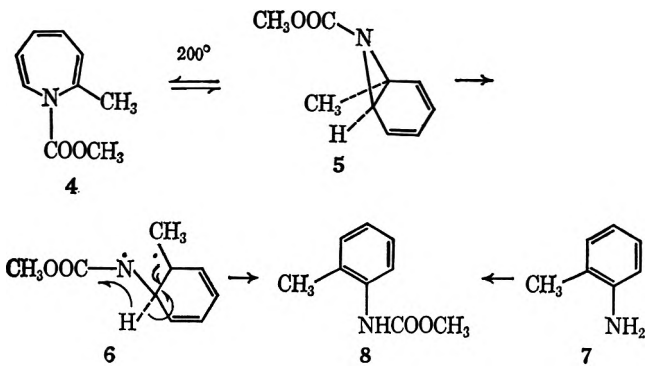
In contrast to N-carbalkoxy-1H-azepines and their 3- and 4-methyl derivatives which undergo ready dimerization at elevated temperatures, 2-methyl-N-carbomethoxyazepine and a number of disubstituted and annelated congeners are seen to aromatize or rearrange when heated. This behavior is not shared by 2,7-dimethyl-N-carbomethoxyazepine, which is stable at 250°, but decomposes above that temperature; no characterizable products are produced. A mechanistic interpretation of these results derived in part on product analysis and founded to some degree of thermodynamic considerations is advanced. Acid-catalyzed rearrangements of these same azepines are also discussed, since the bond reorganizations noted in this aspect of the work provide parallel mechanistic insight into the structural requirements for the changes which occur.

At temperatures approaching 130°, 1H-azepine derivatives lacking ring substituents and the 3- or 4-methyl derivatives undergo rapid kinetically controlled dimerization by way of a mechanism that involves (6 + 4)π *exo* cycloaddition to give the dimer **3**.[3] No aromatization was detected under the conditions used. We were then led to examine the behavior of azepines with substituents at the positions directly involved in the dimerization (*cf.* **1** and **2**). In this paper we report the sharply contrasting behavior of variously substituted derivatives.



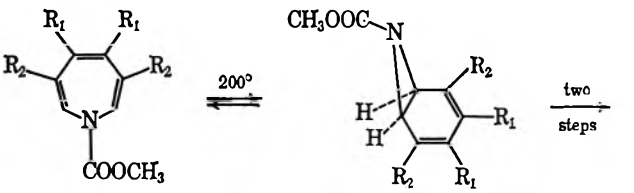
1 **2** **3**

Thermal Rearrangement of Monocyclic 1H-Azepines. —Heating of 2-methyl-N-carbomethoxyazepine (**4**) at 130° for periods of time ranging up to 2 hr led to no reaction, but at 200° **4** was converted in 64% yield to the aromatic urethan **8**, which was synthesized as shown.



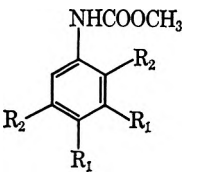
4 **5** **6** **8** **7**

Similarly, the 4,5-dimethyl congener (**9**) was transformed in this temperature range to **11** (68% yield), and the 3,6-dimethyl derivative **12** led to **14**. There was no evidence of dimerization on any of these reactions.



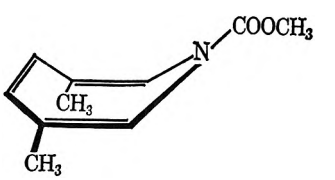
9, $R_1 = CH_3$; $R_2 = H$
12, $R_1 = H$; $R_2 = CH_3$

10, $R_1 = CH_3$; $R_2 = H$
13, $R_1 = H$; $R_2 = CH_3$



11, $R_1 = CH_3$; $R_2 = H$
14, $R_1 = H$; $R_2 = CH_3$

These observations suggest that the dimerization of 1H-azepines is subject to pronounced steric rate retardation. Because the presence of methyl groups at the "strategic" 2, 4, and 7 positions of the ring substantially retards the rate of the (6 + 4)π cycloaddition process, aromatization becomes the kinetically favored reaction pathway. In the case of **12**, methyl groups at positions 3 and 6 also inhibit dimerization. Dreiding models of **12** provide further support for the steric argument, because the location of the methyl substituents in this azepine blocks facile approach to the bottom side of its boat conformation (see **15**).



15

The major structural changes involved in passing from **4**, **9**, and **12** to the corresponding aromatic isomers can best be rationalized in terms of azanorcaradiene valence tautomers as **5**, **10**, and **13**. Homolytic rupture

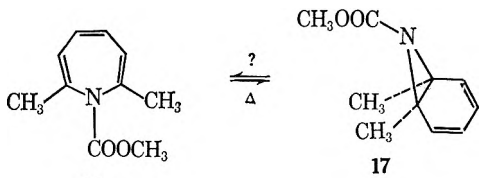
(1) For previous paper, see L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, 2866 (1969).

(2) National Institutes of Health Predoctoral Fellow, 1965–1968.

(3) L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Amer. Chem. Soc.*, **91**, 3616 (1969).

of the more highly substituted C–N bond[4] with synchronous hydrogen atom transfer leads to benzenoid stabilization. Since signals due to azanorcaradiene tautomers are not seen in the nmr spectra of these azepines,[1] the concentration of such reactive intermediates is not large. It is striking that thermally induced suprafacial sigmatropic shifts of order [1,5][5] of the type observed in tropilidene skeletal rearrangements[6] are not operative in these heterocyclic examples under the conditions examined.

The 2,7-dimethyl derivative **16** was remarkably stable and withstood prolonged heating (24 hr) at 200° without noticeable dire effects. No spectral changes (nmr) were noted on heating a solution of **16** in Cl_2=

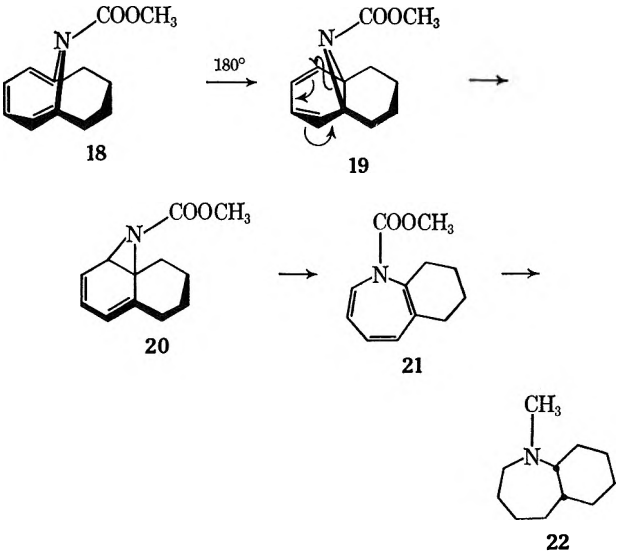


16 **17**

CCl_2 under nitrogen at 250° for 30 min; at 300° the sample darkened gradually and the various nmr signals were seen to fade. No characterizable product could be isolated.

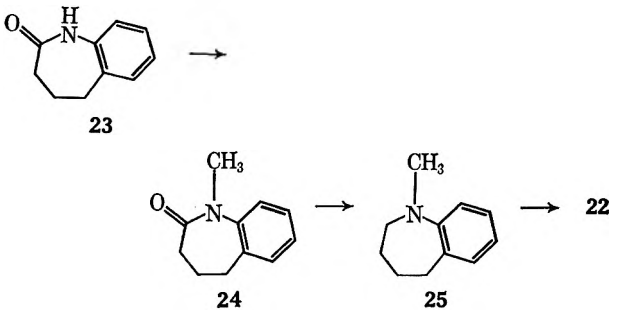
Thermal Rearrangement of Annelated Azepines.— We next investigated the thermochemical behavior of the related annelated substances **18** and **26**. As reported earlier,[1] the structures of **18** and **26** differ significantly; whereas the former is simply a bridged 2,7-disubstituted 1H-azepine, steric factors produced by the trimethylene bracket force **26** to exist in the aziridine form. Models indicate that valence tautomeric ring opening of the central bond in **26** is severely inhibited, and any rearrangements in **26** would likely occur from the tricyclic structure.

Pyrolysis of a neat sample of **18** in a sealed tube proceeded at a convenient rate at 180°. The process of the rearrangement was initially followed by thermolysis of small samples and gas chromatographic analysis at various intervals. After an optimal time of 30 min, molecular distillation of the crude mixture afforded a new azepine (**21**) in 87% yield. The structure of **21** was elucidated by spectra and partial degradation. The uv spectrum of **21** in ethanol displays the typical two bands characteristic[1] of several substituted N-carbalkoxyazepines at 213.5 (ϵ 19,500), and 289.5 mμ (ϵ 1500). The nmr spectrum of **21** in carbon tetrachloride solution shows four vinyl protons in the δ 5.39–6.11 region, a sharp three-proton methoxyl singlet at 3.58, and a broad eight-proton multiplet at 1.14–2.92, in excellent agreement with this azepine formulation. Structure **21** was further confirmed by catalytic hydrogenation and lithium aluminum hydride reduction to *cis*-2-azabicyclo-



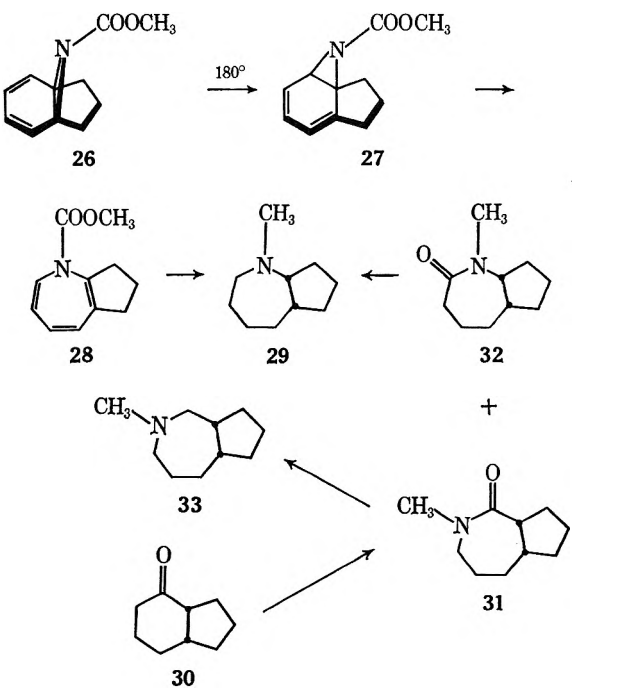
18 **19** **20** **21** **22**

[5.4.0]undecane (**22**). An authentic sample of **22** was synthesized in three well-precedented steps from homodihydrocarbostyril (**23**).



23 **24** **25** **22**

The thermal behavior of **26** was completely analogous to that of **18**. When heated at 180° for 30 min, **26** was transformed in 93% yield into 2,3-trimethylene-N-carbomethoxyazepine (**28**), the identity of which was similarly established by spectroscopic and chemical means. In this instance, the rate of the rearrangement could be measured by nmr techniques. The following



26 **27** **28** **29** **32** **33** **31** **30**

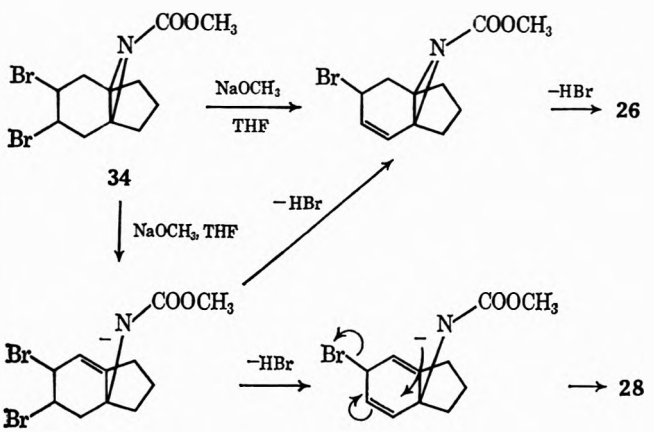
(4) A radical mechanism for these thermal reactions has not been established experimentally. However, the intervention of radicals seems most plausible in view of the elevated temperatures required for aromatization and the general acceptance of diradicals in somewhat related thermal bond reorganizations [J. A. Berson, *Accounts Chem. Res.*, **1**, 152 (1968); M. R. Wilcott, III, and C. J. Boriack, *J. Amer. Chem. Soc.*, **90**, 3287 (1968)]. For these reasons, radical intermediates are utilized herein, although it should be understood that the dipolar alternative to this mechanism has not been ruled out (however, see below).

(5) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965).

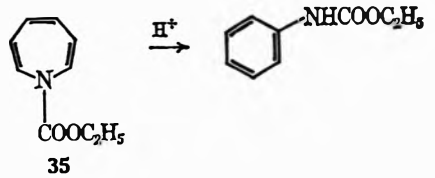
(6) (a) J. A. Berson and M. R. Wilcott, III, *ibid.*, **88**, 2494 (1966); (b) J. A. Berson, P. W. Grubb, R. A. Clark, D. R. Hartter, and M. R. Wilcott, III, *ibid.*, **89**, 4076 (1967).

first-order rate constants and thermodynamic parameters were determined: $k_{158°} = 1.32 \times 10^{-4}$ sec^{-1}; $k_{168°} = 4.31 \times 10^{-4}$ sec^{-1}; $\Delta H^{\ddagger} = 4.38$ kcal/mol; $\Delta S^{\ddagger} = 24.6$ eu.[7] The simplest representation of the conversion of **26** to **28** requires the intervention of azanorcaradiene tautomer **27**. In principle, two mechanisms for the initial isomerization of **26** to **27** could be operative: (a) concerted suprafacial sigmatropic rearrangement of order [1,5] without intermediates, or (b) intramolecular 1,5 shift of nitrogen *via* diradical intermediates. The first process is permitted, but not required, by orbital symmetry considerations.[5,8] The large positive entropy of activation suggests a two-step mechanism for the rearrangement of **26** to **27**. That is to say, whereas a concerted mechanism would be expected to have a negative entropy, a transition state leading to a diradical should have more degrees of freedom than the ground state, resulting in a positive $\Delta S^{\ddagger}$. This conclusion is, of course, based on the reasonable assumption that **26** → **27** is rate determining.

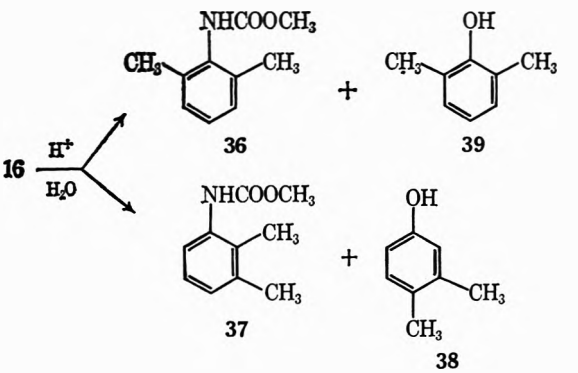
Before discussing the acid-catalyzed rearrangements of 1H-azepines, the anomalous behavior[1] of dibromide **34** on dehydrobromination should be mentioned. Thus, it was shown that treatment of **34** with powdered sodium methoxide in anhydrous tetrahydrofuran gave rise not only to **26**, but also to substantial quantities of **28**.[1] Since **26** proved to be totally stable to the alkaline reaction conditions base-catalyzed rearrangement of **26** to **28** cannot be implicated. Rather, **28** must arise directly from dibromide **34**. Two plausible mechanisms are advanced below. Apparently the carbamate function can compete successfully with a bromine substituent as the preferred leaving group, perhaps for reasons of internal strain; recyclization to a new, less strained aziridine with ejection of bromide ion ultimately affords **28**.



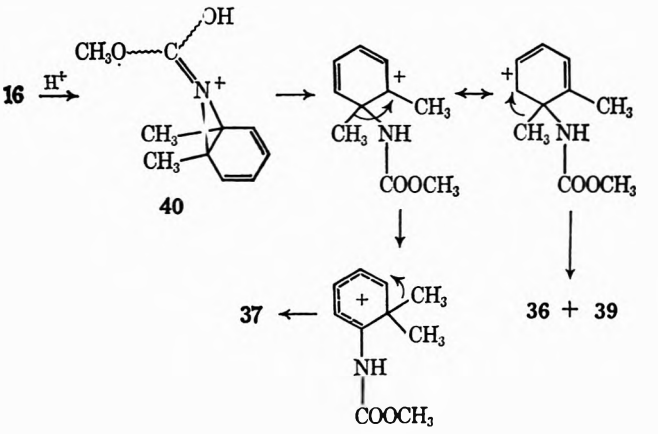
Acid-Promoted Rearrangements.—Hafner has noted that reaction of N-carbethoxyazepine (**35**) with dilute acids leads rapidly to N-phenylcarbamate.[9] More recently, Marsh and Simmons reported that acid hydrolysis of the mixture of isomeric fluoro-N-cyanoazepines obtained from fluorobenzene and cyanogen azide gave *o*- and *p*-fluorophenylureas in a 1:1 ratio containing less than 0.5% *meta* isomer.[10] Because of the relationship to the thermally induced bond reorganizations just discussed, we undertook an investigation of this cationic rearrangement with selected 1H-azepines. Most significantly, the temperatures of the two reactions differed widely.



Initially, attention was directed to the differing behavior of 3,6-dimethyl- (**12**) and 2,7-dimethyl-N-carbomethoxyazepines (**16**) toward acid. After exposure of a dilute dioxane solution of **12** to 10% sulfuric acid at room temperature for 2 hr, an 82% yield of **14** was obtained. Similar treatment of **16** for 4 hr led only to a high-yield recovery of unreacted starting material. However, when the same mixture was heated at reflux for 1 hr, **16** was completely transformed into a viscous brown oil. The major identifiable component (16%) of this oil was shown to be 2,6-dimethyl-N-carbomethoxyaniline (**36**). A second carbamate which was isolated in 1% yield was identified as the 2,3-dimethylaniline derivative **37**. In addition, two phenols were produced in equally low yield. These were defined as 3,4-dimethylphenol (**38**, 6%) and 2,6-dimethylphenol (**39**, 1%). The remainder of the crude product was polymeric in nature.



A mechanistic rationalization of the formation of **36**–**39** involves the assumption that **16** is first converted to **40**, which leads to **36**, **37**, and **39** through a series of carbonium ion rearrangements. On the other hand, the



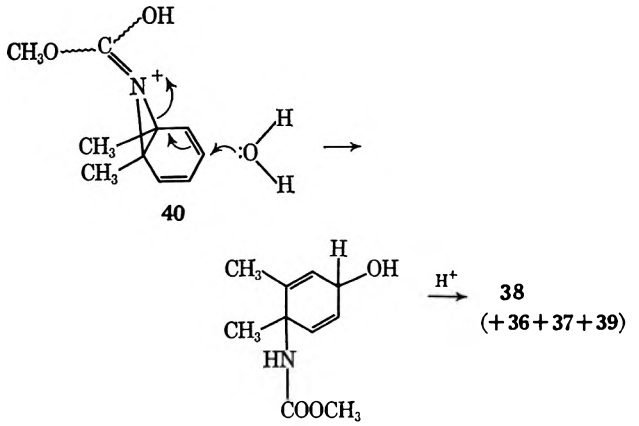
(7) Similar studies with **18** were complicated because of interference of crucial nmr absorptions by peaks due to minor by-products arising from aromatization of **21**.

(8) The observed rearrangement finds analogy in the thermal rearrangement of certain tropilidenes [ref 6 and E. Ciganek, *J. Amer. Chem. Soc.*, **89**, 1458 (1967)] and 1,6-methano[10]annulene [footnote 2, V. Rautenstrauch, H. J. Scholl and E. Vogel, *Angew. Chem. Intern. Ed. Engl.*, **7**, 288 (1968)].

(9) K. Hafner, *Angew. Chem.*, **75**, 1041 (1963); *Angew. Chem. Intern. Ed. Engl.*, **3**, 165 (1964).

(10) F. D. Marsh and H. E. Simmons, *J. Amer. Chem. Soc.*, **87**, 3529 (1965).

formation of 3,4-dimethylphenol (**38**) appears to be the result of a direct attack of water on **40**. In mechanistic

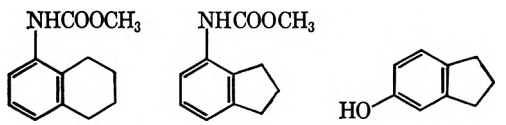


40

38 (+**36**+**37**+**39**)

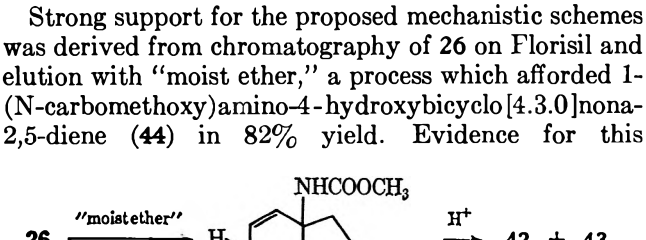
detail, the acid-catalyzed rearrangement of **16** parallels closely the behavior of 2,7-dimethyloxepin under similar conditions.[11]

At room temperature in the presence of small quantities of dilute sulfuric acid, azepines **18** and **21** undergo almost quantitative conversion to **41**. 2,3-Trimethylene-N-carbomethoxyazepine (**28**) behaved analogously to give **42** in 86% yield. Under the same conditions, the more highly strained tricyclic isomer **26** was likewise converted to **42**, but in low yield (7%). The major product of the rearrangement was 5-indanol (**43**, 42%). Presumably, therefore, attack by water on the protonated intermediate is kinetically favored over 1,5-sigmatropic shift of nitrogen, a property that allows for the formation of major amounts of **43**. Since an analogous phenol was not detected in the rearrangement of **18**, it would seem that the less strained nature of protonated **18** is more conducive to the migration of nitrogen.



41 **42** **43**

Strong support for the proposed mechanistic schemes was derived from chromatography of **26** on Florisil and elution with "moist ether," a process which afforded 1-(N-carbomethoxy)amino-4-hydroxybicyclo[4.3.0]nona-2,5-diene (**44**) in 82% yield. Evidence for this



44

structure was derived from elemental analysis and the various spectra of the substance (see Experimental Section). Acid-catalyzed rearrangement of **44** gave rise only to **42** (8%) and **43** (56%), the ratio approximating that seen in the direct aromatization of **26**. Significantly, 1,2 migration of the carbamate group during the dienol–benzene rearrangement of **44** attests to the high probability that the quantity of **42** produced from acid treatment of **26** does not arise uniquely, if at all, from a 1,5-sigmatropic nitrogen shift.

Lastly, azepine **18** was seen to be inert to the above chromatographic conditions.

(11) E. Vogel and H. Günther, *Angew. Chem. Intern. Ed. Engl.*, **6**, 385 (1967).

Experimental Section[12]

Pyrolysis of 2-Methyl-N-carbomethoxyazepine (4).—A 1.10-g (6.65-mmol) sample of **4**[4] was heated in a sealed tube at 200° for 10 min. The dark product was chromatographed on Florisil (50 g). Elution with hexane–ether (19:1) yielded 685 mg (62.4%) of **8** as a fluffy white solid, mp 60.0–60.5° (from hexane–ether); ir $\nu_{max}^{CCl_4}$ 3345 (NH) and 1740 cm^{-1} (C=O). No other product was obtained on continued elution of the column with solvents of increasing polarity.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.32; H, 6.51; N, 8.61.

2-Methyl-N-carbomethoxyaniline (8).—*o*-Toluidine (10.7 g, 0.10 mol) and methyl chloroformate (4.72 g, 0.05 mol) in 100 ml of tetrahydrofuran were stirred at room temperature for 30 min. The precipitated hydrochloride salt was removed by filtration and the filtrate was concentrated *in vacuo* to give 8.25 g (100%) of **8**, mp 60–60.5° (from ether–hexane); nmr $\delta_{TMS}^{CCl_4}$ *ca.* 7.6 (m, 1 H, H-6), *ca.* 6.95 (m, 3 H, H-3,-4,-5), 6.4 (br, 1 H, NH), 3.17 (s, 3 H, $-OCH_3$), and 2.14 (s, 3 H, $-CH_3$).

Pyrolysis of 4,5-Dimethyl-N-carbomethoxyazepine (9).—A 200-mg (1.1 mmol) sample of **9** was heated in a sealed tube at 200° for 10 min. Chromatography of the dark product on Florisil (elution with hexane) gave 136 mg (68%) of **11**, mp 59–60° (from ether–hexane); ir $\nu_{max}^{CCl_4}$ 3448 (NH) and 1755 cm^{-1} (C=O). No other product was obtained on continued elution of the column.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.40; N, 7.67.

3,4-Dimethyl-N-carbomethoxyaniline (11).—Reaction of 12.1 g (0.10 mol) of 3,4-dimethylaniline with 4.72 g (0.05 mol) of methyl chloroformate in the predescribed manner afforded 8.95 g (100%) of **11**, mp 59–60°; nmr $\delta_{TMS}^{CDCl_3}$ 7.05 (m, 4 H, aromatic protons and NH), 3.69 (s, 3 H, $-OCH_3$), and 2.15 (s, 6 H, $-CH_3$).

Pyrolysis of 3,6-Dimethyl-N-carbomethoxyazepine (12).—A 600-mg (3.34 mmol) sample of **12**[1] was heated in a sealed tube at 200° for 10 min. The dark product was chromatographed on Florisil (50 g). Elution with hexane–ether (19:1) yielded 281 mg (46.8%) of **14** as a fluffy white solid, mp 86.5–87.0°; ir $\nu_{max}^{CCl_4}$ 3400 (NH) and 1740 cm^{-1} (C=O). No other product was obtained on continued elution of the column.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.86; H, 7.31; N, 7.95.

2,5-Dimethyl-N-carbomethoxyaniline (14).—Reaction of 12.1 g (0.10 mol) of 2,5-dimethylaniline with 4.72 g (0.05 mol) of methyl chloroformate in the above manner gave 8.95 g (100%) of **14**, mp 86.5–87.0° (from ether–hexane); nmr $\delta_{TMS}^{CDCl_3}$ 7.46 (m, 1 H, H-6), 6.90 (m, 2 H, H-3,-4), 6.50 (br, 1 H, NH), 3.61 (s, 3 H, $-OCH_3$), 2.16 and 2.03 (s, 3 H each, $-CH_3$).

Pyrolysis of 1-Carbomethoxy-11-azabicyclo[4.4.1]undec-1,3,5-triene (18).—A 286-mg (1.44 mmol) sample of **18**[1] sealed in a Pyrex test tube was placed in an oil bath preheated to 180° for 30 min. Molecular distillation of the dark product [bp 100–110° (0.05 mm)] gave 248 mg (87%) of **21** as a pale yellow viscous liquid, ir $\nu_{max}^{CCl_4}$ 1718 cm^{-1} (C=O); uv λ_{max}^{hexane} 213.5 (ϵ 19,500) and 299 mμ (ϵ 1340); λ_{max}^{EtOH} 212 (ϵ 19,440), and 289.5 mμ (ϵ 1500); nmr $\delta_{TMS}^{CCl_4}$ 5.39–6.11 (m, 4 H, vinyl protons), 3.58 (s, 3 H, $-OCH_3$), 1.14–2.92 (m, 8 H, $-CH_2-$).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.44; H, 7.52; N, 6.80.

Conversion of 21 to 2-Methyl-*cis*-azabicyclo[5.4.0]undecane (22).—A solution of 200 mg (0.97 mmol) of **21** in 75 ml of tetrahydrofuran was hydrogenated over 5% rhodium on carbon at 60 psig for 36 hr. The catalyst was separated by filtration and the filtrate was added dropwise to a stirred slurry of 2.0 g of

(12) Melting points are corrected and boiling points are uncorrected. The microanalyses were performed by the Microanalytical Laboratory, Herlev, Denmark. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrometer fitted with a sodium chloride prism. Ultraviolet spectra were recorded with a Cary Model 14 spectrometer. The nmr spectra were determined with Varian A-60 or A-60A spectrometers purchased with funds made available through the National Science Foundation.

lithium aluminum hydride in 50 ml of anhydrous tetrahydrofuran. The reaction mixture was refluxed for 18 hr and worked up in the customary alkaline manner.[1] There was obtained 146 mg (89.6%) of **22** as a light yellow oil. An analytically pure sample was prepared by preparative scale vpc (5 ft × 0.25 in. aluminum column packed with 10% SF-96 on 60–80 mesh Chromosorb G at 152°). The spectral data of this sample were identical to those of the authentic sample of **22**. The picrate was obtained as yellow crystals, mp 171–172° (from ethanol); a mixture melting point was undepressed.

Alternative Synthesis of 22. A. N-Methylhomodihydrocarbostyril (24).—To a solution of 10.0 g (0.062 mol) of homodihydrocarbostyril (**23**)[13] in 50 ml of dry dimethylformamide was added 2.5 g of 60% sodium hydride–mineral oil dispersion (0.062 mol) and the mixture was heated at 50° for 1 hr. The flask was then cooled in ice while 14.2 g (0.10 mol) of methyl iodide was added dropwise during 5 min. The ice bath was removed and the mixture was stirred at room temperature for 1 hr. Ether (150 ml) was added and the precipitated solid was separated by filtration. The filtrate was evaporated *in vacuo* and the residual brown oil was vacuum distilled to give 9.66 g (89.0%) of **24** as a colorless liquid, bp 97–100° (0.1 mm); ir $\nu_{max}^{CCl_4}$ 1665 cm^{-1} (C=O); nmr $\delta_{TMS}^{CCl_4}$ 6.99–7.26 (m, 4 H, aromatic protons), 3.25 (s, 3 H, NCH_3), 2.51–2.85 (br t, 2 H, benzylic protons), and 1.90–2.26 (m, 4 H, methylene protons).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.82; H, 7.77; N, 8.02.

B. N-Methyl-2,3-benzohexamethylenimine (25).—A 7.90-g (0.045-mol) sample of **24** was reduced with 4.0 g of lithium aluminum hydride in 150 ml of tetrahydrofuran as previously described. There was isolated 6.92 g (94.5%) of **25** as a colorless liquid, bp 58–60° (0.1–0.2 mm). The derived picrate melted at 144–145.5°.

Anal. Calcd for $C_{17}H_{18}N_4O_7$: C, 52.31; H, 4.68; N, 14.35. Found: C, 52.29; H, 4.69; N, 14.35.

C. Hydrogenation of 25.—A solution of 1.0 g (6.2 mmol) of **25** in 50 ml of ethanol was hydrogenated over 5% rhodium on carbon at 60 psig for 72 hr. The catalyst was filtered, the filtrate was concentrated, and the residue was distilled to give 920 mg (88.9%) of **22** as a colorless liquid, bp 72–74° (2 mm). The picrate melted at 171–172°.

Anal. Calcd for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10; N, 14.14. Found: C, 51.36; H, 6.35; N, 13.98.

Pyrolysis of 10-Carbomethoxy-10-azatricyclo[4.3.1.0^{1,6}]deca-2,4-diene (26).—A 100-mg (0.52 mmol) sample of **26**[1] was heated in a sealed tube for 30 min at 180°. Sublimation of the crude product at 50° and 0.05 mm afforded 93 mg (93%) of **28** as a light yellow solid, mp 61–63° (from pentane); ir $\nu_{max}^{CCl_4}$ 1727 cm^{-1} (C=O); uv λ_{max}^{hexane} 217 (ε 20,725), 253 sh (ε 1165), and 324 mμ (ε 1060); λ_{max}^{EtOH} 216.5 (ε 18,950), 249 sh (ε 905), and 312 mμ (ε 1270); nmr $\delta_{TMS}^{CDCl_3}$ 5.37–6.18 (m, 4 H, vinyl protons), 3.75 (s, 3 H, $-CH_3$), and 1.70–2.85 (m, 6 H, methylene protons).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.17; H, 7.00; N, 7.10.

Conversion of 28 to 2-Methyl-*cis*-2-azabicyclo[5.3.0]decane (29).—A 152-mg (0.80 mmol) sample of **28** was hydrogenated and reduced with lithium aluminum hydride as described for **21**. The resulting pale yellow oil was subjected to vpc purification (same column, 126°); there was obtained 68 mg (55.6%) of **29** as a colorless liquid. The picrate of **29** was obtained as light yellow needles from ethanol, mp 192.5–194°.

Anal. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.56; H, 6.03; N, 14.67.

Unequivocal Synthesis of 29. A. Schmidt Ring Expansion of *cis*-Bicyclo[4.3.0]nonan-2-one (30).—A stirred ice-cold solution of 5.53 g (0.04 mol) of *cis*-bicyclo[4.3.0]nonan-2-one (**30**)[14] in 25 ml of concentrated hydrochloric acid was treated with 4.04 g (0.062 mol) of powdered sodium azide in small portions. After stirring for 3 hr, the mixture was evaporated *in vacuo* and the residue was dissolved in 35 ml of water and basified with 30% sodium hydroxide solution. The organic product was extracted with chloroform, dried, and evaporated to give 6.0 g of yellow-white solid. This material was recrystallized with difficulty from acetone–hexane to give 4.71 g (77%) of a mixture of isomeric amides, mp 102–109°.

Methylation of 4.15 g (0.027 mol) of this mixture with sodium hydride and methyl iodide in dimethylformamide in the predescribed manner yielded 4.02 g (88.4%) of a colorless liquid, bp 78–82° (0.1–0.25 mm), composed of approximately equal amounts of **31** and **32**.

B. Hydride Reduction of 31 and 32.—A 3.0-g (0.018 mol) sample of the mixture of **31** and **32** was reduced with 1.5 g (0.039 mol) of lithium aluminum hydride in 150 ml of tetrahydrofuran to produce 2.48 g (89.8%) of amine mixture, bp 68–70° (2–4 mm). The two amines (**29** and **33**) were cleanly separated by preparative vpc [10 ft × 0.25 in. aluminum column packed with 20% Apiezon L/KOH (4:1) on 60–80 mesh Chromosorb W at 134°]. The most rapidly eluted amine (**29**) was identical in all respects with the saturated amine prepared from azepine **28**; the picrate melted at 192.5–194°; a mixture melting point was undepressed.

The second amine was assigned structure **33**. Its picrate was obtained as yellow crystals from ethanol, mp 166–168° dec.

Anal. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.19; H, 5.85; N, 14.59.

Acid-Catalyzed Rearrangement of 3,6-Dimethyl-N-carbomethoxyazepine (12).—To a solution of 600 mg (3.34 mmol) of **12** in 90 ml of dioxane was added 10 ml of 10% sulfuric acid, and the mixture was stirred at room temperature for 2 hr. The major portion of the solvent was removed *in vacuo* and the residue was treated with 400 ml of water and 500 ml of ether. The aqueous phase was further extracted with two 150-ml portions of ether and the combined organic layers were dried, filtered, and evaporated. There was obtained 548 mg of an off-white solid. Recrystallization of this material from ether–hexane gave 496 mg (82.6%) of **14**, mp 86–87°, identical in all respects with the authentic sample.

Acid-Catalyzed Rearrangement of 2,7-Dimethyl-N-carbomethoxyazepine (16).—A solution of 2.0 g (11.2 mmol) of **16** in 90 ml of dioxane and 10 ml of 10% sulfuric acid was refluxed for 1 hr. After cooling, 300 ml of water was added and the aqueous mixture was extracted with four 200-ml portions of ether.[15] There was obtained a viscous brown oil which was chromatographed on neutral alumina (activity I). Elution with hexane–ether (7:3) separated two fractions, each of which was found (vpc analysis) to be composed of a major and a minor component. Preparative vpc separation (5 ft × 0.25 in. aluminum column packed with 10% Carbowax 20M on 60–80 mesh Chromosorb W at 136°) afforded 81 mg (6%) of 3,4-dimethylphenol (**38**), mp 66–68°, identical with an authentic sample. The minor product (15 mg, 1%) was shown to be 2,6-dimethylphenol (**39**). The yield of the phenol mixture prior to vpc separation was 121 mg (9%).

Preparative vpc separation of the second fraction (5 ft × 0.25 in. aluminum column packed with 10% SF-96 on 60–80 mesh Chromosorb G at 148°) yielded 320 mg (16%) of 2,6-dimethyl-N-carbomethoxyaniline (**36**), mp 103–105°, and 20 mg (1%) of 2,3-dimethyl-N-carbomethoxyaniline (**37**), mp 90–92°.

2,6-Dimethyl-N-carbomethoxyaniline (36).—An authentic sample of **36** was obtained in quantitative yield from 2,6-dimethylaniline (12.1 g, 0.10 mol) and methyl chloroformate (4.72 g, 0.05 mol) under the above conditions as a fluffy white solid, mp 103–105° (from ether–hexane); ir $\nu_{max}^{CCl_4}$ 3365 (NH) and 1742 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 6.89 (s, 3 H, aromatic protons), 6.65 (br, 1 H, NH), 3.59 (s, 3 H, $-OCH_3$), and 2.12 (s, 6 H, $-CH_3$).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.99; H, 7.36; N, 7.85.

2,3-Dimethyl-N-carbomethoxyaniline (37).—Reaction of 2,3-dimethylaniline with methyl chloroformate in the predescribed fashion afforded a quantitative yield of **37** as a fluffy white solid, mp 90.5–92° (from ether–hexane); ir $\nu_{max}^{CCl_4}$ 3355 (NH) and 1748 cm^{-1} (C=O); nmr $\delta_{TMS}^{CDCl_3}$ 6.52–7.19 (m, 3 H, aromatic protons), 6.26 (br, 1 H, NH), 3.57 (s, 3 H, $-OCH_3$), 2.13 and 1.98 (s, 3 H each, $-CH_3$).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.01; H, 7.36; N, 7.72.

Acid-Catalyzed Rearrangement of 18.—A solution of 150 mg (0.73 mmol) of **18** in 50 ml of dioxane was treated with 10 ml of 10% sulfuric acid for 2 hr at room temperature according to the generalized procedure described above. Recrystallization of the

(13) L. H. Briggs and G. C. Death, *J. Chem. Soc.*, 456 (1937).

(14) W. Hückel and E. Goth, *Chem. Ber.*, **67**, 2104 (1934); see also E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 164, note 1.

(15) The remaining acidic aqueous layer was basified with 30% sodium hydroxide solution and the extraction process was repeated. A few milligrams of a yellow oil was isolated; this substance was not examined further.

residual solid (146 mg) from ether–pentane gave 133 mg (88.5%) of **41** as a fluffy white solid, mp 58.5–60°.

Acid-Catalyzed Rearrangement of 21.—Treatment of 350 mg (1.7 mmol) of **21** as above gave 326 mg of crude product. Recrystallization of this solid from ether–pentane afforded 294 mg (84%) of **41**, mp 58.5–60°, identical in all respects with an authentic sample.

1-(N-Carbomethoxy)amino-5,6,7,8-tetrahydronaphthalene (14).—Reaction of 1-amino-5,6,7,8-tetrahydronaphthalene (Aldrich Chemical Co.) with methyl chloroformate in the predescribed fashion yielded pure **41** in 91.5% yield, mp 58.5–60°; ir $\nu_{max}^{CCl_4}$ 1742 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.35; H, 7.49; N, 6.80.

Acid-Catalyzed Rearrangement of 28.—A solution of 396 mg (2.07 mmol) of **28** in 50 ml of dioxane was treated with 10 ml of 10% sulfuric acid for 2 hr at room temperature according to the generalized procedure described above. Recrystallization of the crude product from ether–pentane yielded 341 mg (86%) of **42**, mp 69–70.5°, identical in all respects with an authentic sample.

4-(N-Carbomethoxy)aminoindan (42). A. 4- and 5-Aminoindans.—Indane (100 g) was nitrated according to the procedure of Lindner and Bruhin[16] to give a mixture of 4- and 5-nitroindans in approximately 70% yield. Reduction of the mixture with ferrous chloride in aqueous ethanol[16] afforded the derived amines in 80% yield (ratio of isomers 2:3).

B. Carbomethoxylation of 4- and 5-Aminoindans. Reaction of 13.32 g (0.10 mol) of the aminoindan mixture prepared above with 4.73 g (0.05 mol) of methyl chloroformate according to the above procedure gave 9.21 g (96.3%) of a brownish oil. Preparative vpc separation of this two-component mixture (5 ft × 0.25 in. aluminum column packed with 10% SF-96 on 60–80 mesh Chromosorb G, 152°) yielded the two pure carbamates, mp 69–70.5° and mp 63–65°.

The more rapidly eluted component was identified as **42**, mp 69–70.5°; ir $\nu_{max}^{CCl_4}$ 1715 cm^{-1} (C=O), by difference (see below).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.06; H, 6.83; N, 7.31.

The less rapidly eluted component was identified as 5-(N-carbomethoxy)aminoindan, mp 63–65°, on the basis of independent synthesis from authentic 5-aminoindan (Aldrich Chemical Co.); ir $\nu_{max}^{CCl_4}$ 1745 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.25; H, 6.79; N, 7.38.

Acid-Catalyzed Rearrangement of 26.—A solution of 100 mg (0.576 mmol) of **26** in 50 ml of dioxane was treated with 10 ml of 10% sulfuric acid for 2 hr at room temperature as above. Column chromatography of the residue (no **26** remaining on the basis of nmr spectrum) on Florisil afforded 32 mg (42%) of 5-hydroxyindan (**43**), mp 51–53°, identical with an authentic sample (K + K Laboratories), and 7 mg (7%) of **42**, mp 69–70.5°. Elution of the column was achieved with hexane–ether (9:1).

Rearrangement of 26 on Florisil.—A mixture of 250 mg (1.31 mmol) of **26**, 50 ml of ether, 5 ml of water and 1 g of Florisil was evaporated to dryness at room temperature on a rotary evaporator. The resulting powder was placed on top of a column of 50 g of Florisil. Elution with hexane–ether (99:1) yielded 22 mg of unrearranged **26**. Elution with hexane–ether (19:1) afforded 186 mg (81.5%) of **44** as white needles, mp 137–138° (from ether–hexane); ir $\nu_{max}^{CCl_4}$ 3448, 3310 (-OH and NH) and 1725 cm^{-1} (C=O); uv λ_{max}^{EtOH} only end absorption; mass spectrum *m/e* 209; nmr $\delta_{TMS}^{CDCl_3}$ 5.87–6.39 (m, 3 H, vinyl protons), 5.52 (br, 1 H, NH), 4.22–4.48 (br, 2 H, CHOH), 3.65 (s, 3 H, $-OCH_3$), 1.34–2.73 (m, 6 H, methylene protons). Addition of D_2O results in the disappearance of the 5.52 peak and gross simplification of the 4.22–4.48 absorption (intensity decreasing to 1 H).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.34; H, 7.27; N, 6.78.

Acid-Catalyzed Rearrangement of 44.—A solution of 150 mg (0.72 mmol) of **44** in 50 ml of dioxane was treated with 10 ml of 10% sulfuric acid at room temperature for 2 hr in the above fashion. The resulting viscous brown oil (94 mg) was chromatographed on Florisil. Elution with hexane–ether (9:1) afforded 54 mg (56%) of 5-hydroxyindan (**43**), mp 51–53°, and 11 mg (8%) of **42**, mp 68–70°.

Registry No.—**8**, 14983-92-7; **11**, 20642-87-9; **14**, 20642-88-0; **21**, 20642-89-1; **22**, 20642-49-3; **22** (picrate), 20642-68-6; **24**, 20678-82-4; **25**, 20642-90-4; **25** (picrate), 20642-91-5; **28**, 20642-92-6; **29** (picrate), 20642-50-6; **31**, 20642-51-7; **32**, 20642-52-8; **33** (picrate), 20642-53-9; **36**, 20642-93-7; **37**, 20642-94-8; **38**, 95-65-8; **41**, 20642-96-0; **42**, 20642-97-1; **44**, 20642-98-2; 5-(N-carbomethoxy)aminoindan, 20642-99-3.

Acknowledgment.—The authors wish to thank the National Institutes of Health and the Ciba Corporation for grants employed in the financial support of this research.

(16) J. Lindner and J. Bruhin, *Chem. Ber.*, **60**, 435 (1927).

Unsaturated Heterocyclic Systems. LIV. Photorearrangements of the Methyl-N-carbomethoxyazepines[1]

LEO A. PAQUETTE AND DONALD E. KUHLA[2]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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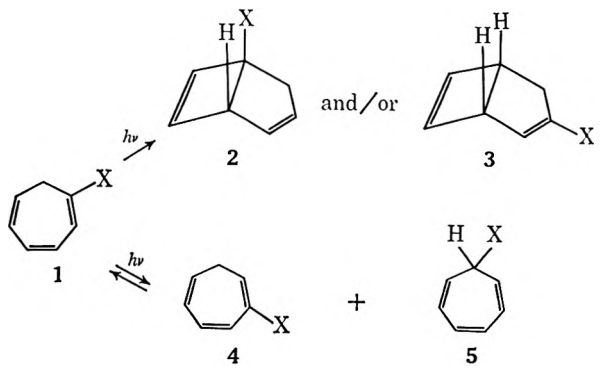
Irradiation of methanol solutions of 2-, 3-, and 4-methyl-N-carbomethoxyazepines (**10**, **14**, and **17**, respectively) with a Hanovia 450-W mercury arc under nitrogen through Pyrex yields in each instance a two-component mixture containing both possible bicyclic valence tautomers. All of the 2-carbomethoxy-2-azabicyclo[3.2.0]-hepta-3,6-dienes are primary photoproducts which may be considered to arise by disrotatory cyclization from the lowest lying excited states of the three azepines. Only in the case of **10** is product selectivity observed. The origin of this selectivity in terms of steric factors is discussed.

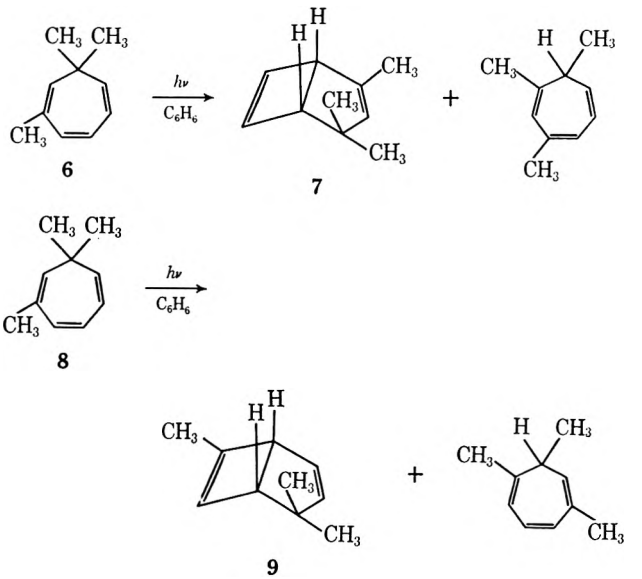
Irradiation of a number of conjugated medium-ring dienes and trienes in solution has been shown to give bicyclic structures which incorporate a cyclobutene ring, and the course of these reactions remains unaltered upon the introduction of heteroatoms into the ring system.[3] *A priori*, placement of a substituent at one of the vinyl carbons of a cyclic triene, *e.g.*, **1**, permits two competitive electrocyclic reactions which can lead to **2** and **3**. A. P. ter Borg[4,5] and Chapman[6] have shown that photoisomerizations of both 1- (**1**) and 7-substituted cycloheptatrienes (**5**) are complicated by 1,7-sigmatropic shifts of hydrogen, but nevertheless it is



clear that the nature of the substituent exerts a substantial influence on the selectivity of formation of **2** and **3**. This effect appears to be chiefly electronic in nature.

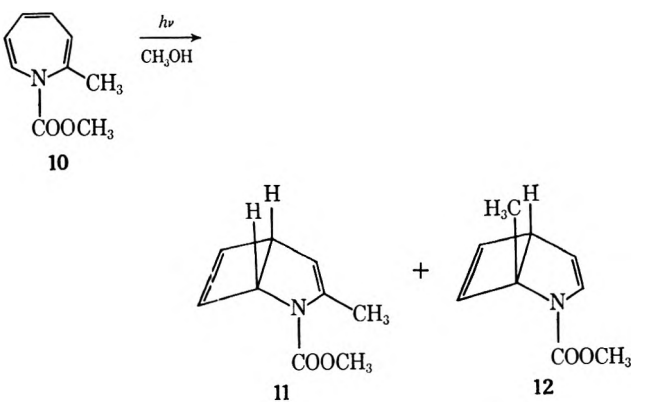
Jones has found that irradiation of 2,7,7- (**6**) and 3,7,7-trimethylcycloheptatriene (**8**) give **7** and **9**, respectively, together with products arising from 1,7 migrations of methyl and hydrogen.[7,8] In these cyclizations, a single isomer of the bicyclic product was formed in each case, indicating that the course of the isomerizations was controlled by steric interactions.

The availability of a series of substituted 1H-azepines[9] has permitted us to examine the effect of



methyl groups on the cause of photochemical electrocyclic reactions in these 8π-heterocyclic systems.

The 2-Methyl Derivative.—Irradiation of 2-methyl-N-carbomethoxyazepine (**10**) in dilute methanol solution for 2 hr gave a mixture which consisted of 2-carbomethoxy-3-methyl-2-azabicyclo[3.2.0]hepta-3,6-diene (**11**, 93.5%) and the corresponding 1-methyl isomer **12** (6.5%). Analysis of the photolysis mixture at various time intervals indicated that **11** and **12** were



primary photoproducts and that neither bicyclic compound was noticeably destroyed upon continued irradiation. The assignments of structure to the photoproducts were based chiefly on spectral data, analysis of which was rendered particularly facile because of the extensively analyzed nmr spectrum of the parent

(1) For previous paper in this series, see L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.*, **34**, 2879 (1969).

(2) National Institute of Health Predoctoral Fellow, 1965–1968.

(3) See, for example, (a) L. A. Paquette and J. H. Barrett, *J. Amer. Chem. Soc.*, **88**, 1718 (1966); (b) L. A. Paquette, J. H. Barrett, R. P. Spitz, and R. Pitcher, *ibid.*, **87**, 3417 (1965); (c) L. A. Paquette, *ibid.*, **86**, 500, 4092 (1964); (d) L. A. Paquette, *Tetrahedron Lett.*, 2027 (1963), and references cited in these papers.

(4) A. P. ter Borg and H. Kloosterziel, *Rec. Trav. Chim.*, **84**, 241 (1965).

(5) A. P. ter Borg, E. Razenberg, and H. Kloosterziel, *Chem. Commun.*, 1210 (1967).

(6) G. W. Borden, O. L. Chapman, R. Swindell, and T. Tezuka, *J. Amer. Chem. Soc.*, **89**, 2979 (1967).

(7) L. B. Jones and V. K. Jones, *ibid.*, **90**, 1540 (1968).

(8) L. B. Jones and V. K. Jones, *ibid.*, **89**, 1880 (1967).

(9) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *ibid.*, **34**, 2866 (1969).

bicyclic (**13**) (Table I).[2a] The nmr spectrum of **11** shows the C-methyl group at δ 2.04 indicative of its attachment to sp^2-hybridized carbon. H-3 in **13** resonates at approximately δ 6.56, and, since this absorption is absent in the spectrum of **11**, it follows that the ring substituent occupies this position. The remaining hydrogens appear as multiplets in the appropriate regions. In the spectrum of **12**, the methyl substituent is positioned at C-1 (δ 1.60).[10] The remaining bridgehead proton is seen as a somewhat broadened doublet at δ 3.26 while the vinyl protons take on the appearance characteristic of **13**. The mass spectra of **11** and **12** also confirm the assigned structures (see below).

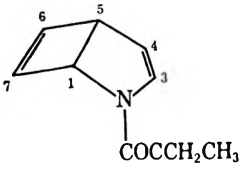


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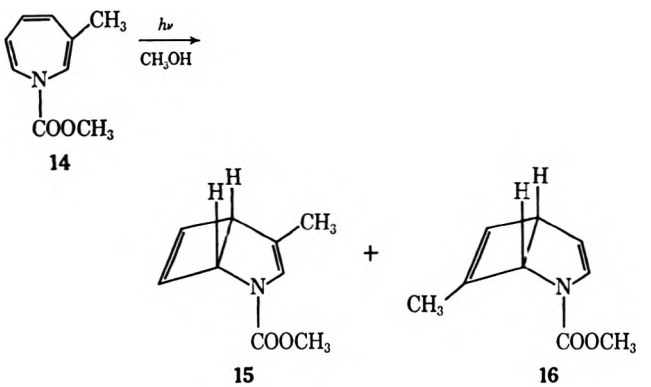
TABLE I

PROTON CHEMICAL-SHIFT VALUES FOR VARICUS 2-CARBALKOXY-2-AZABICYCLO[3.2.0]HEPTA-3,6-DIENES

	δ units					
Compd	H-1	H-3	H-4	H-5	H-6	H-7
13	4.88	6.56	5.18	3.88	6.42	6.04
11	4.75	...	4.80	3.51	6.19	5.89
12	...	6.24	4.87	3.26	6.15	6.05
15	4.79	6.12	...	3.64	6.40	5.99
16	4.71	6.40	5.08	3.60	5.99	...
18	4.38	6.35	4.97	...	6.35	5.89
19	4.69	6.48	5.12	3.66	...	5.72

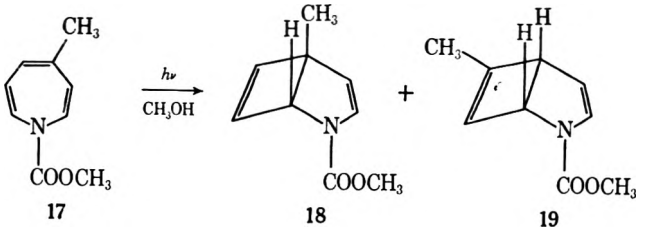
The 3-Methyl Derivative.—When a 3% methanol solution of 3-methyl-N-carbomethoxyazepine (**14**) was irradiated for 12 hr, there resulted the complete disappearance of **14** and the concomitant formation of two photoproducts at equal rates in a 1:1 ratio. There was no indication of product interconvertibility. Preparative scale vpc separation of the mixture afforded pure samples of valence tautomers **15** and **16**. The more rapidly eluted isomer was identified at 4-methyl-2-carbomethoxy-2-azabicyclo[3.2.0]hepta-3,6-diene (**15**). In agreement with this structure, the nmr spectrum of **15** exhibits methyl absorption at δ 1.65 (t, J = 1.5 Hz, allylic coupling to H-3) and lacks the peak characteristic of H-4 (usually found in its isomers at δ 4.8–5.1). The bicyclic skeleton and the location of the methyl substituent on the five-membered ring were confirmed by mass spectral analysis.



The nmr spectrum of photoproduct **16** shows a methyl group on a double bond (δ 1.68). The vinyl protons appear as the expected broadened multiplets with the peak due to the proton at position 7 being absent. The multiplets attributable to H-6 and H-5 appear to be somewhat simplified (relative to the absorptions in **13**) by virtue of the introduction of the methyl group at C-7.

The 4-Methyl Derivative.—Irradiation of a 4% solution of **17** in anhydrous methanol was found to result in the total consumption of starting azepine during 12 hr. After careful removal of solvent, the resulting two-component product mixture was subjected to preparative vpc. The first fraction was found to be the 5-methyl derivative **18** (δ_{CH_3} 1.30), whereas the more slowly eluted substance was the 6-methyl isomer **19** (δ_{CH_3} 1.72). The ratio of **18**:**19** was 1.5:1.

It should be noted that all six possible monomethyl derivatives of 2-carbomethoxy-2-azabicyclo[3.2.0]hepta-3,6-diene have now been isolated. Comparison of the derived nmr spectra of these isomeric bicyclic heterocycles (Table I) provides a source of internal consistency for the experimental observations and structural assignments.



Mass Spectral Studies.—The x-methyl-2-carbomethoxy-2-azabicyclo[3.2.0]hepta-3,6-dienes are rapidly oxidized upon exposure to air.[11] When handled or stored in an inert atmosphere, however, the pure substances appeared to be stable for a period of a few days. In all six cases, mass spectral analysis gave evidence of abundant molecular ion (m/e 165) formation (Table II).

TABLE II

MASS SPECTRAL DATA FOR THE x-METHYL-2-CARBOMETHOXY-2-AZABICYCLO[3.2.0]HEPTA-3,6-DIENES

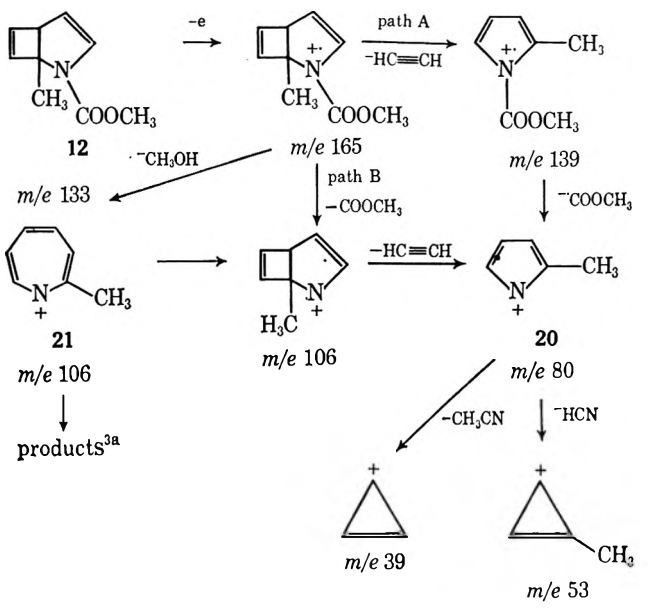
Compd	m/e (% relative abundance)
11	39 (30), 44 (20), 51 (17), 52 (15), 53 (21), 59 (29), 65 (43), 77 (21), 78 (23), 79 (20), 80 (13), 91 (23), 92 (11), 94 (61), 104 (31), 105 (18), 106 (61), 132 (16), 133 (55), 138 (11), 139 (100), 140 (10), 165 (52).
12	39 (29), 50 (11), 51 (18), 52 (11), 53 (16), 59 (20), 63 (10), 65 (51), 77 (22), 78 (23), 79 (19), 80 (13), 91 (18), 94 (42), 104 (25), 105 (15), 106 (100), 107 (11), 132 (15), 133 (43), 139 (53), 165 (52).
15	39 (50), 32 (21), 50 (21), 51 (43), 52 (31), 53 (34), 59 (29), 63 (15), 65 (21), 77 (60), 78 (34), 79 (51), 80 (20), 91 (21), 94 (66), 103 (23), 106 (100), 133 (23), 139 (71), 165 (57).
16	39 (58), 42 (19), 50 (17), 51 (34), 52 (21), 53 (25), 54 (12), 55 (14), 59 (31), 63 (13), 65 (11), 77 (58), 78 (25), 79 (48), 80 (51), 81 (16), 91 (13), 104 (19), 106 (87), 125 (100), 133 (13), 165 (47).
18	39 (11), 44 (13), 50 (11), 51 (19), 52 (16), 53 (11), 59 (11), 77 (29), 78 (19), 79 (28), 91 (25), 94 (19), 104 (24), 105 (14), 106 (64), 132 (57), 133 (100), 134 (12), 139 (33), 165 (47).
19	39 (29), 44 (40), 50 (10), 51 (18), 52 (14), 53 (12), 59 (23), 63 (10), 65 (10), 77 (27), 78 (15), 79 (24), 80 (34), 91 (23), 104 (27) 106 (38), 125 (100), 132 (43), 133 (85), 134 (12), 165 (34).

(10) It seems likely that this methyl chemical shift is a result of deshielding by the neighboring urethan function. Compare the values for δ_{CH_3} displayed by the other bicyclic isomers.

(11) This property precluded combustion analysis.

The principal fragmentation mode of the bicyclic valence tautomers was expected[3a] to be the loss of C-6 and C-7 and their attached substituents as an acetylene derivative, and this was generally observed (path A). Thus, peaks corresponding to M − HC≡CH (*m/e* 139) are clearly seen in the spectra of **11**, **12**, **15**, and **18**, whereas the molecular ions of **16** and **19** fragment with the ejection of neutral propyne and formation of an ion with *m/e* 125. The base peaks in the spectra of **12** and **15** are located at *m/e* 106, indicating that loss of the carbomethoxyl residue (path B) is particularly favored in these instances. In actuality, path B appears to compete favorably with path A in the decomposition of most of these compounds. Convincingly, the various differences and similarities serve to provide firm additional support for the nmr-based structural assignments. Scheme I depicts the proposed fragmentation pathway for **12**.

SCHEME I



Loss of methanol from the molecular ion would also seem to be facile in a number of examples; where this is a major process, an intense peak at *m/e* 133 is seen. Of the many lower molecular weight product ions, the majority can be construed as arising from intermediate ions such as **20**, **21**,[9] or the nonmethylated counterpart of **20**. The ions of mass 39 and 53, for example, are very probably due to the cyclopropenyl cation and its methyl homolog, respectively.[12]

Discussion

Woodward–Hoffmann orbital symmetry arguments for electrocyclic reactions indicate that cyclobutene production very likely occurs by disrotatory motion of π orbital envelopes in the lowest lying excited state. In monosubstituted N-carbomethoxyazepines, however, two different disrotatory cyclizations are possible. The ratio of primary photoproducts from the irradiation of such substituted 1H-azepines reveals the influence exerted by the R group upon the two competitive electrocyclic processes. The irradiation of **10** was seen to be quite selective, leading to **11** and **12** in a ratio of 14:1; the 3-methyl isomer (**14**) gave **15** and **16** in equimolar quantities; lastly, photolysis of **17** afforded **18** and **19** in a ratio of 1.5:1.

Of the two possible 2-azabicyclo[3.2.0]hepta-3,6-dienes derivable from **10**, that in which the ring methyl substituent occupies the more congested angular position (**12**) is produced only in low yield, indicating dominant steric effects in this reaction. On this basis, the observation that **14** produces both possible valence tautomers (**15** and **16**) in equal amounts is not unanticipated, since the photoisomers are not expected to differ measurably in strain energy. Significantly, however, the 4-methyl function in **17** does not exert an overwhelming directive influence on the course of the photoreaction, despite the fact that in **18** the alkyl group is located at an angular position.

It appears, therefore, that the presence of a methyl group at an angular position does not alone constitute a significantly strong deterrent to product formation. Rather, the selectivity noted in the cyclization of **10** is rationalized on the basis of serious nonbonded interactions between the methyl group and the rather bulky substituent on nitrogen (subject, of course, to pyramidal inversion) as disrotation leading to **12** begins. Such repulsive forces, which are absent in the alternative electrocyclization, are apparently sufficient to cause the preferred formation of **11**. As noted earlier, steric factors also seem to control the valence isomerization of *x*,7,7-trimethylcycloheptatrienes.[7,8] In contrast, the photorearrangements of **14** and **17** are not affected by nonbonded interactions and selectivity is not observed. These results are congruent with HMO calculations which indicate no preference for the competitive cyclizations in the absence of polarizable substituents.[8]

Experimental Section[13]

Irradiation of 2-Methyl-N-carbomethoxyazepine (10).—A solution of 4.31 g (0.026 mol) of **10**[9] in 350 ml of methanol was irradiated at room temperature under a nitrogen atmosphere with an immersion type Hanovia 450-W lamp equipped with a Pyrex filter. The progress of the reaction was followed by vpc.[14] After 2 hr, the azepine had completely reacted and the solvent was removed under reduced pressure at 25°. The remaining light yellow liquid was found to be a two-component mixture (ratio of 14:1, vpc analysis). Vacuum distillation gave 3.49 g (81%) of pale yellow liquid, bp 46–48° (0.05 mm); the ratio of components was unaltered. Preparative scale vpc[14] at 130° cleanly separated the two photoproducts. The most rapidly eluted material proved to be **11** (93.5%), ir $\nu_{max}^{CCl_4}$ 1721 cm^{-1}; the minor product was **12** (6.5%), ir $\nu_{max}^{CCl_4}$ 1718 cm^{-1}.

Irradiation of 3-Methyl-N-carbomethoxyazepine (14).—A solution of 1.25 g (7.56 mmol) of **14**[9] in 350 ml of methanol was irradiated as above. After 12 hr, vpc analysis indicated the absence of **14** and the presence of two photoproducts in equal amounts. The reaction mixture was concentrated *in vacuo* at 25° and the residue was distilled to give 1.02 g (81.5%) of a mixture of **15** (50%) and **16** (50%). Preparative scale vpc[14] at 115° afforded pure samples of the two bicyclic valence tautomers.

(12) For a discussion of the mass spectra of pyrroles, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 596–614.

(13) The nmr spectra were determined with Varian A-60 or A-60A spectrometers. The mass spectra were measured with an AEI MS-9 instrument at an ionizing energy of 70 eV. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrometer fitted with a sodium chloride prism.

(14) A 5 ft × 0.25 in. aluminum column packed with 20% SF-96 on 60–80 mesh Chromosorb W at 157° was employed in conjunction with a Varian-Aerograph A-90P3 instrument.

The more rapidly eluted product proved to be **15**, ir $\nu_{max}^{CCl_4}$ 1706 cm^{-1}; the second substance was identified as **16**, ir $\nu_{max}^{CCl_4}$ 1715 cm^{-1}.

Irradiation of 4-Methyl-N-carbomethoxyazepine (17).—A solution of 1.50 g (9.1 mmol) of **17**[9] in 350 ml of methanol was irradiated as described for **10** for 12 hr. The reaction mixture was concentrated and samples of **18** (60%, ir $\nu_{max}^{CCl_4}$ 1712 cm^{-1}) and **19** (40%, ir $\nu_{max}^{CCl_4}$ 1712 cm^{-1}) were collected by gas chromatography[14] at 110°.

Registry No.—**11**, 20628-97-1; **12**, 20628-98-2; **13**, 20628-99-3; **15**, 20629-00-9; **16**, 20629-01-0; **18**, 20629-02-1; **19**, 20629-03-2.

Acknowledgment.—The authors wish to thank the National Institutes of Health and the Ciba Corporation for grants employed in the financial support of this research.

Unsaturated Heterocyclic Systems. LV. Cycloaddition Reactions of Derivatives of 1H-Azepine[1]

LEO A. PAQUETTE, DONALD E. KUHLA,[2] JAMES H. BARRETT, AND LOUIS M. LEICHTER

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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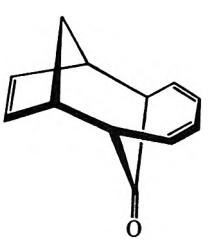
The cycloadditions of N-substituted azepines to various dienophiles and dienes have been studied. With tetracyanoethylene, the azepines add as 1,4-dienes without prior valence bond isomerization; however, a directional specificity is observed with the monomethyl ring substituted examples. With N-phenylmaleimide, there is again evidenced 1,4 addition to the seven-membered ring, the stereochemical outcome (*endo*) being in agreement with orbital symmetry considerations. In the case of isobenzofurans, $(4 + 2)\pi$ cycloaddition to the 4,5 bond of the azepines occurs. Significantly, the stereochemistry of these reactions is likewise *endo*. 2,5-Dimethyl-3,4-diphenylcyclopentadienone functions in a similar fashion. Therefore, this kinetic preference for addition to the double bond of the azepine ring most remote from the nitrogen atom does not appear to be dependent on the electronic characteristics of the 4π donor. These results indicate that the 1H-azepine nucleus is unique in its capability to undergo thermally induced cycloaddition reactions without recourse to prior valence tautomerism.

A common and fundamental property of conjugated medium-ring polyenes is their capability for cycloaddition. Frequently, however, addition of a dienophile to a cyclic polyolefin eventuates in Diels–Alder $[(4 + 2)\pi]$ reaction with the valence tautomer of the triene or tetraene system. Thus, cyclooctatetraenes (**1**), azacyclooctatetraenes (**2**), cycloheptatrienes (**3**), and oxepins (**4**) yield tricyclic adducts formally derived from bicyclo[4.2.0]octatriene,[3] 7-azabicyclo[4.2.0]octatriene,[4] norcaradiene,[5] and benzene oxide[6] intermediates, respectively. The reported exceptions to this general trend appear to be tropone (**5**),[7] certain tropolones and their ethers,[7] and 1H-azepines (**6**).[8] This difference in behavior is understandable in view of the facility with which **1**–**4** equilibrate with their valence tautomers and the contrasting difficulty presumably experienced by **5**[9] and **6**[10] to attain a similar rapid equilibrium with their bicyclic forms. Cycloaddition to the diene tautomers is kinetically preferred because of the favorable increase in coplanarity of the four participating π orbitals in these structures.

More recently, several reports concerning the cycloaddition of cyclic trienes to suitable dienes in a $(6 + 4)\pi$ reaction have appeared. Thus, tropone (**5**) condenses readily with cyclopentadiene to give **7**,[11] whereas both



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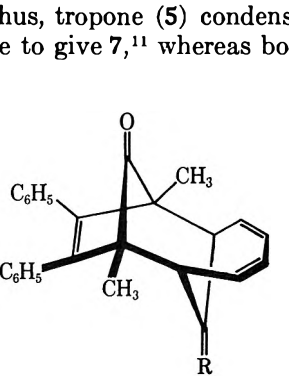


8a, R = O
b, R = H_2

5 and cycloheptatriene add to 2,5-dimethyl-3,4-diphenylcyclopentadienone to afford **8a** and **8b**, respectively.[12] Orbital symmetry considerations indicate that such reactions, if effected with heat, may be concerted and should exhibit a preference for *exo* addition

(1) For previous paper, see L. A. Paquette and D. E. Kuhla, *J. Org. Chem.*, **34**, 2885 (1969).

(2) National Institutes of Health Predoctoral Fellow, 1965–1968.

(3) For a review, consult G. Schröder, "Cyclooctatetraene," Verlag Chemie, Weinheim/Bergstr., Germany, 1965.

(4) L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, **90**, 3897 (1968).

(5) (a) K. Alder and G. Jacobs, *Chem. Ber.*, **86**, 1528 (1953); (b) M. J. Goldstein and A. H. Gervitz, *Tetrahedron Lett.*, 4417 (1965); (c) G. H. Wahl, Jr., *J. Org. Chem.*, **33**, 2158 (1968).

(6) (a) E. Vogel, R. Schubart, and W. A. Böll, *Angew. Chem. Intern. Ed. Engl.*, **3**, 510 (1964); (b) E. Vogel, E. A. Böll, and H. Günther, *Tetrahedron Lett.*, 609 (1965).

(7) (a) T. Nozoe, T. Mukai, K. Takase, and T. Nagase, *Proc. Jap. Acad.*, **28**, 477 (1962); *Chem. Abstr.*, **48**, 2678 (1954); (b) J. Meinwald, S. L. Emerson, N. C. Yang, and G. Buchi, *J. Amer. Chem. Soc.*, **77**, 4400 (1955); (c) O. L. Chapman and D. J. Pasto, *ibid.*, **81**, 3696 (1959); (d) T. Nozoe, T. Mukai, T. Nagase, and Y. Toyooka, *Bull. Chem. Soc. Jap.*, **33**, 1147 (1960); (e) J. Ciabattoni, J. E. Crowley, and A. S. Kende, *J. Amer. Chem. Soc.*, **88**, 2778 (1967); (f) Y. Kitahara, I. Murata, and T. Nitta, *Tetrahedron Lett.*, 3003 (1967); (g) S. Ito, H. Takeshita, Y. Shoji, Y. Toyooka, and T. Nozoe, *ibid.*, 3215 (1968).

(8) (a) J. E. Baldwin and R. A. Smith, *J. Amer. Chem. Soc.*, **87**, 4819 (1965); (b) A. S. Kende, P. T. Izzo, and J. E. Lancaster, *ibid.*, **87**, 5044 (1965).

(9) Valence tautomerism of a tropone or tropolone would lead to an energetically unfavorable cyclopropanone derivative.

(10) (a) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969); (b) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *ibid.*, **34**, 2879 (1969); (c) L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Amer. Chem. Soc.*, **91**, 3231 (1969).

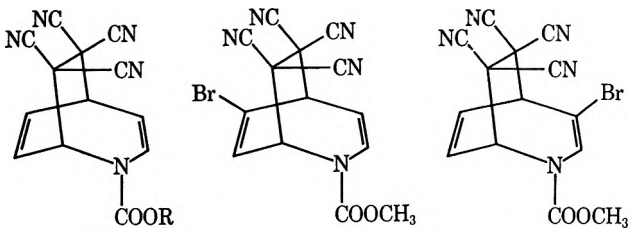
(11) (a) R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.*, 15 (1966); (b) S. Ito, Y. Fujise, T. Okuda, and Y. Inoue, *Bull. Chem. Soc. Jap.*, **39**, 1951 (1966).

(12) R. B. Woodward and K. Houk, unpublished work cited by R. B. Woodward, "Aromaticity," Special Publication No. 21, Chemical Society (London), 1967, pp 242–246.

(observed in the cases of **7** and **8**) if symmetry factors are dominant.[13]

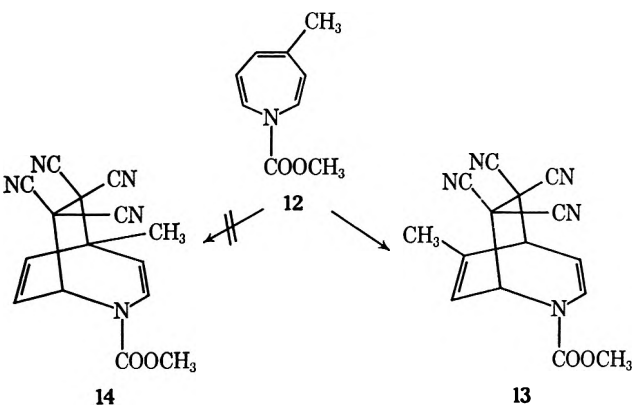
Earlier, the kinetically controlled dimerization of 1-carbalkoxy-1H-azepines was shown to be the result of a similar (6 + 4)π combination with *exo* orientation,[10c] in which the azepine molecules play the rather unique bifunctional role of 6π- and 4π-electron donors. We now report a more detailed investigation of the characteristics of these 8π heterocycles in a variety of cycloaddition reactions.

Tetracyanoethylene.—Only recently have the structures of the adducts produced by reaction of N-carbethoxy- and N-carbomethoxyazepines with tetracyanoethylene (TCNE) been rigorously established as **9a** and **9b**, respectively.[8,14] Kende and Baldwin combined an evaluation of spectral parameters, chemical transformations, and X-ray analysis[15] to demonstrate that the cycloadditions resulted from bonding directly to the nonrearranged seven-membered ring. The reaction of TCNE with a mixture of 1-carbomethoxy–bromoazepines to give **10** and **11** has been described.[8a,16]



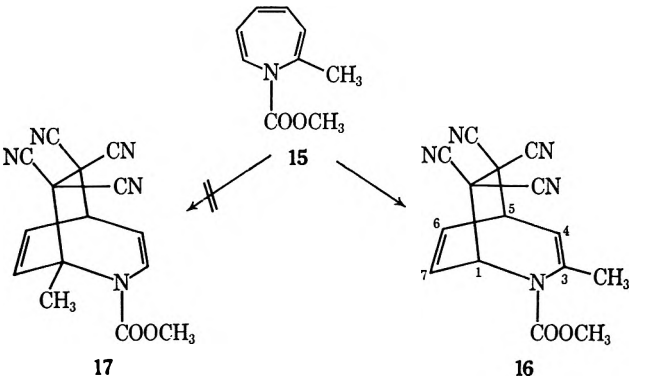
9a, R = C_2H_5
b, R = CH_3 **10** **11**

We have investigated the reaction of TCNE with the three isomerically pure methyl N-carbomethoxyazepines. The 4-methyl isomer (**12**) was found to react readily with TCNE in refluxing toluene solution to produce in 65% yield the previously characterized[8a] (4 + 2)π adduct **13**. There was no evidence that any of the isomeric possibility (**14**) had formed.



14 **13**

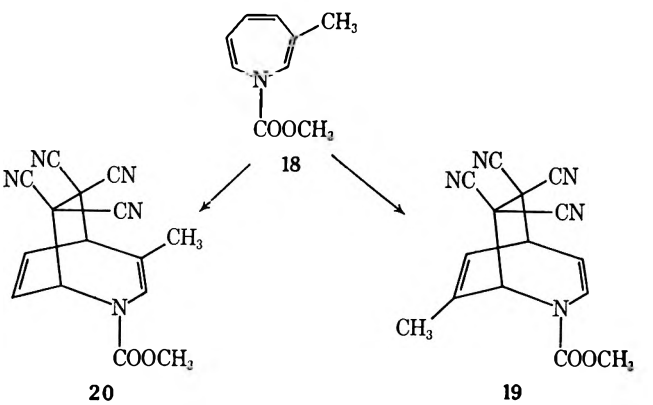
2-Methyl-N-carbomethoxyazepine (**15**) under identical conditions gave **16**, but only in 2.5% yield. The nmr spectrum of **16** in DMSO-d_6 displayed a multiplet at δ 6.28–6.91 characteristic of H_6 and H_7, a one-proton



17 **16**

doublet of doublets centered at 6.04 (J_{16} = 1.4 Hz, J_{17} = 7.5 Hz), multiplets at 5.08–5.31 and 3.85–4.15 (H_4 and H_5, respectively), and C-methyl absorption (d, J = 1.5 Hz) at 2.15. The appearance of the very characteristic pair of doublets at δ 6.04 assignable to H_1 serves to rule out the possibility that the adduct was actually **17**, which bears a methyl group at that position. No indication was ever obtained that **17** was present in the crude reaction mixtures. The only other characterizable product was 2-methyl-N-carbomethoxyaniline (5% yield) which presumably arose from rearrangement of **15**.[10b] The major portion of the reaction mixture was intractable black tar.

Refluxing 3-methyl-N-carbomethoxyazepine (**18**) with TCNE in toluene led to the formation of a mixture of adducts **19** and **20** in 66% yield. The two substances



20 **19**

could not be separated by preparative thin layer or column chromatography. However, when the yellowish oil was treated with a seed crystal of **13**, a white crystalline solid, mp 146.5–148.5°, was deposited. The nmr spectrum of this material (in DMSO-d_6) showed significant absorptions centered at δ 6.45 (two-proton multiplet, H_3 and H_6), 5.76 (broad singlet, H_1), 5.43 (multiplet, H_4), *ca.* 3.81 (multiplet, H_5), and 2.15 (slightly broadened three-proton singlet, C-methyl). The appearance of a signal at δ 5.43, which has a chemical shift assignable to H_4, permitted the assignment of structure **19** to the crystalline product. Other indications that the solid was the 7-methyl derivative were found in the absence of a low field absorption due to H_7, the simplification of the H_1 signal, since spin–spin

(13) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965).

(14) For a previous erroneous structural assignment, see K. Hafner, *Angew. Chem.*, **75**, 1041 (1963); *Angew. Chem. Intern. Ed. Engl.*, **3**, 165 (1964).

(15) J. H. van den Hende and A. S. Kende, *Chem. Commun.*, 384 (1965).

(16) I. C. Paul, J. E. Baldwin, and R. A. Smith, *J. Amer. Chem. Soc.*, **88**, 3653 (1966); R. A. Smith, J. E. Baldwin, and I. C. Paul, *J. Chem. Soc., B*, 112 (1967).

coupling to H_6 is not possible, and the high field position of the methyl resonance.[17]

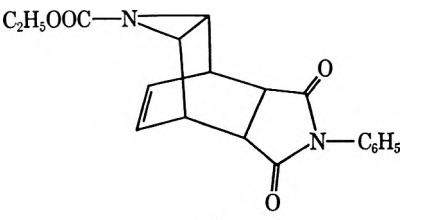
The filtrates from the above crystallization could not be sufficiently enriched in **20** to permit isolation of this adduct in a pure state. However, by careful integration of the C-methyl signals assignable to **19** (δ 2.15) and **20** (δ 2.77) in the nmr spectrum of the crude reaction mixture, the approximate product ratio was determined to be 55:45 in favor of **19**.

These results once again demonstrate the importance of steric effects on 1H-azepine reactivity. The 4-methyl isomer (**12**) gave only that adduct in which the methyl substituent does not occupy a bridgehead position. The same positional selectivity is observed in the case of 2-methyl-N-carbomethoxyazepine (**15**). Since neither of the adducts derivable from the 3-methyl derivative (**18**) has a methyl group at a bridgehead position, substantial quantities of both adducts are formed.

The earlier data of Baldwin and Smith[8a] can now be examined in more quantitative fashion. The isolation of adducts derived principally from 4-substituted N-carbomethoxyazepines seems to be a reflection of their more favorable reactivity with TCNE, the high positional selectivity of the cycloaddition, and the high crystallinity (in a qualitative sense) of these adducts.[18] Since only a 15% yield of **13** was actually isolated from toluene by these workers, interpretation of their results in terms of carbomethoxynitrene selectivity necessarily must remain tentative.[19]

Attempts to form tetracyanoethylene adducts of annelated azepines **21** and **22** afforded only intractable black tars.[20]

N-Phenylmaleimide.—N-Carbalkoxyazepines are rather inert to dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate, even at elevated temperatures in the absence of solvent.[8b] In our hands, N-carbethoxyazepine did, however, undergo reaction with N-phenylmaleimide when heated in toluene at reflux for 16 hr. A crystalline 1:1 adduct was obtained in 25% yield. The complexity of its nmr spectrum (Figure 1) suggested that symmetrical structures such as **23** and **24** could be removed from further consideration. Identification of the structure of the adduct as **25** was achieved through detailed analysis of its spectral properties.



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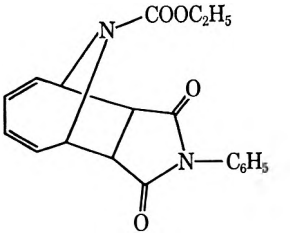
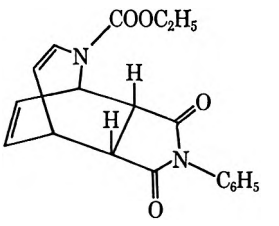


24



25

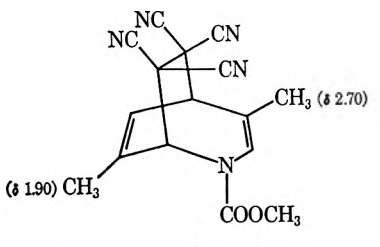
Thus, the infrared spectrum of **25** exhibited, in addition to a carbonyl peak at 1715 cm^{-1}, an intense absorption at 1650 cm^{-1} characteristic of an α,β-unsaturated carbamate double bond.[21] The ultraviolet spectrum of this adduct [$\lambda_{max}^{C_2H_5OH}$ 215 (ϵ 15,700) and 248 sh mμ (ϵ 7700)] lies in good agreement with the absorption previously reported for the >C=CNHCOCH$_3$ chromophore.[22] The nmr spectrum of **25** is illustrated in Figure 1 and the chemical-shift parameters and coupling constants are listed in Table I. The assignments for the spin–spin coupling interactions were tested through double-resonance experiments,[23] which revealed that the "triplets" representing protons B, E, G, and H were truly doublets of doublets. The bridgehead proton B is split by vicinal hydrogens E and H approximately equally. Vinyl protons E and I split one another, a situation which is duplicated with protons G and H; G is also coupled to F. Additionally, the spectrum of **25** bears many similarities to the spectrum of the N-

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR COMPOUND **25**

Proton label	Chemical shift, δ ppm	Principal coupling constants, Hz
A	1.30	J_{AD} = 7.0
B	3.10	J_{BE} = 8.0, J_{BH} = 8.8
C	3.58	J_{CF}, J_{BC} = < 1.0
D	4.25	J_{AD} = 7.0
E	5.11	J_{BE} = 8.0, J_{EI} = 9.5
F	5.50	J_{FG} = 8.0
G	5.97	J_{GH} = 8.7, J_{FG} = 8.0
H	6.51	J_{GH} = 8.7, J_{BH} = 8.8
I	6.67	J_{EI} = 9.5
J	7.35	

(17) In their analysis of the nmr spectrum of i, Baldwin and Smith[8a] noted a significant difference in the chemical shifts of the C_4 and C_7 methyl substituents.

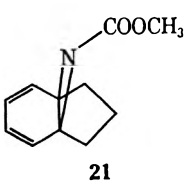


i

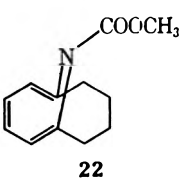
(18) This statement is based on a comparative examination of the crystallinities of **13**, **16**, and **19**.

(19) The fact that carbomethoxynitrene displays no appreciable selectivity in reactions with toluene has recently been confirmed: J. A. Baldwin and R. A. Smith, *J. Org. Chem.*, **32**, 3511 (1967); K. Hafner, personal communication.

(20) The thermal sensitivity of **21**[10b] precluded the use of solvents with boiling points higher than that of benzene. Although the propensity for rearrangement exhibited by **22** was a less serious problem, the application of forcing conditions to any cycloaddition invariably resulted in skeletal rearrangement.[10b]



21



22

(21) See footnote 10a for a discussion of this point.

(22) G. Rosencranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).

(23) J. D. Baldeschwieler and E. W. Randall, *Chem. Rev.*, **63**, 81 (1963).

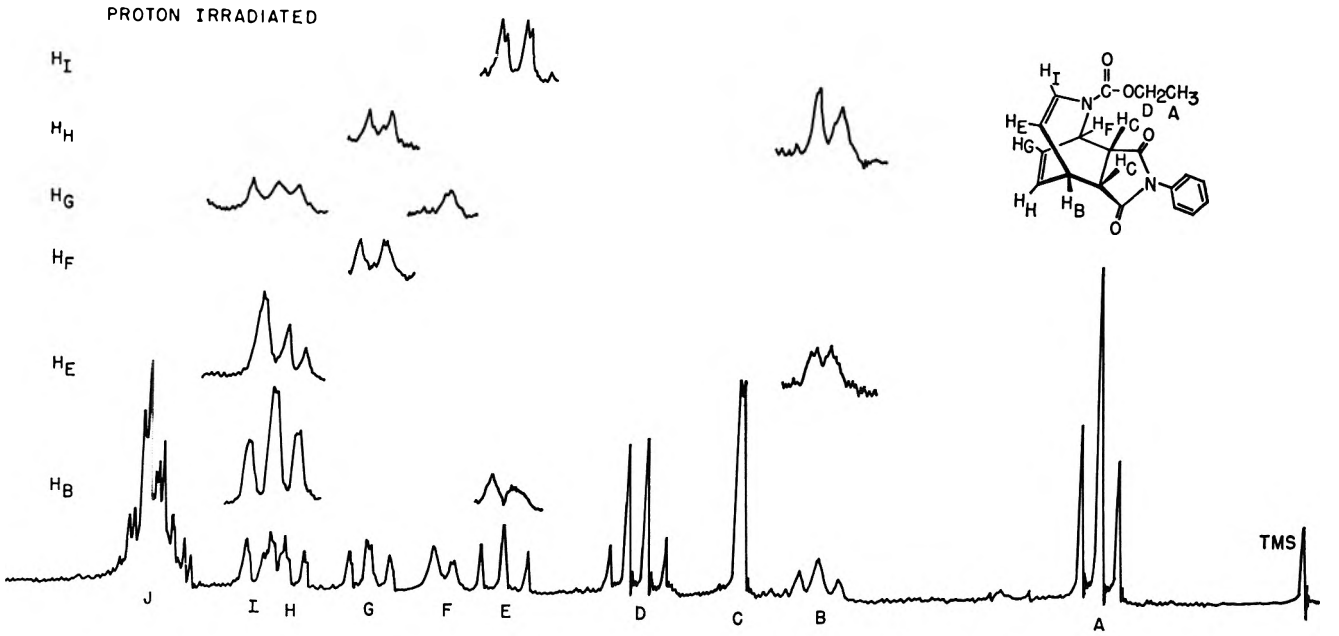
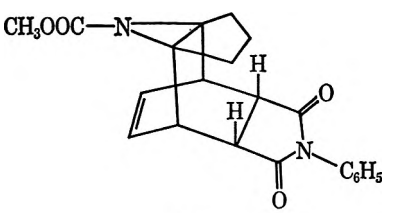


Figure 1.—Proton nmr spectrum of **25** ($CDCl_3$ solution) at 60 MHz.

carbethoxyazepine–TCNE adduct[8b] as it should, since the six carbon atoms of the azepine ring are in quite comparable chemical environments.

A significant final observation on the spectrum of **25** concerns the magnitude of the J_{BC} and J_{CF} coupling constants (<1.0 Hz). That the bridgehead hydrogens are not significantly coupled with the neighboring α-carbonyl protons is a phenomenon that can best be accommodated by an *endo* orientation for the succinimide ring. The relevant dihedral angles are seen from Dreiding models to be approximately 82° for the *endo* isomer and 48° for the *exo* counterpart.[24] Therefore, from expectations based on the Karplus correlation,[25] spin–spin coupling constants of ~1.0 and ~4.0 Hz should be observed for the respective two isomers.[26] The *endo* mode of addition is therefore indicated; the over-all reaction is then a (4 + 2)π cycloaddition to the unrearranged azepine nucleus with *endo* stereochemistry, in agreement with the Woodward–Hoffmann rules for such processes.[27]

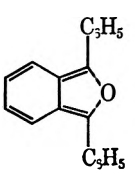
Interestingly, addition of N-phenylmaleimide to **21** proceeded smoothly in refluxing benzene during several hours to give a colorless crystalline substance in high yield. Assignment of structure **26** to this adduct is based on the uniquely symmetrical features of its nmr spectrum which establishes, *inter alia*, the presence of two vinyl protons (multiplet centered at δ 6.35), two α-carbonyl protons (broadened multiplet at 3.62), two allylic bridgehead protons (slightly split band at 3.38),



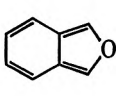
26

and the trimethylene chain (broad six-proton absorption in the 1.16–2.31 region). The imide ring in **26** is assigned *syn* to the double bond for reasons of preferred steric accessibility by the dienophile, in accordance with established precedence,[28] and maintenance of favorable secondary orbital interactions throughout the bond-forming procedure.[27] Especially noteworthy is the fact that **26** represents the lone example at this time of a Diels–Alder addition to the azanorcaradiene tautomer of a 1H-azepine.[29]

Isobenzofurans.—In an attempt to obtain information concerning the possible intermolecular 6π donor capability of 1H-azepines, the addition of two reactive dienes,[30] isobenzofurans **27** and **28**, to these heterocycles has been examined.



27



28

When a solution of **27** and N-carbethoxyazepine in benzene was refluxed under nitrogen for 72 hr, a single reaction product was obtained in 52% yield. The substance exhibited ir bands at 1720 (urethan carbonyl),

(24) As nearly as can be determined from molecular models, the dihedral angles between the two H_C atoms and their adjacent bridgehead neighbors, H_B and H_F, are equivalent.

(25) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963); *J. Chem. Phys.*, **30**, 11 (1959).

(26) Stereochemical analysis of a bicyclo[3.2.2]nonadiene system in this fashion gives results which are diametrically opposed to the geometric conclusions derivable from a bicyclo[2.2.1]heptane, or norbornene, framework. In this latter structural type, the "pinching effect" exerted by the single atom bridge causes the relevant dihedral angles between *endo* and bridgehead protons to approach 90°. Lack of coupling in such molecules is then generally construed as an indication of *exo* substitution. Consult, for example, L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965); see particularly footnote 16.

(27) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965).

(28) L. A. Paquette and J. C. Philips, *ibid.*, **90**, 3898 (1968).

(29) Azepine **22** was found to be unreactive toward N-phenylmaleimide in refluxing benzene for periods of time up to 8 hr.[20]

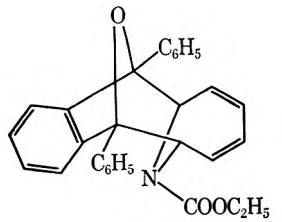
(30) See, for example, (a) M. S. Newman, *J. Org. Chem.*, **26**, 2630 (1961); (b) L. F. Fieser and M. J. Haddadin, *J. Amer. Chem. Soc.*, **86**, 2081 (1964); *Can. J. Chem.*, **43**, 1599 (1965); (c) L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965); L. A. Paquette and T. R. Phillips, *ibid.*, **30**, 3883 (1965).

TABLE II

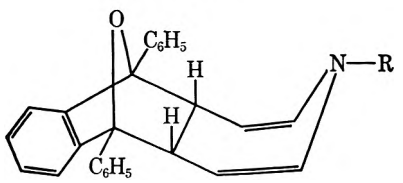
SPECTRAL PARAMETERS FOR THE AZEPINE–ISOBENZOFURAN ADDUCTS

		$\delta^{CDCl_3}_{TMS}$, multiplicity, J			
Compd	$\lambda_{max}^{C_2H_5OH}$, mμ (ε)	Bridgehead protons	β-Vinyl protons	α-Vinyl protons	H—C—O—C—H
30	235 (12,700)	3.62, m	6.42, d, 10Hz	4.77, d, 10Hz	...
31	234 (15,100)	3.60, m	6.30, d, 10Hz	4.98, d, 10Hz	...
32	Strong end absorption	3.63, m	6.20, d, 10Hz	4.92, d, 10Hz	...
36a	232 (15,000)	3.24, m	6.42, d, 10Hz	4.77, d, 10Hz	5.58, m
36b	230 (19,200)	3.17, m	6.20, d, 10Hz	4.68, d, 10Hz	5.12, m
36c	251 (10,700)	3.24, m	6.33, d, 10Hz	4.92, d, 10Hz	5.23, m
36d	235 (3,100)	3.23, m	6.16, d, 10Hz	4.72, d, 10Hz	5.12, m

1680, and 1600 cm^{-1} (olefinic bonds), and uv absorption at 235 mμ (ε 12,700). The nmr spectrum was compatible only with a symmetrical structure such as **29** or **30**, since



29

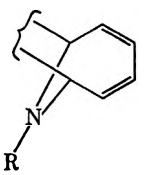


30, R = $COOC_2H_5$
31, R = $COOCH_3$
32, R = SO_2CH_3

it displayed, *inter alia*, two equivalent pairs of vinyl protons as doublets (J = 10.0 Hz) centered at δ 6.42 and 4.77 and two bridgehead protons as a multiplet at δ 3.62.[31]

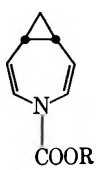
Before considering the structure of the above adduct, it is significant to note that this cycloaddition is apparently entirely general in nature. Thus, N-carbomethoxy- and N-methanesulfonylazepine were found to condense with **27** to form analogous adducts (Table II). Likewise, *in situ* generation of isobenzofuran (**28**)[30b] in the presence of a number of N-substituted azepines resulted in the formation of a structurally related addition product in each instance. Comparison of the spectral properties (Table II) leaves no doubt that the series of adducts derived from the two isobenzofurans have the same fundamental structure. The nmr spectrum of the adduct from isobenzofuran and N-carbethoxyazepine was identical with that of the diphenylisobenzofuran adduct except for the appearance of a doublet of doublets at δ 5.58 assignable to the protons on carbon bonded to the bridgehead oxygen atom.

The appreciable difference in chemical shift (1.28–1.65 ppm) between the pairs of vinyl protons in these adducts is not to be expected from a diene component such as that found in structure **29**. Rather, in those compounds where the moiety defined by **33** is found, the vinyl proton absorption corresponds to a pseudosinglet or a slightly broadened multiplet.[21,32] Con-



33

versely, in a structure such as **30**, the two vinyl protons β to the nitrogen atom would be expected to be diamagnetically shifted relative to the α protons.[10a,33] Furthermore, the chemical shifts of these protons should be affected by changes in the electronegativity of the nitrogen substituent, and this is observed (Table II). In addition, the infrared and ultraviolet parameters correspond well with the spectral characteristics of homoazepines **34a**[33a] [ν_{max}^{film} 1725 and 1670 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 231 mμ (ε 11,430)] and **34b**[33b] [ν_{max}^{film} 1725 and 1665 cm^{-1}; λ_{max}^{hexane} 232 mμ (ε 13,000)]. As expected from structures **30–32**, the position of the ultraviolet maximum is dependent on the nature of the



34a, R = CH_3
b, R = C_2H_5

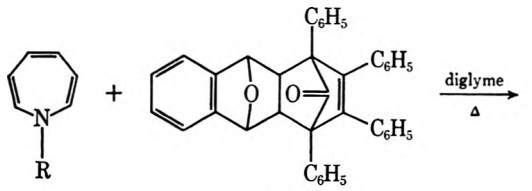
nitrogen substituent because of the direct involvement of the nitrogen atom in the chromophoric group. This would not be the case with **29**, where the nitrogen center is effectively insulated from the diene component.

These data suggested that the cycloadducts have the gross stuctures **30–32** and **36**. In order to confirm these assignments, **36b** was hydrogenated. Two equivalents of hydrogen were consumed and a tetrahydro derivative (**37**) was produced which, when dehydrated with polyphosphoric acid, was readily converted to the disubsti-

(31) The possibility of accidental coincidence of nmr signals from differently oriented protons in an unsymmetrical structure was eliminated by alteration of the nmr solvent (benzene, etc.) and the electronic characteristics of the nitrogen substituent (see ensuing discussion). A symmetrical pattern remained apparent in all instances.

(32) (a) L. A. Paquette and J. H. Barrett, *J. Amer. Chem. Soc.*, **88**, 2590 (1966); (b) A. L. Johnson and H. E. Simmons, *ibid.*, **88**, 2591 (1966); **89**, 3191 (1967); (c) K. Hafner and J. Mondt, *Angew. Chem.*, **78**, 822 (1966); *Angew. Chem. Intern Ed. Engl.*, **5**, 839 (1966); (d) W. S. Murphy and J. P. McCarthy, *Chem. Commun.*, 1155 (1968).

(33) (a) L. A. Paquette and R. J. Haluska, *ibid.*, 1370 (1968); (b) W. H. Okamura, W. H. Snider, and T. J. Katz, *Tetrahedron Lett.*, 3367 (1968); (c) E. L. Stogryn and S. J. Brois, *J. Org. Chem.*, **30**, 88 (1965).



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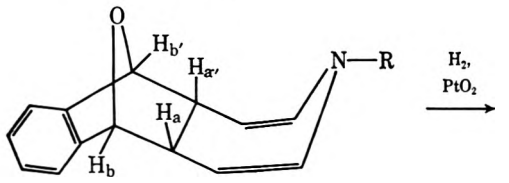
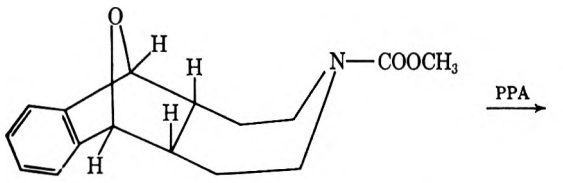


36a, R = $COOC_2H_5$ **c**, R = $COCH_3$
b, R = $COOCH_3$ **d**, R = SO_2CH_3



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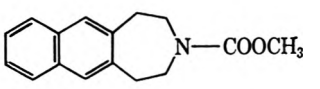
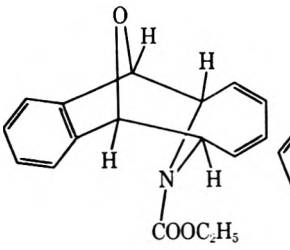


38

tuted naphthalene **38**. The ultraviolet spectrum of **38** (see Experimental Section) is unequivocally that of a naphthalene.[34] The 2,3 disubstitution pattern on the aromatic system was clearly evident from the aryl proton region of the nmr spectrum, which exhibited an absorption pattern identical to that found in 2,3-dimethylnaphthalene.[35] The eight methylene protons are easily recognizable as an A_2B_2 system, the inherent symmetry of which can only be rationalized in terms of structure **38**.

At this point, the stereochemistry of **30–32** and **36** remained to be determined. Molecular models of **36** established that the dihedral angle between H_a and H_b (or $H_{a'}$ and $H_{b'}$) is approximately 45°. In the related *exo* isomer, the dihedral angle is 90°. On the basis of the Karplus relationship,[25,26] J_{ab} (or $J_{a'b'}$) coupling constants of 4 Hz and 0 Hz should be found in the *endo* and *exo* isomers, respectively. Analysis of the doublet of doublets pattern exhibited by H_a and $H_{a'}$ in **36a** shows that two coupling constants of 3.0 and 1.5 Hz exist. A spin-decoupling analysis of the upfield portion of the spectrum indicated that $J_{ab} = J_{a'b'} = 3.0$ Hz, while the smaller coupling (1.5 Hz) was the result of long range spin–spin interaction between H_a and $H_{b'}$ and $H_{a'}$ and H_b. In actuality, the geometry of the bonds linking these protons is seen to correspond exactly to a W-plan coplanar arrangement, a general requirement for coupling across four single bonds.[36] It should be pointed out that the geometrical features required for such long range spin–spin interaction are not present in a structure such as **39** or its *endo* isomer.

From the magnitude of J_{ab} (or $J_{a'b'}$), the *endo* stereochemistry was indicated. Additional confirmation of this assignment came from an unexpected source. The nmr spectrum of **37** displays a two-proton multiplet at exceptionally high field (δ 0.57), signifying that two of the methylene protons occupy positions which are subject to remarkably increased shielding. Examination of Dreiding models of this tetrahydro derivative indicated that the protons labeled H_c (see **40**) are held rigidly below the plane of the benzene ring in the preferred boat conformation. Measurement of the distances from these protons to the center of the aromatic ring in the manner of Johnson and Bovey[37] gives $A = 6$ cm and $B = 3$ cm, which is predicted to result in a diamagnetic shift of approximately 120 Hz, in good agreement with the observed value. Such a ring current effect gives excellent support to the *endo* formulation and additionally verifies the gross structural assignments.



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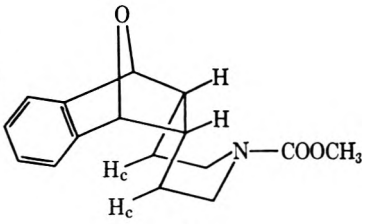


40

The adducts from N-substituted azepines and isobenzofurans result from $(4 + 2)\pi$ cycloaddition rather than from $(6 + 4)\pi$ cycloaddition. These reactions are presumably, although not necessarily, concerted processes, since the demonstrated high *endo* stereoselectivity is very likely the result of secondary orbital symmetry control in the bond-forming transition state.[27] Because addition to the 4,5 bond of the 1H-azepines occurred exclusively, and since the reasons for this unexpected behavior were not clearly understood, there arose a need for comparison with similar reactions of cyclopentadienones. The results of this study follow.

2,5-Dimethyl-3,4-diphenylcyclopentadienone.—The failure of 1H-azepines to function as 6π donors toward isobenzofurans could conceivably be caused by an adverse electronic effect in the isobenzofurans. Thus, these dienes may be considered as electron-rich 4π donors. Since electronic effects on $(6 + 4)\pi$ cycloadditions have not yet been investigated, it is conceivable that the electron nature of the isobenzofurans is not conducive to ready $(6 + 4)\pi$ cycloaddition with 1H-azepines bearing electronegative substituents on nitrogen. In other words, the possibility exists that $(6 + 4)\pi$ cycloadditions may be subject to subtle electronic demands in much the same fashion as Diels–Alder reactions.[38]

Derivatives of cyclopentadienone are electron-deficient 4π donors and thus were considered to be appropriate examples of the "inverse" electronic situation. Upon heating a solution of N-carbethoxyazepine and **41**

(34) For comparison purposes, see R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1951, Spectra No. 195–228.

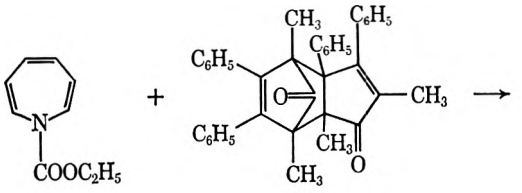
(35) For example, compare 2,3-dimethylnaphthalene: W. Brügel, "Nuclear Magnetic Resonance Spectra and Chemical Structure," Vol. I, Academic Press, Inc., New York, N. Y., 1967, p 128.

(36) For a review, see S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(37) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(38) For recent discussions of the inverse electron demand in Diels–Alder reactions, consult (a) J. Sauer, *Angew. Chem. Intern. Ed. Engl.*, **6**, 16 (1967); (b) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968); (c) C. K. Bradsher and J. A. Stone, *ibid.*, **33**, 519 (1968); (d) R. A. Carboni and R. V. Lindsey, *J. Amer. Chem. Soc.*, **81**, 4342 (1959).

in benzene under nitrogen for 20 hr, there was obtained after careful column chromatography a 41.4% yield of **42** and a 50% yield of **43** or **44**. Initially, the molecular



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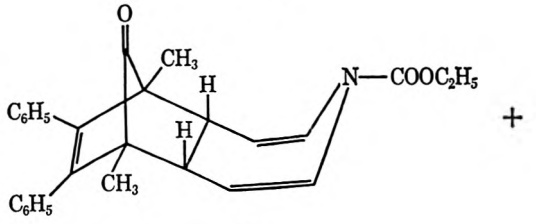
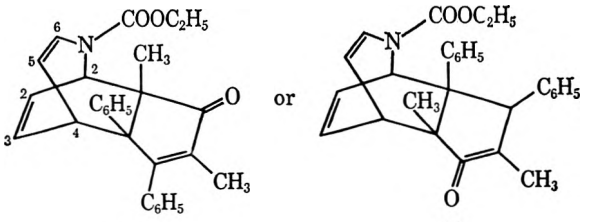


42



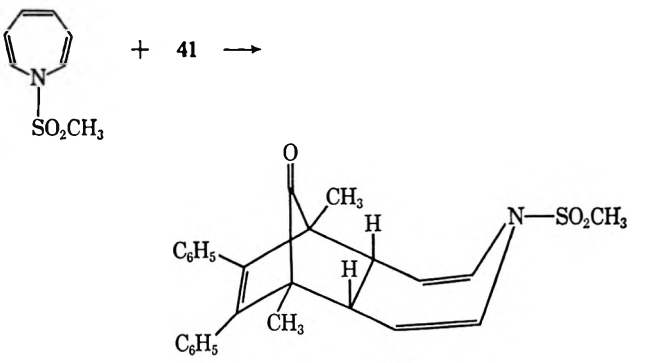
43 **44**

frameworks of **42** and **36** (or **30**) were seen to be closely related. The presence of moiety **33** was apparent from the nmr spectrum, which revealed the presence of two high field protons as a slightly broadened singlet absorption at δ 2.95, two vinyl protons β to nitrogen as a doublet (J = 11 Hz with additional small coupling) at 5.02, and two vinyl protons α to nitrogen (peak overlaps with phenyl absorption at *ca.* 7.05). Again, the symmetry of the molecule was apparent. Further, its infrared spectrum (in Nujol) indicated the presence of a bridged β,γ-unsaturated carbonyl group (1765 cm^{-1}),[39] a urethan carbonyl function (1725 cm^{-1}), and the C=C–N–C=O groupings (1680 cm^{-1}). The presence of the unsaturated urethan linkages in **42** could also be derived from its ultraviolet spectrum, which exhibited absorption in ethanol at 251 mμ (ϵ 11,800) in addition to the *cis*-stilbene band at 281 mμ (ϵ 15,850).[40]

The nmr spectrum of the second 1:1 adduct ($CDCl_3$ solution) clearly shows the magnetic nonequivalence of the methyl substituents adjacent to the carbonyl group, there being two singlets at δ 0.94 and 1.90. The first methyl group is obviously bonded to saturated carbon while the second is attached to sp^2-hybridized carbon. The remaining portion of the spectrum consists of absorptions characteristic of the azepine ring to which 1,4 bonding has occurred (see Figure 1). H_1 is seen as a doublet (J = 8.5 Hz) at δ 5.30, whereas H_2, H_3, H_4, and H_5 appear as the expected doublet of doublets at δ 6.23, 6.78, 2.64, and 5.08, respectively, and H_6 consists of a doublet at 6.86. The ultraviolet spectrum in ethanol has a maximum at 227 mμ (ϵ 27,850) and a shoulder at 270 mμ (ϵ 6700). The infrared spectrum shows a conjugated cyclopentenone carbonyl band at 1670 cm^{-1} and double-bond stretching modes at 1665 and 1640 cm^{-1}.

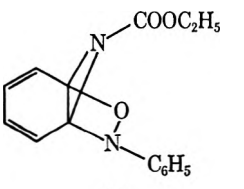
Comparison of the nmr spectra of this adduct and **25** revealed that H_4 (δ 2.64) has undergone a substantial upfield shift relative to H_B (δ 3.10), whereas the chemical shifts of H_1 (δ 5.50) and H_F (δ 5.30) have remained essentially invariant. These observations are in best agreement with structure **43**, since in this formulation, H_4 is not *vis-a-vis* a carbonyl group but is proximate to two phenyl groups. On the other hand, the chemical environment about H_1 is only little altered from that found in **25**. The reverse structural alternatives are at play in **44**. Further support for **43** was derived from its sizable dipole moment, 3.38 D in benzene.[41]

In similar fashion, the interaction of **41** and N-methanesulfonylazepine led to the formation of a lone adduct (**45**) in 42% yield. The structure **45** was likewise ascertained on the basis of spectral evidence (see Experimental Section).



45

With the establishment of structures **42** and **45**, it was clear that the electronic nature of the 4π donor is not a significant factor in the direction taken by the cycloaddition. Subsequent to the completion of this study, however, a report appeared which described the 1,6 addition of nitrosobenzene and N-carbethoxyazepine to give **46**.[32d] At the present time, these differing



46

modes of chemical behavior are not readily reconcilable from the theoretical viewpoint It is nevertheless significant to note that the 1H-azepine ring is unique in its capability to function as a 2π, 4π, and 6π donor without recourse to valence tautomerism in thermally induced cycloaddition reactions.[41a]

(39) Compare the bands for the bridged carbonyl groups in **41** (1760 cm^{-1}) and 7-ketonorbornene (1780 cm^{-1}) [P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964)].

(40) For *cis*-stilbene: uv $\lambda_{max}^{C_2H_5OH}$ 224 (ϵ 24,400) and 280 mμ (ϵ 10,500) [R. N. Beale and E. M. F. Rowe, *J. Chem. Soc.*, 2755 (1953)].

(41) We thank Professor Norman L. Allinger for this determination.

(41a) NOTE ADDED IN PROOF.—Since the submission of this paper, a report by J. R. Wiseman and B. P. Chong has appeared [*Tetrahedron Lett.*, 1619 (1969)] which reports the related (4 + 2) cycloaddition of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene to the 4,5 bond of N-carbethoxyazepine.

Experimental Section[42]

Addition of TCNE to 4-Methyl-N-carbomethoxyazepine (12).—To a solution of 1.20 g (7.3 mmol) of **12** in 10 ml of toluene was added a solution of 960 mg (7.5 mmol) of freshly sublimed TCNE in 90 ml of the same solvent. The reaction mixture was stirred at room temperature for 15 hr and then refluxed for 1 hr. The solvent was evaporated until 15 ml of liquid remained. Cooling of this material caused 1.37 g (64.5%) of **13** to be deposited. Additional recrystallization from toluene gave pure **13** as a fluffy white solid, mp 139–141° (lit.[8a] mp 128–130°). An nmr spectrum of the crude reaction mixture and thin layer chromatography showed no indication that any of isomeric adduct **14** was formed.

Anal. Calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.46; H, 3.98; N, 24.14.

Addition of TCNE to 2-Methyl-N-carbomethoxyazepine (15).—When 2.40 g (14.5 mmol) of **15** and 1.92 g (15.0 mmol) of TCNE in 100 ml of toluene were reacted as above, there was obtained only a brown oil after concentration of this solution. This oil was chromatographed on Florisil (100 g) to give 121 mg (5%) of 2-methyl-N-carbomethoxyaniline, mp 59.5–60.5°, upon elution with hexane–ether (19:1) and 103 mg (2.5%) of **19** upon elution with hexane–ether (4:1). Again in this instance, nmr and thin layer analyses of the crude reaction mixture provided no indication of the formation of **17**.

Pure **19** was obtained by recrystallization from acetone–hexane as a white solid, mp 149–151° (prior sintering beginning at 130°).

Anal. Calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.46; H, 4.08; N, 23.90.

Addition of TCNE to 3-Methyl-N-carbomethoxyazepine (18).—Treatment of 730 mg (4.4 mmol) of **18**, 570 mg (4.4 mmol) of TCNE, and 75 ml of toluene in the above manner gave 1.2 g of a viscous brown oil. Rapid chromatography of this oil on Florisil (50 g) with ether–hexane (1:3) elution gave 860 mg (66%) of yellow oil. An nmr analysis of this crude oil indicated the presence of **19** and **20** in a ratio of 55:45 by integration of the two methyl peaks at δ 2.15 and 2.77. Thin layer chromatography [3 developments with hexane–ether (7:3) on activity II alumina] showed the oil to be composed of two substances with nearly identical R_f values. When an acetone–hexane solution of this oil was seeded with a crystal of **13**, 312 mg (24%) of an off-white solid was isolated. Four recrystallizations of this material from the same solvent pair gave pure **19**, mp 146.5–148.5°; ir ν_{max}^{KBr} 1727 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.55; H, 3.91; N, 23.84.

The combined filtrates, when concentrated, cooled, and seeded, yielded no additional crystalline material.

Ethyl 3,5-Dioxo-4-phenyl-4,8-diazatricyclo[5.3.2.0^{2,6}]dodeca-9,11-diene-8-carboxylate (25). A solution of 3.3 g (20 mmol) of N-carbethoxyazepine and 3.46 g (20 mmol) of N-phenylmaleimide in 15 ml of toluene was refluxed for 16 hr. The solvent was removed under reduced pressure and the resulting semisolid mixture was chromatographed on Florisil (100 g) using pentane and gradually increasing amounts of ether. A white solid (1.72 g, 25.4%) was isolated which gave an analytical sample upon recrystallization from methanol, mp 177–179°, ir $\nu_{max}^{CHCl_3}$ 1715 (C=O) and 1650 cm^{-1} (C=N–C=O); uv $\lambda_{max}^{C_2H_5OH}$ 215 (ϵ 15,700) and 248 mμ (ϵ 7700).

Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.33; H, 5.44; N, 8.19.

Addition of N-Phenylmaleimide to 10-Carbomethoxy-10-azatricyclo[4.3.1.0^{1,6}]deca-2,4-diene (21).—A solution of 270 mg (1.4 mmol) of **21** and 245 mg (1.4 mmol) of N-phenylmaleimide in 25 ml of benzene was blanketed with nitrogen, stirred at room temperature for 3 hr, and finally heated at reflux for 3 hr. Solvent removal *in vacuo* yielded 510 mg (99%) of a white solid, mp 115–118°. Recrystallization from benzene–hexane afforded 430 mg of **26** as white crystals, mp 218.5–220°; ir $\nu_{max}^{CDCl_3}$ 1715 and 1664 cm^{-1}.

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.51; H, 5.31; N, 7.58.

Addition of Diphenylisobenzofuran (27) to 1H-Azepines.—A solution of 1.65 g (0.01 mol) of N-carbethoxyazepine and 2.70 g (0.01 mol) of **27**[30a] in 30 ml of benzene was refluxed under nitrogen for 72 hr. The resulting orange solution was concentrated under reduced pressure to give a tan solid. Column chromatography on 70 g of Florisil and elution with hexane followed by hexane–ether (9:1) gave 2.26 g (52%) of **30**, mp 120–121° (yellows at 115°: reverse cycloaddition); ir $\nu_{max}^{CCl_4}$ 1720, 1680, and 1660 cm^{-1}.

Anal. Calcd for $C_{29}H_{25}NO_3$: C, 79.97; H, 5.79; N, 3.22. Found: C, 79.92; H, 5.84; N, 3.12.

From 6.93 g (0.026 mol) of **27** and 3.90 g (0.026 mol) of N-N-carbomethoxyazepine in 80 ml of benzene (reflux 100 hr), there was isolated 4.8 g (44%) of **31**, mp 119.5–121° (from ether–hexane); ir $\nu_{max}^{CCl_4}$ 1725 and 1685 cm^{-1}.

Anal. Calcd for $C_{28}H_{23}NO_3$: C, 79.79; H, 5.50; N, 3.32. Found: C, 79.75; H, 5.40; N, 3.34.

From 6.75 g (0.025 mol) of **27** and 4.28 g (0.025 mol) of N-methanesulfonylazepine in 150 ml of benzene (reflux, 56 hr), there was isolated 3.97 g (36%) of **32**, mp 138–139° dec (from methylene chloride–hexane).

Anal. Calcd for $C_{27}H_{23}NO_3S$: C, 73.45; H, 5.25; N, 3.17. Found: C, 73.26; H, 5.19; N, 3.14.

Addition of Isobenzofuran (28) to 1H-Azepines.—To 100 ml of purified diglyme which had been preheated to 140° was added in one portion 13.2 g (25 mmol) of **35**[30b,c] and 3.3 g (20 mmol) of N-carbethoxyazepine. The solution was refluxed for 2 hr and then concentrated under reduced pressure to give a tan solid. This solid was chromatographed on 300 g of Florisil using hexane with graduated amounts of benzene. The first compound eluted was 1,2,3,4-tetraphenylbenzene, 8.8 g (92%), mp 190°. Elution, with pure benzene gave 1.21 g (21.8%) of **36a** as a white solid, mp 132.5–133° (from ether); ir $\nu_{max}^{CHCl_3}$ 1725 and 1695 cm^{-1}. No other material was isolated.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.84; H, 6.21; N, 4.91.

From 14.0 g (26.5 mmol) of **35** and 3.78 g (25 mmol) of N-carbomethoxyazepine in 100 ml of diglyme, there was obtained 3.16 g (47%) of **36b**, white crystals from benzene–pentane, mp 132–139° dec, with yellowing; ir $\nu_{max}^{CHCl_3}$ 1725 and 1695 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.66; H, 5.56; N, 5.01.

From 1.74 g (3.3 mmol) of **35** and 446 mg (3.3 mmol) of N-acetylazepine in 25 ml of diglyme, there was obtained 414 mg (49.5%) of **36c**, white crystals from methylene chloride–pentane, mp 186–188.5° dec; ir $\nu_{max}^{CHCl_3}$ 1695 and 1660 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.62; H, 6.01; N, 5.46.

From 1.55 g (2.93 mmol) of **35** and 502 mg (2.93 mmol) of N-methanesulfonylazepine in 50 ml of diglyme, there was obtained 196 mg (23%) of **36d**, long white needles from benzene–pentane, mp 162–164°; ir $\nu_{max}^{CHCl_3}$ 1680, 1350, and 1165 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.36; H, 5.22; N, 4.74.

N-Acetylazepine.—To a stirred solution of 12.2 g (0.128 mol) of 1,2-iminocyclohex-4-ene[10a] and 13.1 g (0.130 mol) of triethylamine in 180 ml of anhydrous ether was added dropwise a solution of 9.65 g (0.128 mol) of acetyl chloride in 60 ml of the same solvent with ice cooling. After the reaction mixture had stirred for 2 hr, amine hydrochloride was filtered and the filtrate was evaporated. Distillation of the residue afforded 13.2 g (76.5%) of the N-acetyl derivative, bp 55–58° (0.5 mm); ir $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}.

Anal. Calcd for $C_8H_{11}NO$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.62; H, 6.01; N, 5.46.

The dibromide was obtained as an oil which was subjected directly to the action of potassium *t*-butoxide in dry tetrahydrofuran.[10a] Distillation of the residual orange oil gave 1.63 g (14.9%), bp 71° (0.3 mm); ir $\nu_{max}^{CHCl_3}$ 1670 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 2.08 (s, 3 H) and 5.12–6.30 (m, 6 H).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 71.19; H, 7.26.

Hydrogenation of 36b.—A 1.0-g sample of **36b** was hydrogenated at atmospheric pressure over Adams catalyst in tetrahydrofuran solution (50 ml). The uptake of hydrogen ceased after the uptake of 2 mol equiv. Recrystallization of the resulting solid from benzene–pentane gave **37** as white crystals, mp 148.5–149°; ir $\nu_{max}^{CCl_4}$ 1695 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 0.57 (br t, 2 H), 1.87 (br d, 2 H), 2.53–3.12 (m, 4 H), 3.59 (s, 3 H), 3.80–4.25 (m, 4 H), 5.20 (slightly split m, 2 H), and 7.28 (s, 4 H).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: 70.42; H, 6.97; N, 5.02.

(42) The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were determined with a Cary 14 spectrometer and the nmr spectra were recorded with a Varian A-60A spectrometer.

Dehydration of 37.—A mixture of 500 mg (1.83 mmol) of **37** and 15 ml of polyphosphoric acid was heated on a steam bath for 3 hr with occasional stirring. After standing overnight at room temperature, this mixture was added to 80 ml of ice water. The organic product was extracted with four 75-ml portions of chloroform and the combined organic layers were washed with water. The solution was dried and evaporated, and the residue was chromatographed on 10 g of alumina. Elution with ether–hexane (1:1) gave 387 mg (83%) of **38**, mp 138.5–139° (from benzene–hexane); ir $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 261 (ϵ 4500), 269 (ϵ 5600), 279 (ϵ 5600), and 289 mμ (ϵ 3400); nmr $\delta_{TMS}^{CDCl_3}$ 3.00 and 3.62 (centrosymmetric A_2B_2 pattern, 2 H each), 3.72 (s, 3 H), and 7.46 (characteristic m for 2,3-disubstituted naphthalene).

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.40; H, 6.71; N, 5.45.

Addition of 2,5-Dimethyl-4,5-diphenylcyclopentadienone to 1H-Azepines.—A solution of 3.30 g (20.0 mmol) of 1-carbethoxyazepine and 5.22 g (10.0 mmol) of **41**[43] in 40 ml of benzene was refluxed under nitrogen with magnetic stirring for 20 hr. The solvent was evaporated under reduced pressure and the residue was chromatographed carefully on Florisil. Elution with 2% ether in hexane gave 3.0 g of recovered **41**, mp 186–187° dec. Elution with 5% ether in hexane gave 1.45 g (41.4%) of **42**, mp 140–141° dec (from ether). Elution with 10% ether in hexane and 25% ether in hexane gave 1.75 g (50%) of **43**, mp 146–147° (from ether–hexane).

42 had ν_{max}^{Nujol} 1765, 1725, and 1680 cm^{-1}; uv $\lambda_{max}^{C_2H_5OH}$ 251 (ϵ 11,800) and 281 mμ (ϵ 15,850); for nmr, see text.

Anal. Calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29 Found: C, 78.84; H, 6.24; N, 3.04.

43 had ir ν_{max}^{Nujol} 1670, 1665, and 1460 cm^{-1}; uv $\lambda_{max}^{C_2H_5OH}$ 227 (ϵ 27,850) and 270 sh mμ (ϵ 6700); for nmr, see text.

Anal. Calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 78,75; H, 6.04; N, 3.06.

From 5.2 g (10 mmol) of **41** and 3.42 g (20 mmol) of N-methanesulfonylazepine in 40 ml of benzene (reflux, 20 hr), there was obtained 1.2 g of recovered **41** and 2.74 g (42%) of **45**, fine white needles from methylene chloride–pentane, mp 158° dec; ir $\nu_{max}^{CHCl_3}$ 1760, 1350, and 1155 cm^{-1}; uv $\lambda_{max}^{CH_2Cl_2}$ 222 sh (ϵ 20,700) and 253 sh mμ (ϵ 9200); nmr $\delta_{TMS}^{CDCl_3}$ 1.39 (s, 3 H), 2.90 (s, 3 H), *ca.* 2.90 (m, 2 H), 5.00 (br d, J = 10.5 Hz, 2 H), 6.70–7.2 (m, 12 H, aromatic and α-vinyl protons).

Anal. Calcd for $C_{26}H_{25}NO_3S$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.35; H, 5.89; N, 3.14.

Registry No.—**19**, 20678-91-5; **25**, 20629-04-3; **26**, 20629-05-4; **30**, 20629-06-5; **31**, 20629-07-6; **32**, 20629-08-7; **36a**, 20629-09-8; **36b**, 20629-10-1; **36c**, 20629-11-2; **36d**, 20678-92-6; **37**, 20629-12-3; **38**, 20629-13-4; **41**, 13360-84-4; **42**, 20629-15-6; **43**, 20629-16-7; **45**, 20629-17-8; N-acetylazepine, 20629-18-9; N-acetyl derivative of 1,2-iminocyclohex-4-ene, 20629-19-0.

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(43) F. W. Gray, *J. Chem. Soc.*, **95**, 2131 (1909); C. F. H. Allen and J. A. Van Allan, *J. Amer. Chem. Soc.*, **64**, 1260 (1942).

Unsaturated Heterocyclic Systems. LVI. The Reaction of a Mesocyclic Dienamine with Sulfene[1]

LEO A. PAQUETTE AND ROBERT W. BEGLAND

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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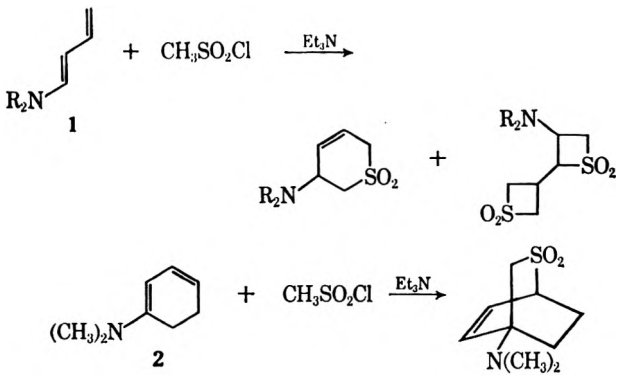
Reaction of 1-dimethylamino-1,3-cyclooctadiene (**3**) with sulfene, generated *in situ* from methanesulfonyl chloride and triethylamine, in tetrahydrofuran solution was found to yield seven crystalline sulfones after chromatographic work-up. The product composition was seen to be dependent upon temperature, rate of addition of the sulfonyl chloride, rate of elution from the chromatography column, and adsorbent. The structure of each of the adducts has been assigned on the basis of elemental analysis, spectral (particularly nmr) data, and chemical transformations in a number of instances. 3-Aminothietane dioxide **7** was shown to be the precursor of sulfones **8**, **9**, **10**, and **11**; the mechanisms of these transformations are presented. Pathways for the formation of **6** and **12** are also proposed. The particular role played by the medium-sized ring of **3** in these reactions is discussed.

Although a stable free sulfene remains to be isolated,[2] the transient generation of these reactive intermediates in the reaction of numerous alkyl, cycloalkyl, and aralkyl sulfonyl chlorides with tertiary amines has been widely accepted and has attracted much recent attention.[3-5] The chemical reactivity of sulfenes is characterized chiefly by their propensity for (2 + 2) cycloaddition to electron-rich double and triple bonds. With dienamines of type **1** and **2**, (4 + 2) cycloaddition is found to compete favorably with the formation of bithietane tetroxides.[5-7] In a significant number of



instances, the sulfene–enamine condensation has been observed to produce open-chain products;[8] also, rearrangement products have been isolated from the reaction of sulfenes with certain 1,3-bis(dimethyl-

(1) For the previous paper in this series, see L. A. Paquette, D. E. Kuhla, J. H. Barrett, and L. M. Leichter, *J. Org. Chem.*, **34**, 2888 (1969).

(2) For a more extensive discussion of this topic, see L. A. Paquette, J. P. Freeman, and R. W. Houser, *ibid.*, **34**, 2901 (1969).

(3) T. J. Wallace, *Quart. Rev.*, **20**, 67 (1966).

(4) G. Optiz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 107 (1967).

(5) L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967).

(6) G. Opitz and F. Schweinsberg, *Angew. Chem.*, **77**, 811 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 786 (1965).

(7) G. Opitz and F. Schweinsberg, unpublished results noted in footnote 121 of ref 4.

(8) Consult, for example, (a) G. Opitz, H. Schempp, and H. Adolph, *Ann.*, **684**, 92 (1965); (b) J. J. Looker, *J. Org. Chem.*, **31**, 2973 (1966); A. M. Hamid and S. Trippett, *J. Chem. Soc., C*, 1612 (1968).

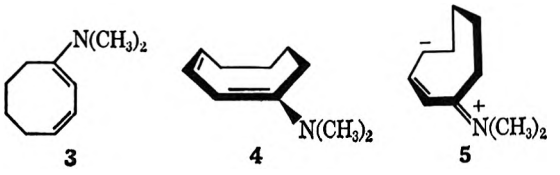
TABLE I

PRODUCT COMPOSITIONS IN THE CONDENSATION OF 1-DIMETHYLAMINO-1,3-CYCLOOCTADIENE WITH SULFENE

Conditions employed	CH_3SO_2Cl, equiv	Chromatog adsorbent	Yield, % 6	7	8	9	10	11	12
THF, −10°	1	Alumina	3.3		17.2			0.8	3.1
THF, −10°	2	Alumina	0.7		10.2	9.4		0.8	8.3
THF, −10°, heated briefly on steam bath with adsorbent prior to chromatography	1	Alumina			41.8			0.7	4.9
Same as above	2	Alumina			35.6			0.5	13.5
THF, −10°, sulfonyl chloride added over 3 hr instead of 30 min	1	Alumina	15.8		14.7				
THF, 25°	1	Alumina				2.4		5.6	
THF, −10°	2	Silica gel			8.9		34		3.3
THF, −10°	2	Florisil					33		7.5
Eluted immediately and rapidly with ether	2	Florisil		5.2			36.8		5.3

amino)-1-alkenes.[5] These apparent anomalies very likely reflect the intervention of zwitterions at some point along the reaction profile.

With this information as background, we set out to examine the addition of sulfene to a mesocyclic dienamine.[9] 1-Dimethylamino-1,3-cyclooctadiene (**3**) was selected for this purpose because of its ready availability.[10] An electron-rich medium-sized-ring diene such as **3** was expected to offer new insight into our limited knowledge of sulfene–dienamine interactions. Thus, the conjugated diene unit in **3** is considerably distorted from planarity, this twisting being enforced by the substantially lower energy of its "tub" conformation (**4**). As a result, transmission of electron density from the nitrogen atom at C-1 to the 4 position as in **5** can be expected to be reduced significantly relative to molecules such as **1** and **2** which can readily adopt planar conformations. Also, the geometry of medium-sized rings is such that substantial nonbonded steric compression between transannular groups exists, and this strain was expected to promote unprecedented reactions.



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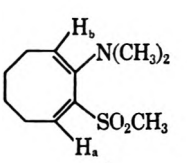
Results

In the generalized procedure, a solution of **3** in tetrahydrofuran containing 1–2 equiv of triethylamine was treated dropwise with a corresponding equivalence of methanesulfonyl chloride. The resulting viscous oils, when chromatographed on alumina, Florisil, or silica gel, afforded a total of seven crystalline sulfones. The yields of these products were found to be quite dependent upon the reaction temperature, the rate of addition of methanesulfonyl chloride, the rate of elution from the chromatography column, and the adsorbent employed. Table I summarizes the available data.

Structural Assignments.—Sulfone **6** was shown to be a monoaddition product by combustion analysis. This substance exhibited infrared bands at 1618 and 1635 cm^{-1}, indicative of an enamine function, and ultraviolet absorption in isooctane at 204 (ϵ 9900) and 286 mμ (ϵ 1350) due to extended conjugation. In agreement with the assigned formulation, the nmr spectrum diplayed a one-proton doublet of doublets (J = 9.3 and 7.3 Hz) at δ 7.00, a one-proton triplet (J = 7.9 Hz) at δ 4.90,[11] a three-proton singlet at δ 2.78 characteristic of a methanesulfonyl group, a six-proton singlet at δ 2.58 for the dimethylamino residue, and a complex multiplet (8H) in the δ 1.0–2.5 region. To eliminate from consideration structures similar to **6** in which the two vinyl protons were adjacent, the nmr spectrum was spin decoupled. Irradiation of H_a (δ 7.00) produced no change in the H_b pattern, and *vice versa*. In contrast, irradiation of the δ 2.0–2.1 absorption caused both H_a and H_b to appear as slightly broadened singlets. This



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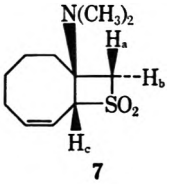

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combination of data agrees only with the 2-dimethylamino-3-methanesulfonyl-1,3-cyclooctadiene assignment.

Sulfone **7** proved very elusive and was obtained only by rapid elution of the crude reaction mixture from a Florisil column. Its instability was further reflected in the fact that **7** was cleanly converted to **9** upon standing in chloroform solution at ambient temperatures for 2 days. Nmr studies in deuteriochloroform indicated, *inter alia*, the presence of two vinyl protons (multiplet centered at δ 5.83), a dimethylamino substituent (singlet of area 6 at δ 2.42), and four methylene groups (broad multiplet of area 8 at δ 1.1–2.3). Particularly revealing in this instance were the absorptions of the remaining three protons, which were characteristic of a thietane dioxide ring. Thus, the broad one-proton peak at δ 5.17 is properly shifted for the allylic α-sulfonyl environment (H_c), whereas doublets of doublets are seen for H_a (J = 14 and 3 Hz) and H_b

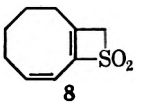
(9) "Mesocyclic" is herein employed as an alternative to "medium-sized ring" [N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Amer. Chem. Soc.*, **82**, 4075 (1960)].

(10) L. A. Paquette and R. W. Begland, *ibid.*, **88**, 4685 (1966).

(11) The vinyl proton of 1-cyano-2,3-diethyl-1,3-cyclooctadiene is seen as a triplet (J = 7.3 Hz) at τ 5.60: J. G. Atkinson, D. E. Ayer, G. Büchi, and E. W. Robb, *ibid.*, **85**, 2257 (1963).

(J = 14 and 1 Hz). H_a (δ 4.32) is downfield shifted relative to H_b (δ 3.42) because of the paramagnetic shielding induced by the proximate *cis*-oriented nitrogen atom. The differences in the diagonal coupling constants (J_{AC} = 3 Hz; J_{BC} = 1 Hz) are in good agreement with values reported for cyclobutane derivatives.[12] From these data, it was clear that structure **7** represented a unique fit to the spectral parameters.

The structure of sulfone **8** was revealed from its elemental analysis, which indicated addition of sulfene ($CH_2{=}SO_2$) and loss of dimethylamine, its ultraviolet spectrum [λ_{max}^{EtOH} 246 mμ (ϵ 5860)], which denoted extended conjugation, and its nmr spectrum in carbon tetrachloride, which showed a multiplet of area 2 at δ 5.96 for the vinyl protons, a singlet at δ 4.20 for the two protons α to the sulfonyl group, a four-proton multiplet at δ 2.2–2.7 for the allylic hydrogens, and upfield absorption for the remaining four saturated protons.



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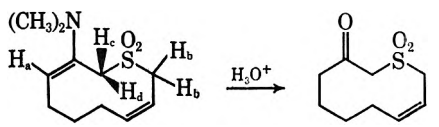
The elemental analysis of sulfone **9** indicated that this substance was isomeric with **7**; the previously mentioned rearrangement of **7** is therefore a true bond reorganization. This colorless solid exhibited pertinent infrared absorption (CCl_4) at 1637 cm^{-1} and an ultraviolet maximum (C_2H_5OH) at 237 mμ (ϵ 5770) strongly suggestive of the presence of an enamine chromophore. This conclusion was confirmed by acid hydrolysis of **9**, which gave a keto sulfone identical in all respects with **10**. The nmr spectrum of **9** consisted of a two-proton multiplet at δ 5.65 (–CH=CH–), a four-proton multiplet at δ 3.7–4.5 (H_a, 2 H_b, and H_c), and a peak of area 1 at δ 2.92 (H_d), in addition to a singlet (6 H) at δ 2.71 assignable to the dimethylamino group and a high field multiplet of area 6 due to the remaining methylene hydrogens. Dreiding models of **9** clearly show that the

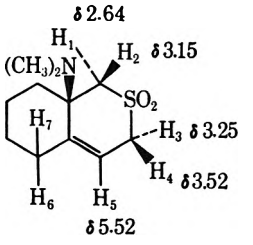


9 **10**

upfield shift of the H_d adsorption can be traced to its proximity to the shielding cone of the transannularly disposed double bond. Thus, it may be concluded that the conversion of **7** to **9** is the result of rupture of the bond common to the thietane and cyclooctene rings (see below).

Sulfone **10** was obtained only when the crude reaction mixture was chromatographed on Florisil or silica gel, apparently at the expense of **7** and **9**. Suspicion that **10** was the end product of (a) the rearrangement of **7** to **9** (see above) and (b) hydrolysis of the latter sulfone during the chromatographic procedure was confirmed by the finding that the action of dilute acid on **9** readily gave **10**. The presence of a carbonyl function was indicated by an intense infrared band at 1725 cm^{-1} and confirmed by the preparation of a 2,4-dinitrophenylhydrazone derivative. A molecular formula of $C_9H_{14}O_3S$ was derived from the elemental analysis. Again in this situation the nmr spectrum was most enlightening; the multiplet at δ 5.75 was assigned to the –CH=CH– group, the two-proton singlet at δ 4.21 to the methylene group positioned between the carbonyl and sulfonyl functions, and a doublet (J = 8 Hz) of area 2 at δ 3.80 to the allylic α-sulfonyl protons.[13] Two distinctly broader multiplets at δ 2.40–2.65 (2 H) and 1.60–2.35 (6 H) comprise the peaks expected for the remaining allylic and saturated $-CH_2-$ groups.

Monoaddition product **11** was obtained in very low yield. Its infrared spectrum lacked bands usually associated with enamine, carbonyl, and conjugated olefinic groups, and the ultraviolet spectrum was characterized only by end absorption. The 60-MHz spectrum of **11** established the presence of a lone vinyl proton, an α-sulfonyl methylene group, and a $=CH-CH_2SO_2-$ linkage.[13] Substantiation for the assigned structure was found in its spin-decoupled 100-MHz spectrum. On the basis of these measurements, this rearrangement product was deduced to possess a singly unsaturated sulfone-containing six-membered ring bearing a dimethylamino group at a ring juncture position. The various significant coupling constants



11

were seen to be $J_{1,2}$ = 14.5 Hz; $J_{3,4}$ = 16.8 Hz; $J_{3,5}$ = 7.2 Hz; and $J_{4,5}$ = 2.6 Hz. In addition there was also spin–spin interaction (J = 4.3 Hz) between H-1 and H-3, resumably resulting from the W-plan arrangement of the intervening σ bonds.[14] Molecular models show that the nonidentical spin–spin coupling of H-3 and H-4 to H-5 are the result of widely differing dihedral angle relationships.[15] Finally, the H-5 absorption was seen as a doublet of quartets because allylic coupling to H-6 (J = 1.8 Hz) caused the unsymmetrical doublet of doublets pattern due to the X portion of the ABX system to be split further.

Sulfone **12** was the only bis addition product isolated. The bright yellow color of its crystals, an intense infrared band at 1545 cm^{-1}, and strong ultraviolet absorption [λ_{max}^{EtOH} 218 (ϵ 6580), 263 (ϵ 6580), and 352 mμ (ϵ 13,200)] suggested a highly conjugated chromophore. The nmr spectrum revealed the presence of a lone vinyl proton (singlet at δ 7.74), two methanesulfonyl groups (singlets of area 3 at δ 3.02 and 2.94), and a dimethylamino group (singlet at δ 3.30), in addition to eight

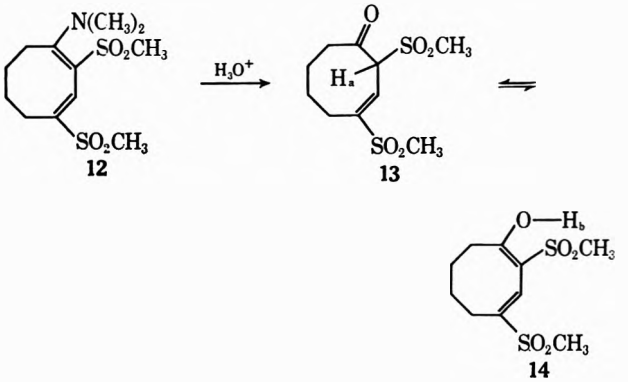
(12) (a) K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Amer. Chem. Soc.*, **87**, 3151 (1965); (b) V. Georgian, L. Georgian, and A. V. Robertson, *Tetrahedron*, **19**, 1219 (1963).

(13) The assignments of chemical shifts given for **9**, **10**, and **11** have been correlated with those of a number of model compounds including, for example, the acyclic sulfones described by C. D. Broaddus, *J. Amer. Chem. Soc.*, **90**, 5504 (1968).

(14) For selected examples of this phenomenon, see J. Meinwald and A. Lewis, *ibid.*, **83**, 2769 (1964); J. Meinwald and Y. C. Meinwald, *ibid.*, **85**, 2514 (1963); K. B. Wiberg, B. R. Lowry, and B. J. Nist, *ibid.*, **84**, 1594 (1962); E. I. Snyder and B. Franzus, *ibid.*, **86**, 1166 (1964).

(15) Similar angular dependences of comparable magnitude have been noted; see, for instance, S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

protons at higher field. Hence this disulfone was considered to have a 1-dimethylamino-1,3-cyclooctadiene skeleton bearing methanesulfonyl groups at C-2 and C-4. Hydrolysis of **12** was found to produce a mixture of ketone **13** (30%) and enol **14** (70%). The infrared



spectrum of this mixture exhibited a medium-intensity band at 1700 cm^{-1} for the keto form and strong absorption at 1603 cm^{-1} for the enol form. The nmr spectrum ($CDCl_3$) displayed a peak of intensity 0.3 H at δ 5.00 for H_a of **13** and a peak of area 0.7 at δ 10.61 for H_b of **14**. The predominance of enol form **14** is not unexpected in view of the behavior of the related carbomethoxy derivative.[10]

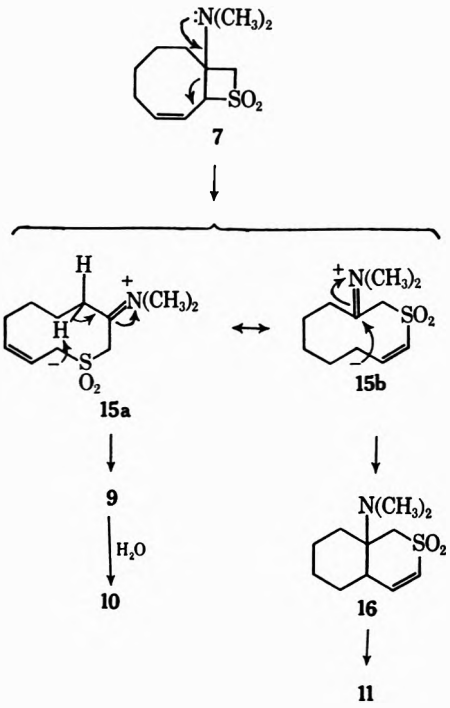
Mechanistic Considerations.—Earlier work has shown that 3-aminothietane dioxides are the customary end products of sulfene–enamine condensations.[3-5] However, in the present study, **7** was isolated only in one instance and in low yield. This observation can be reconciled with the instability of **7**, as noted by its relatively rapid conversion to **9** in chloroform solution at room temperature. When **7** is adsorbed on a chromatographic column packed with such stationary phases as alumina, silica gel, or Florisil, the onset of additional reactions is seen. In fact, only when the crude sulfene reaction mixture was rapidly eluted from a Florisil column to minimize contact time was the direct isolation of **7** possible (Table I).

β elimination of the elements of dimethylamine from **7** can account for the production of **8**. Because the proton which is abstracted is particularly strongly activated owing to its allylic and α-sulfonyl nature, this precedented transformation can be expected to be facile and is probably triggered by the triethylamine present in the sulfene reaction mixture.

The mechanism that prevails in the rearrangement of **7** to **9** is visualized as due to ring opening of the thiabicyclo[6.2.0]decane system to give dipolar species **15** (Scheme I). The allylic delocalization accorded the α-sulfonyl carbanion upon cleavage of the central bond in **7** may perhaps provide the requisite driving force, although the possibility that relief of steric strain is also influential cannot be discounted. Transannular proton transfer *via* a six-centered transition state completes the passage to **9**.

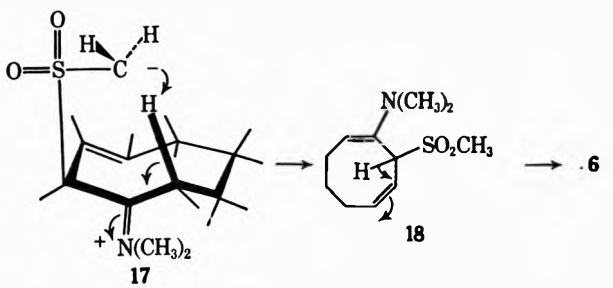
It seemed likely that zwitterion **15** could also serve as a precursor to **11**. The principal feature of this change involves recyclization to form **16** (Scheme I) and base-catalyzed equilibration of **16** to its β,γ-unsaturated isomer (**11**). Although this suggested pathway may seem controvertible, the facts remain that **7** was tranformed into **9** and **11** when allowed to pass

SCHEME I



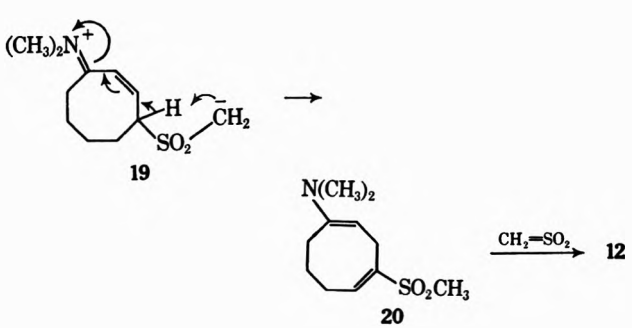
through a column of neutral alumina and that α,β-unsaturated sulfones are frequently less stable than their β,γ-unsaturated counterparts.[13,16]

The formation of **6** can be accommodated by a nonconcerted attack of sulfene at C-2 of the mesocyclic dienamine to produce zwitterion **17**. The carbanionic side chain in **17** can be positioned where it can abstract a proton α to the dimethyliminonium group (as shown)



through a six-membered transition state. Isomerization of the double bond in the enamine thus formed (**18**) leads to **6**.

Disulfone **12** may be produced by stepwise bonding of sulfene to C-4 of the dienamine to afford **19**, proton



(16) C. D. Broaddus, *Accounts Chem. Res.*, **1**, 231 (1968).

transfer in which leads to **20**. Repetition of this reaction sequence at C-2 in **20** gives rise to **12**.[17]

The present work shows that twisting of the π system of a dienamine out of planarity lessens the degree of sulfene bonding at C-4, very likely because of the diminution of nucleophilicity at that position. Furthermore, the isolation of **6** and **12** provides compelling evidence that sulfene reactions may, under certain circumstances, be nonconcerted.[18] Also, since sulfone **7** is the precursor of **8**, **9**, **10**, and **11**, the available evidence is consistent with the fact that 3-aminothietane dioxide formation is again kinetically preferred in the present instance.

Experimental Section

Melting points are corrected. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Infrared spectra were recorded with a Perkin-Elmer Model 237 spectrophotometer and ultraviolet spectra were determined with a Cary Model 14 instrument. The nmr spectra were determined with Varian A-60 and HA-100 spectrometers using tetramethylsilane as internal standard.

Reaction of 1-Dimethylamino-1,3-cyclooctadiene (3) with Sulfene.—In a typical experiment, to a stirred solution containing 1 equiv of **3**[10] and 1 or 2 equiv of triethylamine in dry tetrahydrofuran (usually 5 g of **3** in 75 ml of solvent) at −10° under nitrogen was added dropwise during 0.5 hr an equivalence of methanesulfonyl chloride equal to that of the tertiary amine. The resulting slurry was stirred for 1 hr at −10° and for an additional hour at room temperature. The mixture was filtered to remove the precipitated triethylamine hydrochloride and the solvent was evaporated *in vacuo* at room temperature. The resulting oil was chromatographed.

Under various reaction and work-up conditions (see Table I), seven products were obtained.

Sulfone **6** was obtained as white crystals, mp 85–86°, from ether–hexane.

Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.62; H, 8.35; N, 6.11; S, 13.96. Found: C, 57.56; H, 8.39; N, 6.02; S, 13.94.

Sulfone **7** was obtained as white crystals, mp 89.5–90.5°, from ether–hexane; $\nu_{max}^{CCl_4}$ 1328, 1192, and 1140 cm^{-1} (–SO_2–).

Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.62; H, 8.35; N, 6.11; S, 13.96. Found: C, 57.56; H, 8.38; N, 5.85; S, 13.97.

Sulfone **8** was obtained as white crystals, mp 94–95°, from ether.

Anal. Calcd for $C_9H_{12}O_2S$: C, 58.66; H, 6.59; S, 17.40. Found: C, 58.66; H, 6.60; S, 17.41.

Sulfone **9** was obtained as white crystals, mp 109–110°, from ether–hexane.

Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.62; H, 8.35; N, 6.11; S, 13.96. Found: C, 57.47; H, 8.28; N, 5.94; S, 13.96.

Sulfone **10** was recrystallized from chloroform–hexane to give white crystals, mp 144–145°.

Anal. Calcd for $C_9H_{14}O_3S$: C, 53.46; H, 6.98; S, 15.82. Found: C, 53.43; H, 7.01; S, 15.74.

The 2,4-dinitrophenylhydrazone was obtained as orange crystals, mp 219–220°, from 95% ethyl alcohol.

Sulfone **11** was obtained as white crystals, mp 169.0–170.5°, from ether.

Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.62; H, 8.35; N, 6.11; S, 13.96. Found: C, 57.39; H, 8.30; N, 5.75; S, 14.11.

Sulfone **12** was isolated from methanol as yellow crystals, mp 192–193°.

Anal. Calcd for $C_{12}H_{21}NO_4S_2$: C, 46.90; H, 6.89; N, 4.56; S, 20.82. Found: C, 46.63; H, 6.88; N, 4.41; S, 20.78.

Hydrolysis of 9.—A solution of 170 mg (0.74 mmol) of **9** and 0.5 ml of concentrated hydrochloric acid in 2 ml of water was refluxed for 10 min, cooled, and extracted with methylene chloride. The combined organic layers were dried and evaporated to give 120 mg (80%) of **10**, mp 143–145°, identical in all respects with the previously isolated material.

Hydrolysis of 12.—A solution of 1.30 g (4.2 mmol) of **12** and 4 ml of concentrated hydrochloric acid in 10 ml of water was treated as above. There was obtained 1.01 g (86%) of a mixture of **13** and **14**. Recrystallization of this material from chloroform–hexane gave white crystals, mp 133.0–134.5°.

Anal. Calcd for $C_{10}H_{16}O_5S_2$: C, 42.84; H, 5.75; S, 22.87. Found: C, 42.70; H, 5.74; S, 22.73.

Registry No.—Sulfene, 917-73-7; **6**, 20452-33-9; **7**, 20452-93-1; **8**, 20452-34-0; **9**, 20452-35-1; **10**, 20452-36-2; **10** (2,4-dinitrophenylhydrazone), 20452-37-3; **11**, 20452-94-2; **12**, 20452-38-4; **13**, 20500-57-6; **3**, 14833-75-1.

Acknowledgment.—The authors thank the Army Research Office (Durham) for financial support of this work and Dr. J. R. Malpass for assistance with the spin-decoupling experiments on **11**.

(17) Alternatively, the formation of **12** can be rationalized in terms of the direct reaction of **3** with methanesulfonyl chloride. Although the point has not been proven unequivocally, we consider this pathway less likely in view of the existing evidence that dehydrohalogenation of methanesulfonyl chloride by a tertiary amine normally proceeds faster than displacement of the sulfur-bound halogen by the β carbon of an enamine: I. J. Borowitz, *J. Amer. Chem. Soc.*, **86**, 1146 (1964).

(18) Further discussion about the concertedness or nonconcertedness of sulfene reactions may be found in ref 5. See also G. Optiz, *Angew. Chem. Intern. Ed. Engl.*, **7**, 646 (1968).

Concerning the Electronic Stabilization of Sulfenes[1]

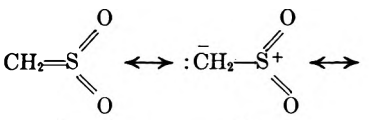
LEO A. PAQUETTE, JOHN P. FREEMAN,[2] AND ROBERT W. HOUSER[3]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

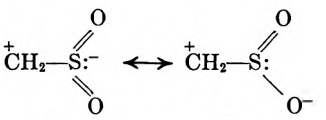
Received January 3, 1969

Sulfenes ($R_2C{=}SO_2$) are known to be capable of (2 + 2) π cycloaddition with activated olefins. Condensation occurs in the direction suggestive that the sulfur atom is electrophilic in nature. Molecular orbital calculations bear out this conclusion. Because stable sulfenes have not been prepared, attempts have been made to stabilize such intermediates by delocalization of the partial negative charge on carbon. Carbalkoxy groups and cyclopentadienyl substituents were employed for this purpose. Despite the fact that the derived sulfenes underwent "normal" cycloaddition, they were not stable in solution. The conclusion is reached that perhaps not only electronic delocalization but also simultaneous retardation of polymerization may be required for the ultimate isolation of a sulfene.

Earlier studies have shown that 1,2 elimination of hydrogen halide from primary and secondary sulfonyl chlorides and bromides can be readily achieved with trialkylamines. Under the usual reaction conditions, sulfenes (1) are believed to result;[4] however, the high reactivity and instability of these heterocumulenes has precluded their isolation and characterization. An



1a 1b



1c 1d

attempt to prepare a stable sulfene has been reported by Opitz and his coworkers. Treatment of methanesulfonyl chloride with triethylamine in acetonitrile at −40° produces mesylsulfene (2) which is stable in this

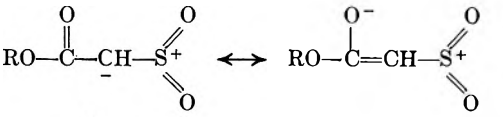
$$CH_3SO_2CH{=}SO_2$$

2

medium at −40° for several days (established by capture experiments), but which decomposes when warmed above −30°.[5a] Although 2 was not characterized, these workers did find that 2 could be isolated as a stable trimethylamine adduct.[5b]

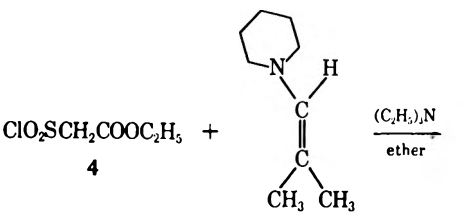
The normally observed reactivity of a sulfene is that corresponding to ylide structure **1b**, in which the sulfonyl group exhibits electrophilic character.[4] In the belief that the relationship between structure and stability of sulfenes would very likely obey the same rules as for other ylides,[6] we have attempted to prepare electronically stabilized sulfenes by several methods. Although success was not achieved, the uncovered information provides new insight into the sulfene question, and consequently our results are described at this time.

For the first part of this investigation, α-carbalkoxy groups were examined for their possible assistance in delocalization of the carbanionic character imparted to the α-sulfonyl carbon (**3**). Initially, it was deemed



3a 3b

advisable to establish that such sulfenes display "normal" chemical behavior.[7] For this purpose, ethyl (chlorosulfonyl)acetate (**4**) was treated with 1-isobutenylpiperidine in the presence of ethereal triethylamine. The cycloaddition reaction gave **5** in 43% yield. Structural assignment to **5** follows from its



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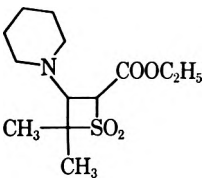


5

spectral properties (see Experimental Section). The stereochemistry of **5** is a point of some interest. The large nmr coupling constant between the two thietane ring protons (9.3 Hz) suggests a dihedral angle between these protons of 0 or 180°.[8,9] The former angle can be achieved only in a planar thietane ring by a *cis* orientation of the bulky piperidino and carbethoxy groups; in this structure an all-eclipsed conformation is seen

(1) This work was supported in part by the National Science Foundation Grant GP-5977.

(2) National Science Foundation Graduate Fellow, 1966–1968; American Chemical Society–Petroleum Research Fund Graduate Fellow, 1968–1969.

(3) NDEA Fellow, 1967–.

(4) For a recent review of sulfene chemistry, see G. Optiz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 107 (1967).

(5) (a) G. Opitz, M. Kleeman, D. Bücher, G. Walz, and K. Rieth, *ibid.*, **5**, 594 (1966); (b) G. Optiz and D. Bücher, *Tetrahedron Lett.*, 5263 (1966).

(6) A. W. Johnson, "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966.

(7) This question has been the subject of a limited amount of earlier work. Fusco, *et al.* [R. Fusco, S Rossi, S. Maiorana, and G. Pagani, *Gazz Chim. Ital.*, **95**, 774 (1965)], for example, have observed that the action of triethylamine on phenacyl sulfonyl chloride in the absence of an electron-rich olefin results in the formation of a sulfene dimer. Ethyl(chlorosulfonyl)acetate (**4**) is claimed not to react with vinyl ethers, while phenacyl sulfonyl chloride gives (4 + 2) cycloadducts with these ethers as opposed to (2 + 2) adducts with enamines.[4]

(8) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(9) Earlier work has shown that application of the Karplus correlation to the thietane dioxide ring system is reliable: L. A. Paquette, *J. Org. Chem.*, **29**, 2854 (1964); L. A. Paquette, M. Rosen, and H. Stucki, *ibid.*, **33**, 3020 (1968).

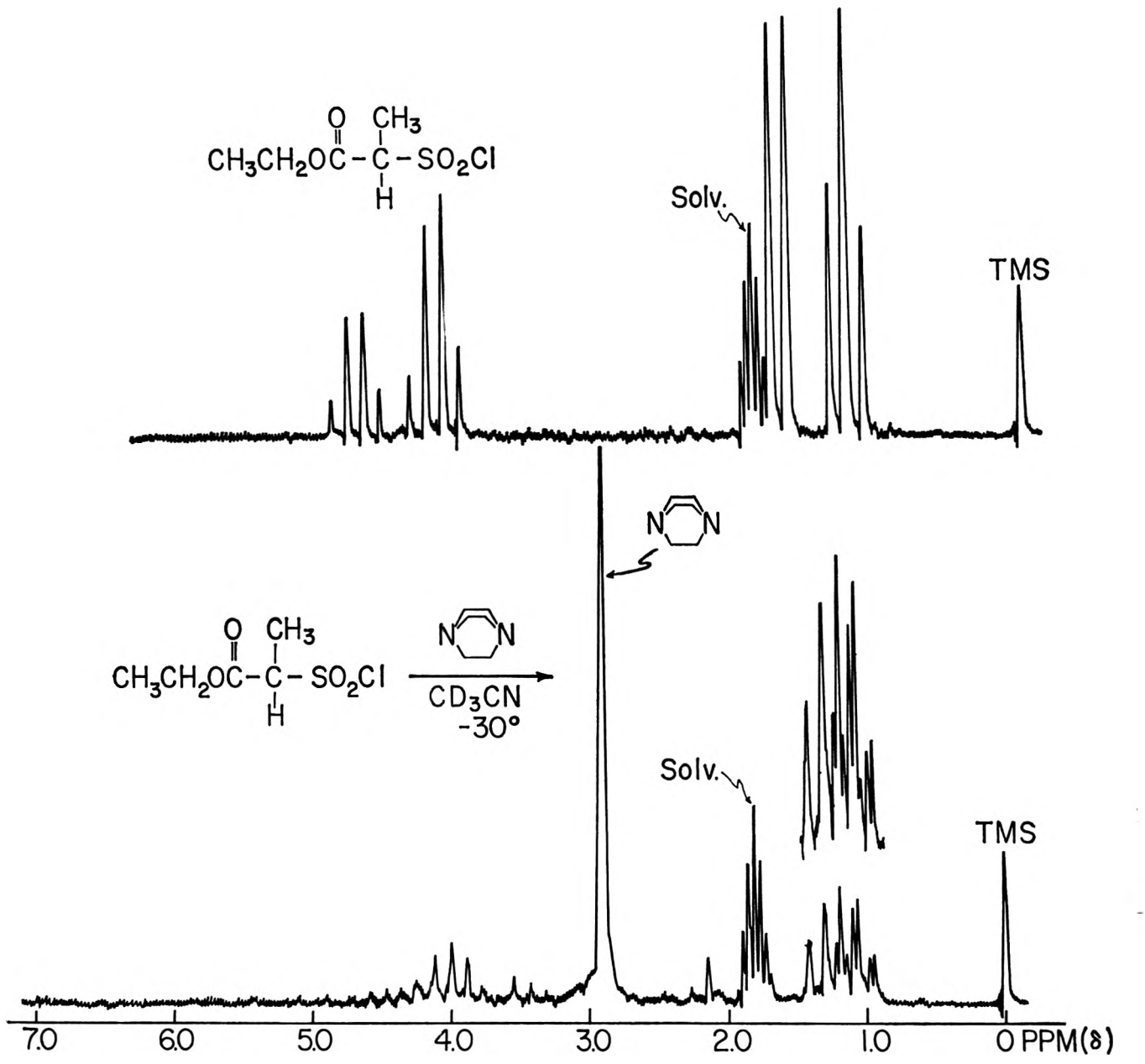


Figure 1.—60-MHz nmr spectrum of **7a** prior to, and subsequent to, the addition of DABCO (CD_3CN solution, −30°).

and thermodynamic instability relative to the *trans* isomer is to be expected. The 180° alignment can be attained only by *trans* substituents in a puckered thietane dioxide ring (**6**).[10] In this structure, a perfectly staggered conformation is present with pseudo-equatorial disposition of the two bulky ring substituents. To distinguish between these two alternatives, **5** was exposed to 0.02 mol equiv of sodium methoxide in methanol. After prolonged treatment, no epimerization was apparent; this observation is congruent with *trans* formulation **6**.

6

In view of this successful trapping of a carbalkoxysulfene, characterization of such an entity by nmr spectroscopy became the next goal. The possibility was considered that esters of 2-(chlorosulfonyl)propionate (**7**) would be best suited to our studies, since conversion to the corresponding sulfene was expected to result in collapse of the doublet methyl absorption of **7** (Figure 1) to a singlet. Addition of slightly greater than 1 equiv of 1,4-diazabicyclooctane (DABCO)[11] to a cold (−30°) acetonitrile-d_3 solution of ester **7a**,

7a, R = C_2H_5
b, R = CH_3

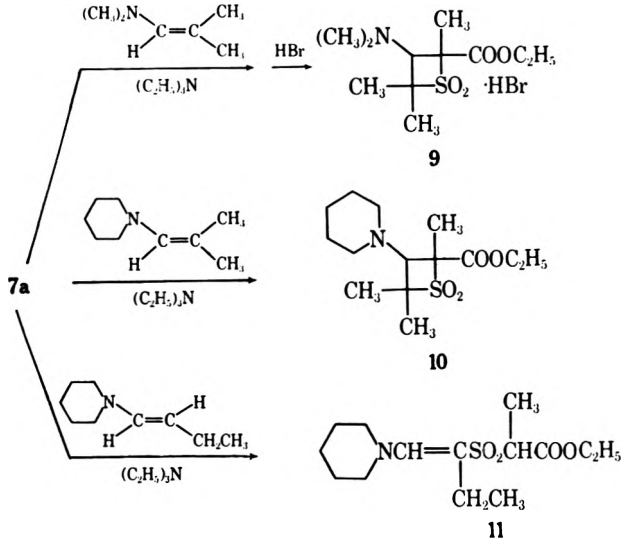
8a, R = C_2H_5
b, R = CH_3

(10) For a review of the evidence in support of the puckered conformation for the thietane dioxide ring system, see L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967), footnotes 17–21.

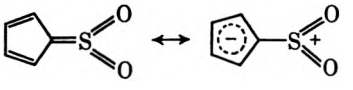
(11) DABCO has been chosen as the tertiary amine because of its exceedingly simple nmr spectrum (see Figure 1).

followed by rapid removal of the precipitated DABCO hydrochloride and nmr determination at this temperature, failed to give interpretable spectral information (Figure 1). The methyl ester **7b** behaved similarly, and the results could be reproduced consistently. The failure of these efforts seemed less surprising when it was discovered that, although **8a** behaved quite normally when generated in the presence of a suitable coreactant (Scheme I), no characterizable products could be isolated if the enamine was added some time (commonly 15–120 min) after the sulfene had been generated. The method of synthesis of **7a** and **7b** and full characterization of adducts **9–11** are described in the Experimental Section.

SCHEME I



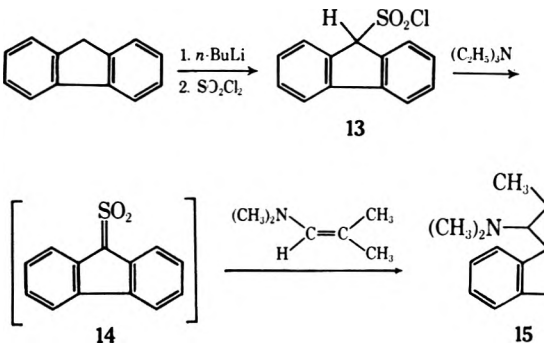
With the removal of carbalkoxy functions as sulfene substituents with sufficient stabilizing influence, attention was directed to a consideration of the sulfonylcyclopentadienes (**12**). This choice was predicated upon



12a **12b**

the recognized stabilizing capacity of a cyclopentadienyl substituent in ylide structures by virtue of negative charge delocalization in the five-membered ring. Notable examples are diazocyclopentadiene,[12] triphenylphosphonium cyclopentadienylide,[13] and 9-sulfinylfluorene.[14]

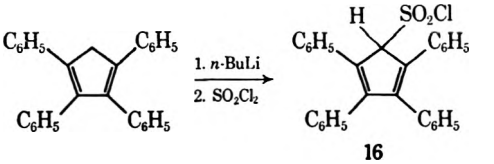
From the synthetic viewpoint, Opitz has generalized that the positioning of two phenyl groups α to a chlorosulfonyl function causes sulfur dioxide elimination, even at room temperature. Over 45 years ago, Wedekind and coworkers reported unsuccessful attempts to prepare 9-fluorenesulfonyl chloride (**13**) in apparent support of this generalization.[15] However, in our hands, fluorenyllithium has been observed to react with excess sulfuryl chloride in ether to afford **13**, mp 86–87.5°, in 32% yield. The structure of **13** was derived from its elemental analysis, its infrared spectrum, which exhibits sulfone stretching bands at 1370, 1180, and 1145 cm^{-1}, and its typical fluorene ultraviolet absorption [$\lambda_{max}^{isooctane}$ 235 (ϵ 24,200) and 273 mμ (ϵ 10,000)]. In addition, the nmr spectrum of **13** consists of a one-proton singlet at δ 5.78 and an eight-proton multiplet at δ 7.80. With authentic **13** in hand, it was possible to demonstrate that the derived sulfene (**14**) readily



undergoes the typical cycloaddition reaction with enamines. In the presence of N,N-dimethyl-1-isobutenylamine and triethylamine, for example, **13** was transformed into thietane dioxide **15** in 88% yield.

Attempts to prepare stable solutions of **14** were, however, without success. Addition of triethylamine to ether solutions of **13** at various temperatures (−80–0°) in a nitrogen atmosphere resulted in the formation of a dark purple solution which, when filtered to remove amine hydrochloride, became dark yellow. Careful evaporation of the ether invariably afforded a bright yellow solid which was polymeric and which exhibited only very weak sulfone absorption in the infrared. Further, if **13** was exposed to an equimolar amount of triethylamine in the above fashion and N,N-dimethyl-1-isobutenylamine was added at a subsequent time (2–4 hr later), no cycloaddition product (**15**) was produced. Lastly, when a dilute (3.13×10^{-5} *M*) solution of **13** in isooctane was treated with 1 drop of triethylamine in a quartz cell, the ultraviolet absorption of **13** was noted to decay rapidly, and none of the spectral features exhibited by fluorenone or 9-sulfinylfluorene[14] was seen.

In order to examine the effect of phenyl substitution on the stabilizing capability of the cyclopentadiene ring, the preparation of tetraphenylcyclopentadienylsulfonyl chloride (**16**) was attempted. Reaction of tetraphenyl-



cyclopentadienyl lithium with sulfuryl chloride in the predescribed manner gave an initial product which proved to be very labile. A solid was generally obtained whose composition varied from run to run and whose molecular weight (mass spectral analysis) was in the range of a dimeric substance. Further studies were not pursued.

(12) W. von E. Doering and C. H. DePuy, *J. Amer. Chem. Soc.*, **75**, 5955 (1953).
(13) F. Ramirez and S. Levy, *ibid.*, **79**, 67 (1967).
(14) W. A. Sheppard and J. Dieckmann, *ibid.*, **86**, 1891 (1964).
(15) E. Wedekind and R. Stüsser, *Ber.*, **56**, 1557 (1923); E. Wedekind and D. Schenk, *ibid.*, **44**, 198 (1911).

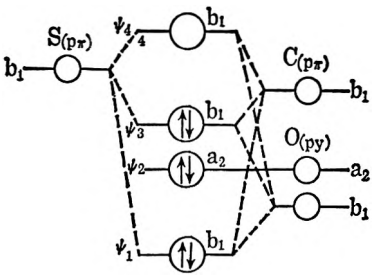
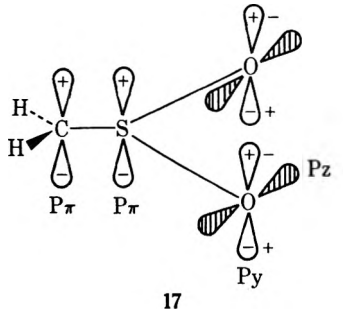


Figure 2.—Molecular orbitals in $CH_2{=}SO_2$.

Discussion

A sulfene molecule can logically be assumed to be planar in its ground state and to consist of sp^2-hybridized carbon and sulfur atoms.[16] If the oxygen atoms are typically sp hybridized, the molecular structure of sulfene is seen to be **17**, the point group of which is



17

C_{2v}. As a result, $C_{(p\pi)}$ and $S_{(p\pi)}$ transform as b_1, while $O_{(py)}$ transforms as b_1, a_2. Assuming that the σ bonding orbitals are very stable and therefore that the σ antibonding orgitals have very high energy, we obtain the schematic energy diagram given in Figure 2. The relative energies of the atomic orbitals are based on the ionization potentials of the relevant atoms.[17] Since the $O_{(pz)}$ electrons are perpendicular to the y plane, they make no net contribution to the π molecular orbital. In view of the fact that only orbitals of like symmetry interact, $S_{(b_1)}$ will mix with $O_{(b_1)}$ and $C_{(b_1)}$, whereas $O_{(a_2)}$ will remain nonbonding. The molecular orbital seen in Figure 2 will then result. Sulfur d orbitals have not beeen considered, since they can be expected to contribute little as a result of their high energy content. It is particularly significant to note that ψ_3 is mostly carbon in nature and that the $C_{p\pi}$–$S_{p\pi}$ electron pair will therefore be polarized toward this atom.

The above analysis suggests that the lowest ground-state molecular orbital of a sulfene exhibits appreciable negative character on carbon. Despite this fact, we have seen that attempts to stabilize a sulfene by delocalization of this electron pair in a classical sense were not successful. Perhaps the relationship between structure and stability is not dictated totally by such electronic stabilization, but rather is also a question of minimizing simultaneously the rate of polymerization. For this reason, the preparation of sterically hindered sulfenes should perhaps be undertaken.

(16) It may be contended that sulfenes are in fact nonplanar in view of what is known about the stereochemistry of α-sulfonyl carbanions. Obviously, this is a moot point in the case of nonstabilized sulfenes. However, if the sulfene carbon is substituted with a carbanion stabilizing group (with attendant charge delocalization), then the assumption of planarity for the sulfene is entirely plausible.

(17) H. B. Gray, "Electrons and Chemical Bonding," W. A. Benjamin, Inc., New York, N. Y., 1965, p 29. The following values are pertinent: O, 13.614 eV; C, 11.264 eV; S, 10.357 eV.

Experimental Section[18]

2-Carbethoxy-4,4-dimethyl-3-piperidinothietane 1,1-Dioxide (5).—To a cold (−20°) solution of 6.07 g (0.060 mol) of triethylamine and 8.36 g (0.060 mol) of 1-isobutenylpiperidine[19] in 240 ml of anhydrous ether was added dropwise with stirring under nitrogen a solution of 11.2 g (0.060 mol) of ethyl (chlorosulfonyl)-acetate[20] in 75 ml of the same solvent. During the addition, the temperature was not allowed to rise above −15°. Stirring was continued at −16° to −10° for 2 hr and at room temperature for 5 hr. The precipitated triethylamine hydrochloride was separated by filtration and washed with ether. The combined washings and filtrate were evaporated under reduced pressure and the crude solid residue (12.0 g) was recrystallized from aqueous ethanol and dried to give 7.5 g (43%) of **5**, mp 92.5–94°. Further recrystallization from hexane gave an analytical sample: mp 93.5–94.5°; ir $\nu_{max}^{CCl_4}$ 1742 (C=O), 1330, and 1200 cm^{-1} (SO_2); nmr $\delta_{TMS}^{CCl_4}$ 4.59 (d, J = 9.3 Hz, 1 H, CO–CH–SO_2), 4.23 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.01 (d, J = 9.3 Hz, 1 H, CH–N), 2.25 (m, 4 H, α-piperidino protons), 1.4–1.7 with spikes at 1.53 and 1.50 (m, 12 H, remaining piperidino protons and ring methyl groups), and 1.32 ppm (t, J = 7 Hz, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{13}H_{23}NO_4S$: C, 53.96; H, 8.01; N, 4.84. Found: C, 54.25; H, 8.01; N, 4.77.

Potassium 1-Carbethoxyethanesulfonate.—To a freshly prepared oxygen-free aqueous solution of potassium sulfite (0.44 mol)[21] was added 76 g (0.42 mol) of ethyl 2-bromopropionate[22] and 70 ml of 95% ethanol. The inhomogeneous mixture was heated at reflux for 13 hr, at which point an additional 5 g of solid potassium sulfite was added and the mixture was refluxed for 2 hr. The mixture was cooled in an ice bath, the solid potassium bromide was filtered, and the filtrate was reduced to near dryness on the rotary evaporator. The residue was recrystallized from absolute ethanol with filtration of additional potassium bromide from the hot solution. Cooling of the filtrate gave a crystalline product (76.7 g, 83%). The material thus prepared still contained a trace of potassium bromide, as revealed by a positive silver nitrate test and a wide melting range (192–205°). Two additional recrystallizations from absolute ethanol produced bromide-free salt: mp 194–196° (lit.[23] mp 214°); ir ν_{max}^{Nujol} 1720 (C=O), 1200, and 1040 cm^{-1} (SO_3^-); nmr $\delta_{TPSS}^{D_2O}$ 4.22 (q, J = 6.8 Hz, 2 H, OCH_2CH_3), 3.91 (q, J = 7.0 Hz, 1 H, CH_3CH), 1.49 (d, J = 7.0 Hz, 3 H, CH_3CH), and 1.27 ppm (t, J = 6.8 Hz, 3 H, OCH_2CH_3).

Anal. Calcd for $C_5H_9KO_5S$: C, 27.26; H, 4.12; S, 14.56. Found: C, 27.42; H, 4.04; S, 14.29.

Ethyl (2-Chlorosulfonyl)propionate (7a).—A 12.6-g (0.057 mol) sample of dry and finely pulverized potassium 1-carbethoxyethanesulfonate was thoroughly mixed with 14.35 g (0.069 mol, 20% excess) of granular phosphorus pentachloride. After the initial exothermic reaction had subsided, the mixture was heated for 1 hr on the steam bath and kept for 4 hr at room temperature. The resulting phosphorus oxychloride was removed by distillation at 80–90 mm. The residue was shaken with 100 ml of crushed ice and 150 ml of ether. After the aqueous layer was shaken with two additional portions of ether, the combined organic layers were shaken with saturated sodium chloride solution and dried. Distillation afforded 6.51 g (57%) of **7a**: bp 87–89° (0.9 mm); $n^{26}D$ 1.4555; ir $\nu_{max}^{CCl_4}$ 1735 (C=O) 1380, 1365, 1190, and 1155 cm^{-1} (SO_2); for nmr, see Figure 1.

Methyl (2-Chlorosulfonyl)propionate (7b).—Treatment of 70.2 g (0.42 mol) of commercial methyl 2-bromopropionate with 0.42 mol of potassium sulfite as above resulted in the formation of 56 g (69%) of potassium 1-carbomethoxyethanesulfonate: mp 192–199° from ethanol; ir ν_{max}^{Nujol} 1727 (C=O), 1195, and 1035

(18) Melting points are corrected while boiling points are uncorrected. The infrared spectra were obtained with a Perkin-Elmer Model 237 Infracord spectrometer. The microanalyses were determined by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The nmr spectra were determined with Varian A-60 or A-60A spectrometers. Ultraviolet measurements were made with a Cary Model 14 recording spectrometer.

(19) C. Mannich and H. Davidsen, *Ber.*, **69B**, 2106 (1936).

(20) R. Vieillefosse, *Bull. Soc. Chim. Fr.*, 351 (1947).

(21) H. F. Johnstone, *Inorg. Syn.*, **2**, 166 (1946).

(22) A. I. Vogel, *J. Chem. Soc.*, 644 (1948).

(23) R. Andreasch, *Monatsh. Chem.*, **46**, 639 (1925).

cm^{-1} (SO_3); nmr $\delta_{TPS}^{D_2O}$ 3.96 (q, J = 7.0 Hz, 1 H, $CH_3CH<$), 3.77 (s, 3 H, OCH_3), and 1.50 ppm (d, J = 7.0 Hz, 3 H, CH_3CH).

Anal. Calcd for $C_4H_7KO_5S$: C, 23.29; H, 3.42. Found: C, 23.03; H, 3.55.

Treatment of 51.6 g (0.25 mol) of this dry salt with 67.8 g (0.325 mol, 30% excess) of powdered phosphorus pentachloride in the predescribed manner afforded 19.9 g (43%) of **7b**: bp 75–78° (1.5 mm); $n^{29}D$ 1.4607; ir $\nu_{max}^{CCl_4}$ 1750 (C=O), 1375, 1315, and 1180 cm^{-1} (SO_2); nmr $\delta_{TMS}^{CD_3CN}$ 4.84 (q, J = 6.9 Hz, 1 H, CH_3CH), 3.80 (s, 3 H, OCH_3), and 1.75 ppm (d, J = 6.9 Hz, 3 H, CH_3CH).

2-Carbethoxy-3-dimethylamino-2,4,4-trimethylthietane 1,1-Dioxide Hydrobromide (9).—A solution of 4.0 g (0.02 mol) of **7a** in 20 ml of acetonitrile was added dropwise at −20° under nitrogen to a stirred solution of 2.0 g (0.02 mol) of triethylamine and 2.0 g (0.02 mol) of N,N-dimethyl-1-isobutenylamine[24] in 78 ml of the same solvent. Stirring was continued at −20° for an additional 1.5 hr and then at room temperature for 7 hr. After filtration of the triethylamine hydrochloride, the filtrate was reduced in volume to *ca.* 5 ml. When enough ether was added to return the solution to its original volume, more hydrochloride precipitated along with some yellow material. To the resultant filtrate was added ethereal hydrogen bromide solution until no further solid was produced. This solid was filtered and air dried to give 5.13 g (74%) of **9**: mp 177–178° (from ethanol); ir ν_{max}^{Nujol} 1727 (C=O), 1310, 1265, and 1210 cm^{-1} (SO_2); nmr $\delta_{TPSS}^{D_2O}$ 5.18 (s, 1 H, $\overset{+}{N}$–CH), 4.23 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 2.70 (br s, 6 H, $(CH_3)_2\overset{+}{N}$), 1.55 and 1.40 (s, 3 H and 6 H, respectively, ring methyl groups), and 1.28 ppm (t, J = 7.0 Hz, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{11}H_{22}BrNO_4S$: C, 38.38; H, 6.44; N, 4.07; S, 9.31. Found: C, 38.47; H, 6.45; N, 4.06; S, 9.54.

2-Carbethoxy-3-piperidino-2,4,4-trimethylthietane 1,1-Dioxide (10).—In a manner similar to that used in the preparation of **5**, 4.17 g (0.03 mol) of 1-isobutenylpiperidine and 6.00 g (0.03 mol) of **7a** were allowed to react in ether solution at −20° in the presence of triethylamine (3.03 g, 0.03 mol). Work-up of the reaction gave 7.49 g (83%) of crude **10**, mp 74–76°. Recrystallization from hexane afforded large white plates: mp 75–76.5°; ir $\nu_{max}^{CCl_4}$ 1735 (C=O), 1318, and 1250 cm^{-1} (SO_2); nmr $\delta_{TMS}^{CCl_4}$ 4.24 (q, J = 7.1 Hz, 2 H, $-OCH_2CH_3$), 3.35 (s, 1 H, N–CH), 2.1–2.4 (m, 4 H, α-piperidino protons), 1.78 (s, 3 H, 2-methyl group), 1.60 and 1.55 (s, 3 H each, *gem*-dimethyl groups), 1.38–1.7 (m, 6 H, remaining piperidino protons), and 1.29 ppm (t, J = 7.1 Hz, OCH_2CH_3).

Anal. Calcd for $C_{14}H_{25}NO_4S$: C, 55.42; H, 8.30; N, 4.62; S, 10.57. Found: C, 55.70; H, 8.30; N, 4.78; S, 10.53.

Addition of 1-Butenylpiperidine to 7a.—Treatment of 15.01 g (0.075 mol) of **7a** with a solution of 10.44 g (0.075 mol) of 1-butenylpiperidine[25] and 7.59 g (0.075 mol) of triethylamine in 340 ml of anhydrous ether at −10° as described above yielded 19.7 g (86%) of **11**: mp 41.5–43.0° from ethyl acetate–hexane; ir $\nu_{max}^{CCl_4}$ 1735 (C=O), 1304, and 1150 cm^{-1} (SO_2); nmr $\delta_{TMS}^{CCl_4}$ 6.75 (s, 1 H, vinyl proton), 4.10 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 3.69 (q, J = 7.0 Hz, 1 H, CH_3CH), 3.34 (br, 4 H α-piperidino protons), 2.34 (q, J = 7.5 Hz, 2 H, $-CH_2CH_3$), 1.64 (br, 6 H, remaining piperidino protons), 1.40 (d, J = 7.0 Hz, 3 H, CH_3CH), 1.28 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), and 1.10 ppm (t, J = 7.5 Hz, 3 H, $-CH_2CH_3$).

Anal. Calcd for $C_{14}H_{25}NO_4S$: C, 55.42; H, 8.31; N, 4.62. Found: C, 55.52; H, 8.24; N, 4.65.

9-Fluorenylsulfonyl Chloride (13).—To a cold (0°) stirred solution of 12.5 g (0.075 mol) of fluorene in 150 ml of anhydrous ether was added under a nitrogen atmosphere 50 ml (0.08 mol) of 1.6 *M* *n*-butyllithium in hexane over a period of 15 min. The resulting yellow solution was added dropwise during 1 hr to 50 ml of cold (0°) sulfuryl chloride under nitrogen. The solvent and excess sulfuryl chloride were then evaporated *in vacuo*, methylene chloride (100 ml) was added, and the solution was washed twice with water (200 ml). The organic phase was dried, filtered, and evaporated, and the resultant yellow oil was refrigerated overnight. The crystalline product was triturated with pentane and filtered to yield 6.5 g (32.5%) of **13**. Further recrystallization from chloroform–pentane (1:1) gave pure **13**: mp 86–87.5° dec; ir $\nu_{max}^{CCl_4}$ 1370, 1180, and 1145 cm^{-1} (SO_2); nmr $\delta_{TMS}^{CDCl_3}$ 7.80 (m, 8 H, aromatic protons) and 5.78 ppm (s, 1 H, $CHSO_2Cl$); uv $\lambda_{max}^{isooctane}$ 235 (ϵ 24,200) and 273 mμ (ϵ 10,000).

Anal. Calcd for $C_{13}H_9ClO_2S$: C, 59.00; H, 3.43; Cl, 13.42; S, 12.10. Found: C, 58.88; H, 3.49; Cl, 13.40; S, 12.17.

Addition of N,N-Dimethyl-1-isobutenylamine to 13.—To a cold (0°) stirred solution of 0.38 g (3.8 mmol) of N,N-dimethyl-1-isobutenylamine and 0.38 g (3.8 mmol) of triethylamine in 150 ml of anhydrous ether was added dropwise under nitrogen a solution of 1.0 g (3.8 mmol) of **13** in 50 ml of ether during 30 min. The slurry was filtered, the filter cake was washed with acetone, and the combined filtrates were evaporated to give 1.09 g (88%) of white solid. Recrystallization of this material from benzene–ethanol (1:1) afforded pure **15**: mp 179–180° dec; ir ν_{max}^{KBr} 1300, 1160, and 1125 cm^{-1} (SO_2); nmr $\delta_{TMS}^{CDCl_3}$ 7.50 (m, 8 H, aromatic prtons), 3.25 (s, 1 H, N–CH), 2.00 and 1.80 (s, 3 H each, CH_3–N), and 1.73 ppm (s, 6 H, *gem*-dimethyl groups); mass spectrum *m/e* 327.

Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.70; H, 6.44; S, 9.79. Found: C, 69.41; H, 6.44; S, 9.77.

Registry No.— Potassium 1-carbethoxyethanesulfonate, 20449-08-5; potassium 1-carbomethoxyethanesulfonate, 20449-10-9; **5**, 20449-07-4; **7a**, 20449-09-6; **7b**, 20449-11-0; **9**, 20449-12-1; **10**, 20449-13-2; **11**, 20449-14-3; **13**, 20449-15-4; **15**, 20449-16-5.

Acknowledgment.—We thank Professor Andrew Wojcicki for a stimulating discussion.

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(25) G. Opitz and A. Griesinger, *Ann.*, **665**, 101 (1963).

The Decomposition of 4,6-Dimethylbenzocyclobutenone *p*-Toluenesulfonylhydrazone

ALFRED T. BLOMQUIST AND CONRAD F. HEINS[1]

Department of Chemistry, Cornell University, Ithaca, New York, and Denver Research Institute, University of Denver, Denver, Colorado 80210

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Pyrolysis of 4,6-dimethylbenzocyclobutenone *p*-toluenesulfonylhydrazone sodium salt (**1b**) in acetamide gave 4,6-dimethylbenzocyclobutenyl *p*-tolyl sulfone (**2**) and 4,6-dimethylbenzocyclobutenylacetamide (**3**). Photolysis of this salt yielded sulfone **2** as well as a hydrocarbon, $C_{20}H_{20}$, tentatively identified as 1,1′-bi(4,6-dimethylbenzocyclobutylidene) (**6**). All of these products could arise through the intermediate formation of the benzocyclobutenyl carbene **5**.

As part of a study of the benzocyclobutene ring system,[2] it was felt that the benzocyclobutenyl carbene would be an interesting species to prepare. Ring contraction analogous to that observed for cyclobutylcarbenes[3,4] would yield methylenebenzocyclopropene, while hydrogen migration would lead to a benzocyclobutadiene structure.

The decomposition of *p*-toluenesulfonyl- (*p*-tosyl-) hydrazone salts was the method chosen to produce the desired carbene. The procedure is straightforward and has been used successfully by many experimenters;[3-7] moreover, carbenes can be generated by either a thermal[6] or a photolytic[7] process.

4,6-Dimethylbenzocyclobutenone *p*-tosylhydrazone (**1a**) was chosen as the starting material. 4,6-Dimethylbenzocyclobutenone[8] was readily prepared from mesitylene by the method of Hart and Fish[9b] and converted into **1a** with *p*-tosylhydrazine.

The thermal decomposition of this tosylhydrazone was carried out using the method of Powell and Whiting.[6] Sodium was dissolved in freshly distilled acetamide to give the sodium salt upon warming to 100°. Powdered 4,6-dimethylbenzocyclobutenone *p*-tosylhydrazone was then added. Heating the mixture at 155° for 5 min resulted in complete decomposition of the tosylhydrazone as measured by nitrogen evolution. Two major products, neither of them hydrocarbons, were isolated from the reaction mixture.

The first, a white, crystalline solid, mp 104–105° was obtained from a pentane extract of the reaction mixture. This compound was identified as 4,6-dimethylbenzocyclobutenyl *p*-tolyl sulfone (**2**). The formation of sulfones by decomposition of tosylhydrazones has been reported by Lemal and Fry, who obtained yields as high as 50% 3-nortricyclyl *p*-tolyl sulfone by photolysis of the corresponding sodium tosylhydrazone derivative.[10]

The second compound, isolated in 38% yield, was assigned the structure of 4′,6′-dimethylbenzocyclobutenylacetamide (**3**) on the basis of its elemental and spectral analyses and degradation products. Hydrolysis of **3** in 15% potassium hydroxide followed by acidification yielded a carboxylic acid, 4′,6′-dimethylbenzocyclobutenylacetic acid (**4**) (Scheme I). The structural assignment was based on elemental analysis and molecular weight.

One way to account for both of these products would be through the intermediate formation of carbene **5**. This species could react with the tolylsulfinate anion formed by initial heterolysis in a manner analogous to that suggested by Lemal and Fry[10] to give a relatively stable sulfone anion which, during work-up, would be protonated to sulfone **2**. Amide **3** could arise by carbene insertion into the solvent, acetamide.[11] Both **2** and **3** could have arisen without the intermediate formation of carbene **5**, although such reactions are more difficult to rationalize considering the conditions that were employed.

A portion of the pentane extract of the reaction mixture was analyzed by means of a gas chromatographic unit connected to a mass spectrometer. None of the products isolated and identified by this procedure proved to be hydrocarbons derived from the 4,6-dimethylbenzocyclobutenyl carbene.

Photolysis gave somewhat different results. The tosylhydrazone salt, formed with sodium hydride, was suspended in purified dioxane and irradiated for 30 min using a 550-W Hanovia mercury vapor insertion lamp. The reaction mixture was poured into water and extracted with pentane and benzene. Chromatography of the carefully washed organic extracts afforded three products. One, obtained in 14% yield, was identified as sulfone **2** on the basis of its melting point and infrared spectrum. The second was a hydrocarbon, mp 188–189°, obtained in 8.3% yield. The material gave a correct analysis for the structure $C_{10}H_{10}$, the empirical formula of carbene **5**. Mass spectral analysis showed it to be a dimer, $C_{20}H_{20}$ (mol wt 260). The infrared spectrum exhibited a weak peak at 1705, medium peaks at 1600, 1470, 1320, 1265, and 1040, and two strong peaks at 850 (very strong) and 725 cm^{-1}. The nuclear magnetic resonance spectrum showed three singlets at τ 3.23, 6.27, and 7.68, with a ratio of 0.98:

(1) National Science Foundation Postdoctoral Fellow, 1962–1963. Author to whom correspondence should be addressed: University of Denver, Denver, Colo. 80210.

(2) (a) A. T. Blomquist and C. G. Bottomley, *N. Y. Acad. Sci. Trans.*, **24**, 823 (1962); (b) A. T. Blomquist and V. J. Hruby, *J. Amer. Chem. Soc.*, **86**, 5041 (1964).

(3) L. Friedman and H. Schechter, *ibid.*, **82**, 1002 (1960).

(4) G. Maier and M. Strasser, *Tetrahedron Lett.*, 6453 (1966).

(5) E. Chinoporos, *Chem. Rev.*, **63**, 235 (1963).

(6) J. W. Powell and M. C. Whiting, *Tetrahedron*, **12**, 168 (1961).

(7) W. G. Dauben and F. G. Willey, *J. Amer. Chem. Soc.*, **84**, 1497 (1962).

(8) As was pointed out in a previous paper,[9a] this nomenclature is more convenient and easier to visualize than the more systematic name (3,5-dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-one) and will be used throughout.

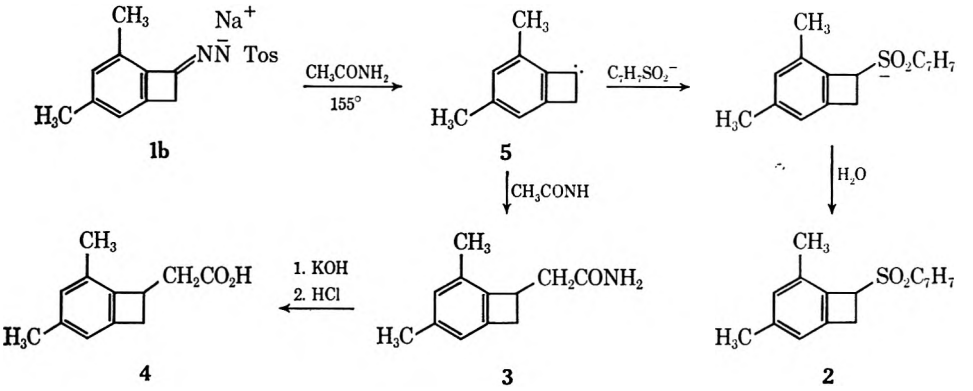
(9) (a) H. Hart, J. A. Hartlage, R. W. Fish, and R. R. Rafos, *J. Org. Chem.*, **31**, 2244 (1966); (b) H. Hart and R. W. Fish, *J. Amer. Chem. Soc.*, **82**, 749 (1960).

(10) D. M. Lemal and A. J. Fry, *J. Org. Chem.*, **29**, 1673 (1964).

(11) Although only one amide was recovered from the reaction mixture, it is possible that the N-substituted isomer was formed and not isolated. There is no clear precedent for either insertion reaction, since little has been reported on reactions of carbenes with amides.[12]

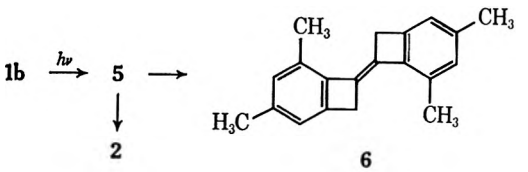
(12) J. Maas, G. B. R. DeGaaff, and H. J. Denttertog, *Rec. Trav. Chim.*, **74**, 175 (1955).

SCHEME I



1.00:3.09, respectively. A tentative structure for this hydrocarbon consistent with the spectral evidence is 1,1′-bi(4,6-dimethylbenzocyclobutylidene) (6) (see Scheme II). It could be formed by dimerization of carbene **5** or by reaction of the carbene with the tosylhydrazone salt **1b** or the corresponding diazo compound.

SCHEME II



Besides these two products, a yellow oil was obtained which could not be induced to crystallize.

Infrared analysis indicated the presence of both aromatic and ether groups, suggesting that carbene **5** may have reacted with the ether solvent.[13]

Experimental Section[14]

Preparation of 4,6-Dimethylbenzocyclobutenone.—The procedure was that of Hart and Fish.[9] Trichloromethylmesitylene (53 g, 74.4% yield) was prepared from 36 g (0.03 mol) of mesitylene, 80 g (0.6 mol) of anhydrous aluminum chloride, and 200 ml of carbon tetrachloride. When heated at 170° for 15 hr under a slow stream of nitrogen, trichloromethylmesitylene was converted almost quantitatively into 1,1-dichloro-4,6-dimethylbenzocyclobutene, mp 54–56° (reported mp 55–57°).[9] Hydrolysis was effected by refluxing an aqueous acetone solution (60%) of the *gem*-dichloride for 12 hr. Distillation through an 8-in. Vigreux column gave 26.1 g of 4,6-dimethylbenzocyclobutenone, bp 65° (0.45 mm), yield 79.5%, based on trichloromethylmesitylene. The ketone exhibits a split carbonyl absorption at 1750 and 1780 cm^{-1} and readily forms an azine derivative, mp 177–178°, with hydrazine hydrate.

Anal. (of azine). Calcd for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99. Found: C, 83.01; H, 7.14.

Preparation of 4,6-Dimethylbenzocyclobutenone *p*-Tosylhydrazine.—A solution of 8.0 g (0.055 mol) of 4,6-dimethylbenzocyclobutenone and 10.2 g (0.055 mol) of *p*-tosylhydrazine in 50 ml of absolute ethanol containing 1 ml of acetic acid was heated under reflux for 5 min and stored overnight in the refrigerator. The white solid which precipitated was collected on a Büchner funnel and dried to yield 14.6 g (84.4%) of 4,6-dimethylbenzocyclobutenone *p*-tosylhydrazone, mp 166–167° dec. Two recrystallizations from ethanol gave an analytically pure sample, mp 169–170° dec.

Anal. Calcd for $C_{17}H_{18}SO_2N_2$: C, 64.95; H, 5.77; S, 10.18; N, 8.91. Found: C, 64.68; H, 5.83; S, 10.21; N, 9.09.

Pyrolysis of 4,6-Dimethylbenzocyclobutenone *p*-Tosylhydrazone Sodium Salt.—The procedure is patterned after that of Powell and Whiting.[6] Freshly cut pieces of sodium (0.69 g, 0.03 g-atom) were placed in a 100-ml flask containing 20 g of distilled acetamide. The flask was evacuated on an air pump and heated to 100°. The sodium rapidly reacted with the liquid acetamide, forming a pale yellow solution. The vacuum was broken and 3.14 g (0.01 mol) powdered 4,6-dimethylcyclobutenone *p*-tosylhydrazone was added. The reaction mixture was then heated in an oil bath maintained at 155°. Decomposition occurred rapidly at this temperature, and within 5 min nitrogen evolution had ceased. The mixture was poured into 300 ml of water and the aqueous solution was extracted with four 75-ml portions of pentane. The organic solution was washed with eight 75-ml portions of water and dried over sodium sulfate. Removal of solvent from the filtered solution left a tan oil which slowly solidified. Recrystallization from hexane–benzene gave 0.60 g of a white solid, mp 104–105°. Identification of the compound as 4,6-dimethylbenzocyclobutenyl *p*-tolyl sulfone (2) was made on the basis of its nmr spectrum. The aromatic protons of the tolyl group appear as a symmetrical quartet between τ 2.38 and 2.95, the benzocyclobutenyl aromatic protons as two singlets at 3.26 and 3.49, the butenyl proton next to the sulfone as a triplet centered at 5.37 (J = 5 cps), the other two butenyl protons as a doublet at 6.87 and 6.96 (J = 5 cps), and the nine methyl protons as three singlets at 7.64, 7.79, and 7.83.

Anal. Calcd for $C_{17}H_{18}SO_2$: C, 71.31; H, 6.34; S, 11.16; mol wt, 286. Found: C, 71.41; H, 6.38; S, 11.11; mol wt, 286 (mass spectroscopy).

A portion of the original pentane extract was analyzed on a gas chromatographic apparatus utilizing a 50 ft × 0.02 in. SCOT column (phenylmethylsilicone stationary phase) connected to a mass spectrometer by means of a Biemann molecular separator. Twelve components were separated and a mass spectrum of each was obtained. The following compounds were tentatively identified on the basis of their mass spectra: sulfone 2, 4,6-dimethylbenzocyclobutenone, 4,6-dimethylbenzocyclobutenol, and 2,4-dimethylphenylacetic acid. The other materials were not identified other than establishing the fact that they were not hydrocarbons derived from the 2,4-dimethylbenzocyclobutenyl carbene (m/e 130 or a multiple thereof).

The tan precipitate which remained after pentane extraction was collected on a Bücher funnel, then recrystallized from ethanol–benzene to give 0.72 g of 4,6-dimethylbenzocyclobutenylacetamide, mp 193–194°.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40; mol wt, 189. Found: C, 75.76; H, 8.14; N, 7.33; mol wt, 189 (mass spectroscopy).

A small portion of amide was hydrolyzed by heating it on a steam cone for 5 hr with a 15% solution of potassium hydroxide containing a small amount of ethanol. Acidification with 6 *N* hydrochloric acid formed a white solid. Recrystallization from 95% ethanol gave white needles of 4′,6′-dimethylbenzocyclobutenylacetic acid, mp 155–156°.

(13) See, for example, W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Amer. Chem. Soc.*, **83**, 2019 (1961).

(14) Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Infrared spectra were recorded on a Varian Infracord. Nmr spectra were measured at 60 Mcps on a Varian A-60 spectrometer. Mass spectra were determined using an AEI Model MS-12 mass spectrometer. Samples were introduced either by direct probe or by employing a Beckman GC-4 gas chromatograph coupled to the spectrometer *via* a Biemann molecular separator.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; mol wt, 190. Found: C, 75.56; H, 7.49; mol wt, 190 (mass spectroscopy), 189 (titration).

Photolysis of 4,6-Dimethylbenzocyclobutenone *p*-Tosylhydrazone Sodium Salt.—The salt prepared from 3.14 g (0.01 mol) of 4,6-dimethylbenzocyclobutenone *p*-tosylhydrazone and 0.5 g (0.011 mol) of 54% sodium hydride dispersion in mineral oil was suspended in 250 ml of dry dioxane and irradiated for 30 min at 25° using a Hanovia 550-W mercury vapor insertion lamp. The reaction mixture was poured into 400 ml of water and extracted with three 75-ml portions of pentane and then three 75-ml portions of benzene. The combined organic extracts were dried over calcium chloride. Removal of solvent left 1.6 g of a brown gummy oil which was chromatographed on 80 g of acid-washed alumina. Elution with 8% ether–pentane gave a total of 108 mg of a white solid which melted at 188–189° after two recrystallizations from heptane. The infrared spectrum of this compound exhibited a weak peak at 1705, medium peaks at 1600, 1470, 1320, 1265, and 1040, and two strong peaks at 850 (very strong) and 725 cm^{-1}. The nmr spectrum showed three singlets at τ 3.23, 6.27, and 7.68, with a ratio of 0.98:1.00:3.09, respectively. Mass spectral analysis gave a molecular weight of 260. The material was assigned the structure of 1,1′-bi(4,6-dimethylbenzocyclobutylidene) on the basis of its elemental analysis and spectra.

Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74; mol wt, 260. Found: C, 91.96; H, 8.08; mol wt, 260 (mass spectroscopy).

Elution with 25% ether gave 0.2 g of a yellow oil which could not be induced to crystallize. The infrared spectrum showed peaks at 3020, 2900, 1610, 1500, 1130, and 890 cm^{-1}, indicating that both aromatic and ether groups were present. This material was not characterized further. With 50–75% ether, a total of 0.4 g (14%) of 4,6-dimethylbenzocyclobutenyl *p*-tolyl sulfone, mp 102–104°, was isolated. The infrared spectrum of this material was identical with that of the product obtained by pyrolysis; a mixture melting point of the two samples was not depressed.

Registry No.—4,6-Dimethylbenzocyclobutenone, 6670-28-6; 4,6-dimethylbenzocyclobutenone (azine derivative), 20643-22-5; **1a**, 20643-23-6; **2**, 20678-94-8; **3**, 20643-24-7; **4**, 20643-25-8; **6**, 20643-26-9.

The Sulfation of Hydroxamic Acids

FRANCIS A. DANIHER

George M. Moffett Technical Center, CPC International, Inc., Argo, Illinois

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The reaction of hydroxamic acids with sulfur trioxide–tertiary amine complexes proceeds by O sulfation to give crystalline water-soluble *t*-ammonium N-acylhydroxylamine-O-sulfonates. The reaction of a solution of any of these salts with a base generates an isocyanate function *in situ*. If the base employed is a primary or secondary amine, urea derivatives are obtained in good yield. Carbamates are formed by the decomposition of the salts with phenoxide ion. Aliphatic isocyanates are prepared in good yield by treatment of the salts with tertiary amine in the presence of an inert solvent.

The Lossen rearrangement is a useful method for the preparation of organic isocyanates.[1] This conversion is accomplished by treating a hydroxamic acid with a dehydrating agent such as acetic anhydride, phosphorus pentoxide, or a carbodiimide,[2] forming an isocyanate. The reaction proceeds through an O-ester intermediate which is converted either thermally or by base treatment to an isocyanate and the acid corresponding to the O ester or its conjugate base. The ease of the rearrangement has been shown to be directly related to the acidity of the departing acid.[3]

The preparation of sulfate esters of hydroxamic acids has been examined. These products have been found to undergo a facile Lossen rearrangement to form isocyanates.

Discussion

Sulfation Reactions.—Treatment of benzohydroxamic acid with trimethylamine–sulfur trioxide gave a crystalline, water-soluble product in moderate yield.

$$C_6H_5CONHOH + R_3N{:}SO_3 \longrightarrow C_6H_5CONHOSO_2HNR_3$$
I, $R_3 = (CH_3)_3$
II, $R_3 = C_5H_5$

Elemental analysis and the nmr spectrum of this material indicated a 1:1 adduct. The latter in deuterium oxide contained a nine-proton singlet at 2.68 ppm [$DN(CH_3)_3^+$] and a five-proton multiplet (C_6H_5) centered at 7.45 ppm. The infrared spectrum contained bands at 3225 cm^{-1} (NH), 1663 cm^{-1} (C=O), and 1200 and 1256 cm^{-1} (O=S=O).[4] Dissolution of the adduct in 5% ammonium hydroxide solution at room temperature gave an 82% yield of phenylurea, while treatment with hot 1.5 *N* potassium hydroxide solution gave a 68% yield of *sym*-diphenylurea. These data are consistent with the O-sulfation product (I).

A similar reaction was performed with the more reactive sulfating agent pyridine–sulfur trioxide.[5] The adduct (II) was obtained in 80% yield, employing conditions which were far milder than those required with the trimethylamine reagent. Owing to the high reactivity of this complex, further studies of the scope of the sulfation reaction were conducted with this material.

A number of other mono- and dihydroxamic acids have been treated with pyridine–sulfur trioxide to form the pyridinium N-acylhydroxylamine-O-sulfonates in yields of 70 to 89%. The data are summarized in Table I. With the exception of the stearic acid derivative, all of the salts are water soluble and quite stable in aqueous solution.[6] Another characteristic of these salts is the presence in their infrared spectra of two strong bands between 1200 and 1300 cm^{-1}. Generally, they occur at 1250 and 1300 ± 10 cm^{-1}. These are attributed to the symmetric and asymmetric stretching vibrations of the sulfonic acid function.[4]

(1) R. G. Arnold, J. A. Nelson, and J. J. Verbane, *Chem. Rev.*, **57**, 47 (1957); H. L. Yale, *ibid.*, **33**, 209 (1943).

(2) D. G. Hoare, A. Olson, and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **90**, 1638 (1968).

(3) R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1959.

(5) E. E. Gilbert, "Sulfonation, Related Reactions," Interscience Publishers, Inc., New York, N. Y., 1965, p 12.

(6) A 10% aqueous solution of II underwent less than 5% decomposition during 10 days at room temperature.

TABLE I

SULFATION OF HYDROXAMIC ACIDS

$RCONHOH + C_5H_5N{:}SO_3 \longrightarrow RCONHOSO_3HNC_5H_5$

R	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	75	140–141	48.64	4.08	9.45	48.23	4.32	9.26
p-Cl-C_6H_4[a]	88	172–174	43.57	3.35	8.47	43.81	3.47	8.40
$CH_2{=}C(CH_3)$[b]	70	109–110	41.53	4.64	10.76	41.28	4.60	10.33
n-C_7H_{15}[c]	76	109–110	49.03	6.96	8.79	48.96	6.82	8.46
n-$C_{11}H_{23}$[c]	85	119–121	54.55	8.02	7.50	54.44	8.08	7.44
n-$C_{17}H_{35}$[c]	71	116–117	60.22	9.23	6.10	60.16	9.32	6.01
$CH_2{=}CH(CH_2)_8$[d]	75	111–112	53.60	7.25	7.82	53.75	7.49	7.79
$(CH_2)_4$[e]	75	156–157	38.86	4.44	11.33	38.77	4.39	11.24
$(CH_2)_6$[e]	95	160–161	41.37	5.01	10.72	40.99	5.17	10.84

[a] Reference 8. [b] H. Smith, British Patent 852,176 (Oct 26, 1960). [c] Y. Inone and H. Yukawa, *Bull. Chem. Soc. Jap.*, **16**, 510 (1940); *Chem. Abstr.*, **35**, 731[2] (1941). [d] G. Kurono, T. Sakai, and Y. Kagotam, *Yakugaku Zasshi*, **84**, 463 (1964); *Chem. Abstr.*, **61**, 4968 (1964). [e] C. D. Hurd and D. G. Batteron, *J. Org. Chem.*, **11**, 207 (1946).

The preference for O sulfation of hydroxamic acids can be anticipated from a consideration of the reactivity of these substrates with acylating and sulfonating agents.[7]

Preparation of Ureas and Carbamates.—The behavior of I with potassium and ammonium hydroxide indicated that phenyl isocyanate was being formed in solution. Upon generation of the anion (III), isocyanate should form rapidly by loss of sulfate.[8]

$$\underset{\text{III}}{C_6H_5CONOSO_3^-} \longrightarrow C_6H_5NCO + SO_4^{2-}$$

When a salt was added to an aqueous solution containing 2 to 3 equiv of primary or secondary amine, the isocyanate formed was intercepted by the amine, yielding a urea derivative. Representative amines used in

$$RCONHOSO_3HNR'_3 + R''R'''NH \longrightarrow RNHCONR''R'''$$

this reaction include methyl, *n*-butyl, dimethyl, and diethyl. With multifunctional amines such as ethanolamine and D-glucamine, urea derivatives were formed to the virtual exclusion of urethans. With ethylenediamine, a diurea was formed. In some instances, such as ethylenediamine and D-glucamine, it was not desirable to use an excess of amine. In these cases, a tertiary amine such as triethyl- or trimethylamine was added to assist isocyanate formation. A total of 20 examples of urea formation using this procedure have been recorded. The yields range from 60 to 93% with the majority being 80% or greater (see Experimental Section).

The addition of these salts to an aqueous solution of phenoxide ion gave the corresponding phenyl carbamates.

$$RCONHOSO_3HNR_3' + C_6H_5OK \longrightarrow RNHCOOC_6H_5$$

The behavior of the methacrylic acid derivative (IV) in basic media was examined. When this material was added to potassium hydroxide solution, an 82% yield of acetone, isolated as its 2,4-dinitrophenylhydrazone derivative, was obtained. The rearrangement generated a vinyl isocyanate derivative which then underwent hydrolysis to form acetone.

(7) F. M. Hershenson, L. Bauer, and K. F. King, *J. Org. Chem.*, **33**, 2543 (1968), and references cited therein.

(8) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **77**, 3651 (1955).

The decomposition of IV with diethylamine gave a 61% yield of urea derivative (V). The nmr spectrum

$$\underset{\text{IV}}{CH_2{=}C(CH_3)CONHOSO_3HC_5H_5N} + R_2NH \longrightarrow (CH_3)_2C{=}NCONR_2$$

V, R = C_2H_5
VI, R = $CH_2CH{=}CH_2$

$$(CH_3)_2C{=}NCONR_2 \rightleftharpoons CH_2{=}C(CH_3)NHCONR_2$$

of this material indicated that it existed exclusively in the form of the C=N tautomer. The spectrum (neat) contained a pair of overlapping triplets at 1.03 and 1.13 ppm (J = 7.0 Hz) and a pair of overlapping quartets at 3.19 and 3.38 ppm (J = 7.0 Hz). These are assigned to the methyl and methylene groups, respectively, of the N-ethyl groups. Their magnetic nonequivalence is due to restricted rotation about the nitrogen–carbonyl bond.[9] A pair of singlets at 1.97 and 2.03 ppm are also present in the spectrum. These are assigned to the methyl groups of the isopropylidene function. This nonequivalence results from *syn* and *anti* isomerism about the imine double bond.

The position of the equilibrium between the tautomers was found to be solvent independent when examined by nmr. The spectra were recorded in carbon tetrachloride, deuterated acetone, and deuterated dimethyl sulfoxide. No change was noted in the spectra except that the methyl groups of the isopropylidene coalesced to a singlet at 2.00 ppm. Contributions from the vinylurea tautometer were not found in any of the spectra.

The urea derivative (VI) from diallylamine was formed in 63% yield. The equilibrium position of this product was the same as that of the diethyl derivative on the basis of nmr data.

The thermal isomerization of vinylureas to their ketimine derivatives has been demonstrated by Sato.[10] Since the infrared spectra of crude products before distillation are essentially identical with that of the pure product, the isomerization is probably also base catalyzed owing to the presence of pyridine and excess amine in the reaction mixture. Attempts to prepare a similar derivative using ethylenimine were unsuccessful. The crude product was quite unstable, and it decomposed to a dark brown resinous solid.

Preparation of Isocyanates.—The *in situ* formation of an isocyanate by treatment of a sulfated hydroxamic

(9) R. H. Bible, "Interpretation of NMR Spectra: An Empirical Approach," Plenum Press, New York, N. Y., 1965, p 66.

(10) M. Sato, *J. Org. Chem.*, **26**, 770 (1961).

acid with a tertiary amine was employed in the preparation of certain carbamate and urea derivatives. A similar technique was employed for the isolation of the isocyanates. The sulfated hydroxamic acid was treated with a tertiary amine in aqueous solution in the presence of an inert solvent such as petroleum ether or carbon tetrachloride. As the isocyanate was formed it was extracted into the organic layer. Work-up of the reaction gave the crude isocyanate, which was purified by distillation.

$$RCONHOSO_3HC_5H_5N + R'_3N \longrightarrow RNCO + C_5H_5N(NR'_3)H_2SO_4$$

This procedure is quite satisfactory for the preparation of aliphatic isocyanates. Yields ranging from 63 to 75% were obtained. The fatty acid derivatives often produced emulsions, which made it difficult to separate the organic phase. In most cases, this problem was overcome by addition of a small amount of acetonitrile to the reaction mixture. With the stearic acid derivative, however, the problem was too severe, and prevented isolation of heptadecyl isocyanate. The infrared spectrum of the crude mixture showed bands assignable to isocyanate and urea.

The preparation of phenyl isocyanate by this procedure gave only a 20% yield of product. In addition, a 45% yield of *sym*-diphenylurea was also formed. These data reflect the greater reactivity of aromatic *vs.* aliphatic isocyanates.

A number of unsuccessful attempts were made to prepare aliphatic diisocyanates by this method. In all cases, polymeric materials were obtained.

Experimental Section

Nuclear magnetic resonance spectra were run on a Varian A-60 spectrometer in the appropriate solvent, with tetramethylsilane as an internal or external standard. Infrared spectra were recorded on a Beckman Model IR-12 or a Perkin-Elmer 137 infrared spectrophotometer. Melting points were obtained using a Thomas–Hoover melting point apparatus and are uncorrected.

Preparation of Starting Materials.—The hydroxamic acids were prepared according to literature procedures. The pyridine sulfur trioxide was prepared according to the method of Baumgarten.[11] The trimethylamine sulfur trioxide was obtained from the American Cyanamid Co., New York 20, N. Y.

Sulfation of Benzohydroxamic Acid with Trimethylamine–Sulfur Trioxide.—A mixture of 40.0 g (0.29 mol) of benzohydroxamic acid and 40.0 g (0.29 mol) of trimethylamine–sulfur trioxide was slurried in 300 ml of acetone at ambient temperature for 5 days. The mixture was filtered and evaporated to dryness. The residue was dissolved in 200 ml of hot ethanol and cooled to give 33 g (0.12 mol, 41%) of trimethylammonium N-benzoylhydroxylamine-O-sulfonate (I), mp 150–154°. An analytical sample was prepared by recrystallization from ethanol: mp 155–156°.

Anal. Calcd for $C_{10}H_{16}N_2O_5S$: C, 43.46; H, 5.83; N, 10.13. Found: C, 43.38; H, 5.95; N, 10.13.

General Procedure for the Sulfation of Hydroxamic Acids with Pyridine–Sulfur Trioxide.—A solution of 0.1 mol of hydroxamic acid (or 0.22 mol for dihydroxamic acids) and 0.11 mol of pyridine–sulfur trioxide in 150 ml of acetonitrile was refluxed with stirring for 0.5 to 4.0 hr. The solvent was evaporated at aspirator pressure and the residue was purified by recrystallization from ethanol or acetonitrile. Similar yields may be obtained by keeping the reaction mixture at room temperature for about 18 to 24 hr. With the 10-undecylenic acid derivative, this latter procedure was preferred.

Preparation of Ureas.—The sulfated hydroxamic acid was added portionwise or as a 30–50% aqueous solution to a stirred solution of 2 to 3 equiv of ammonia, or primary or secondary amine in water. (The amine concentration in the aqueous solution was about 5–10% by weight.) The reaction temperature was maintained at 20–30° by external cooling. After addition was complete, the mixture was stirred at ambient temperature for 0.5 hr and filtered. The residue was washed with water and air dried. Using this procedure, the following ureas were prepared: $C_6H_5NHCONH_2$, mp 146–148°, 82%; $C_6H_5NHCON(C_2H_5)_2$, mp 84–85°, 75% (trimethylammonium salt), 89% (pyridinium salt); $C_6H_5NHCONHC_4H_9$-*n*, mp 126–127°, 83% (trimethylammonium salt), 94% (pyridinium salt); $C_6H_5NHCON(CH_3)_2$, mp 127–128°, 87% (trimethylammonium salt); $C_6H_5NHCONHCH_2CH_2OH$, mp 122–123°, 72% (pyridinium salt); *n*-C_7H_{15}NHCONHC$_4$H$_9$-*n*, mp 56–57°, 78%; *p*-Cl-$C_6H_4NHCONHC_4H_9$-*n*, mp 172–174°, 86%; *p*-Cl-$C_6H_4NHCON(C_2H_5)_2$, mp 114–116°, 88%; *n*-$C_{11}H_{23}NHCONHCH_3$, mp 66–67°, 81%; *n*-$C_{17}H_{35}NHCONHCH_3$, mp 99–100°, 89%; CH_2=CH—$(CH_2)_8$NHCONHCH$_2$, mp 69–70°, 82%; $[(CH_2)_2NHCONHCH_3]_2$, mp >280°, 79%; $[(CH_2)_3NHCONHCH_3]_2$, mp 201–203°, 91%; $[(CH_2)_3NHCONHC_4H_9$-*n*$]_2$, mp 192–194°, 88%.

Preparation of 1,1-Diethyl-3-phenylurea Using Trimethylamine as Catalyst.—Pyridinium N-benzoylhydroxylamine-O-sulfonate (3.0 g) was added portionwise to a stirred solution of 4.8 g of 25% trimethylamine in methanol and 1.0 g of diethylamine in 18 ml of water maintained at 20–25° by a cooling bath. After addition was complete, the mixture was stirred at room temperature for 0.5 hr and filtered. The residue was washed with water and air dried to give 1.4 g of product (75%), mp 84–86°. Using the same type of procedure $[C_6H_5NHCONHCH_2]_2$, mp 276–277°, and D-gluco-$C_6H_5NHCONHCH_2(CHOH)_4CH_2OH$, mp 173–174°, were obtained in yields of 61 and 71%, respectively.

Preparation of Phenyl Carbanilate.—Trimethylammonium N-benzoylhydroxylamine-O-sulfonate (3.0 g) was added portionwise at room temperature to a stirred solution of 5.8 g of potassium phenoxide in 25 ml of water. After addition was complete, the mixture was stirred at room temperature for 0.5 hr, filtered, and air dried to give 1.85 g (79%) of product mp 122–123°. Using this procedure, *n*-$C_7H_{15}NHCOOC_6H_5$, mp 36–37°, was prepared in 71% yield.

Reaction of Pyridinium N-Methacryloylhydroxylamine-O-sulfonate with Potassium Hydroxide.—Compound IV, 2.6 g (0.01 mol), was added portionwise with cooling and stirring to 10 ml of 3 *N* potassium hydroxide solution. After addition was complete, this solution was added slowly with cooling and stirring to a solution of 3.0 g of 2,4-dinitrophenylhydrazine in 15 ml of concentrated sulfuric acid, 25 ml of water, and 50 ml of absolute ethanol. The solution was then chilled and filtered to give 1.95 g (82%) of acetone 2,4-dinitrophenylhydrazone, mp 122–124°. A mixture melting point with an authentic sample was undepressed.

Preparation of 1,1-Dialkyl-3-isopropylideneureas.—A 30% aqueous solution of IV was added dropwise to a vigorously stirred solution of 3 equiv of secondary amine in 200 ml of chloroform cooled in an ice water bath. After addition was complete, the chloroform layer was separated and the aqueous layer was extracted with chloroform. The chloroform extracts were combined, dried, and evaporated to give the crude product, which was purified by vacuum distillation. The following ureas were prepared.

(a) 1,1-Diethyl-3-isopropylideneurea[12] (61%): bp 122° (19 mm); n^{25}D 1.4562.

Anal. Calcd for $C_8H_{16}N_2O$: N, 17.93. Found: N, 17.87.

(b) 1,1-Diallyl-3-isopropylideneurea (63%): bp 65° (0.05 mm); n^{25}D 1.4790; nmr (neat) 2.00 [s, 6 H, $(CH_3)_2C$=], 3.83 and 4.05 (d, 4 H, J = 5.0 Hz, CH_2N), and 4.90–6.30 ppm (complex m, 6 H).

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.62; H, 8.95; N, 15.54. Found: C, 66.25; H, 8.87; N, 15.88.

General Procedure for the Preparation of Isocyanates.—A 25% aqueous solution containing 0.25 mol of trimethylamine was added dropwise to a vigorously stirred mixture of a solution of 0.1 mol of N-acylhydroxylamine-O-sulfonic acid *t*-ammonium salt in 150 ml of water and 250 ml of carbon tetrachloride or petroleum ether cooled in an ice bath. After addition was complete, the mixture was stirred at ice-bath temperature for 0.25 hr and then diluted with water. A 100- to 150-ml portion of acetonitrile was added (this was not necessary in the preparation of *n*-heptyl isocyanate or phenyl isocyanate) and the organic layer was separated. The aqueous phase was reextracted with the organic

(11) P. Baumgarten, *Ber.*, **59**, 1166 (1926).

(12) J. B. Dickey, U. S. Patent 2,592,254 (April 8, 1952).

solvent, and the extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to yield the crude isocyanate, which was purified by distillation. The following isocyanates were prepared by this procedure: (a) *n*-heptyl[13] (63%), bp 83–84° (23 mm), $n^{26}D$ 1.4326; (b) *n*-undecyl[13] (54% from petroleum ether, 75% from carbon tetrachloride), bp 144° (18 mm), $n^{26}D$ 1.4358; (c) 9-decenyl[13] (70%), bp 127–128° (17 mm), $n^{26}D$ 1.4446; (d) phenyl (20%), identified by gpc and infrared spectroscopy.

Registry No.—I, 20633-41-4; $C_6H_5NHCONH_2$, 64-10-8; $C_6H_5NHCON(C_2H_5)_2$, 1014-72-8; $C_6H_5NHCONHC_4H_9$-*n*, 3083-88-3; $C_6H_5NHCON(CH_3)_2$, 101-42-8; $C_6H_5NHCONHCH_2CH_2OH$, 3747-47-5; *n*-$C_7H_{15}NHCONHC_4H_9$-*n*, 20633-46-9; *p*-$ClC_6H_4NHCONHC_4H_7$-*n*, 6333-41-1; *p*-$ClC_6H_4NHCON(C_2H_5)_2$, 15737-37-8; *n*-$C_{11}H_{23}NHCONHCH_3$, 20633-56-1; *n*-$C_{17}H_{35}NHCONHCH_3$, 20633-49-2; $CH_2{=}CH{=}(CH_2)_8NHCONHCH_3$, 20633-50-5; $[(CH_2)_2NHCONHCH_3]_2$, 20633-51-6; $[(CH_2)_3NHCONHCH_3]_2$, 20633-52-7; $[(CH_2)_3NHCONHC_4H_9$-*n*$]_2$, 20633-53-8; II, 20633-55-0; $[C_6H_5NHCONHCH_2]_2$, 849-97-8; D-gluco-$C_6H_5NHCONHCH_2(CHOH)_4CH_2OH$, 20642-67-5; phenyl carbanilate, 4930-03-4; *n*-$C_7H_{15}NHCOOC_6H_5$, 2594-41-4; 1,1-diallyl-3-isopropylideneurea, 20642-56-2.

(13) V. E. Shoshoua, W. Sweeney, and R. F. Trietz, *J. Amer. Chem. Soc.*, **82**, 866 (1960).

The Effect of the Imidazole Group on the Hydrolysis of N-[2-(4-Imidazolyl)ethyl]phthalimide[1a]

S. C. K. Su and J. A. Shafer[1b]

Department of Biological Chemistry, The University of Michigan, Ann Arbor, Michigan 48104

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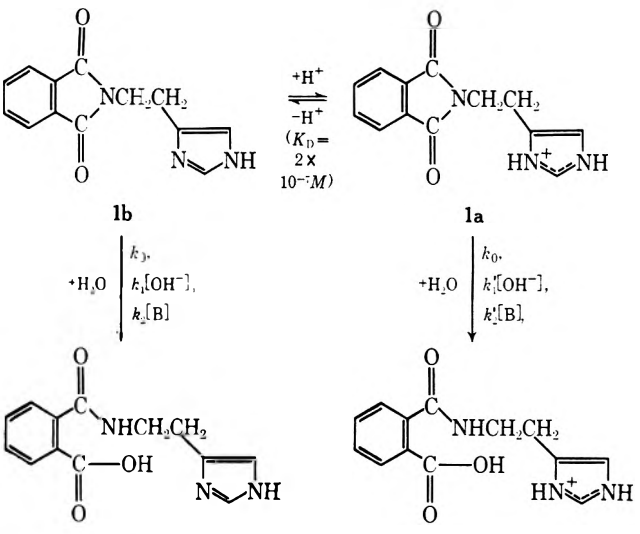
The pH dependencies (at 25°) of the pseudo-first-order rate constants for the hydrolysis (to phthalamic acids) of N-[2-(4-imidazolyl)ethyl]phthalimide (**1**), N-(2-trimethylamincethyl)phthalimido bromide (**2**), N-(3-trimethylaminopropyl)phthalimido bromide (**3**), and N-methylphthalimide (**4**) were determined. The cationic imides **2** and **3** are most susceptible to hydroxide ion catalyzed hydrolysis. Below pH 7, however, **1** hydrolyzes most rapidly. This effect was ascribed to the neighboring imidazole residue functioning as a general base in catalyzing attack by water. A deuterium oxide solvent isotope effect of 2.1 is associated with this process. The possibility that this effect reflects the susceptibility of the protonated form of **1** to attack by hydroxide ion was deemed unlikely, since the second-order rate constant for this reaction would be 333 $sec^{-1}M^{-1}$, while the second-order rate constants for the hydroxide ion catalyzed hydrolysis of cationic imides **2** and **3** with their positive charges closer to the carbonyl carbon atom are 91 and 41 $sec^{-1}M^{-1}$, respectively. Also, cationic imides **2** and **3** are susceptible to direct attack by water, whereas the protonated form of **1** is much less susceptible to attack by water. It is unlikely that a neighboring imidazole residue functions as a general acid in catalyzing attack by hydroxide ion, since the calculated rate constant for this process is not significantly lowered by deuterium oxide. The first-order rate constants for intramolecular catalysis of the hydrolysis of **1** by the neighboring imidazole group (2.9×10^{-5} sec^{-1}) was found to be similar in magnitude to the second-order rate constant for the imidazole-catalyzed hydrolysis of **4** (2.0×10^{-5} $sec^{-1}M^{-1}$).

Neighboring amide groups are potent nucleophiles, and under physiological conditions amide groups can enhance the rate of hydrolysis of adjacent ester and amide residues by several orders of magnitude.[2] Often, the rate-limiting step in these reactions is the hydrolysis of the imide intermediate. Because of the possible importance of the amide group in enzymically catalyzed hydrolytic reactions, we have investigated the effect of the imidazole group on the hydrolysis of N-[2-(4-imidazolyl)ethyl]phthalimide (**1**) (Scheme I).

Scheme I



Experimental Section

Materials.—N-Methylphthalimide was obtained from Eastman Organic Chemicals and recrystallized twice from 95% ethanol: mp 134–135° cor (lit.[3] mp 133–134°).

N-(2-Trimethylaminoethyl)phthalimido bromide was prepared by mixing 5.08 g (20 mmol) of N-(2-bromoethyl)phthalimide (from Eastman Organic Chemicals) dissolved in 75 ml of dioxane with 5.4 g (91 mmol) of trimethylamine (from Eastman Organic Chemicals) dissolved in 150 ml of dioxane. After the mixture stood overnight at room temperature, the precipitate was collected and recrystallized three times from 95% ethanol: dec pt 290–291° cor. *Anal.* Calcd for $C_{13}H_{17}N_2O_2Br$: C, 49.85; H, 5.47; N, 8.95; Br, 25.52. Found: C, 49.59; H, 5.46; N, 8.75; Br, 25.20.

N-(3-Bromopropyl)phthalimide was prepared from potassium phthalimide (from Eastman Organic Chemicals) and 1,3-dibromopropane (from CalBiochem) according to the method of Gabriel:[4] mp 71–73° cor (lit.[4] mp 72–73°).

N-(3-Trimethylaminopropyl)phthalimido bromide was prepared by mixing 2.68 g (10 mmol) of N-(3-bromopropyl)phthal-

(1) (a) This study was supported by a grant (AM-09276) from the National Institutes of Health, U. S. Public Health Service. (b) To whom inquiries regarding this work should be made.

(2) S. C. K. Su and J. A. Shafer, *J. Org. Chem.*, in press, and references therein.

(3) M. Freund and H. Beck, *Ber.*, **37**, 1942 (1904).

(4) S. Gabriel and J. Weiner, *ibid.*, **21**, 2669 (1888).

imide dissolved in 15 ml of dioxane with 1.65 g (28 mmol) of trimethylamine dissolved in 25 ml of dioxane. After the mixture stirred overnight at room temperature, the precipitate was collected and recrystallized once from 95% ethanol and twice from 2-propanol: dec pt 209–211° cor. *Anal.* Calcd for $C_{14}H_{19}N_2O_2Br$: C, 51.38; H, 5.85; N, 8.56; Br, 24.42. Found: C, 51.22; H, 6.15; N, 8.51; Br, 24.21.

N-[2-(4-Imidazolyl)ethyl]phthalimide was prepared by refluxing 2.96 g (20 mmol) of phthalic anhydride (from Eastman Organic Chemicals) with 2.22 g (20 mmol) of histamine (from CalBiochem) in 200 ml of glacial acetic acid. After 30 min, 150–160 ml of acetic acid was distilled from the reaction flask and the remaining solution was cooled and poured into 100 ml of ether. The resulting precipitate was dried at 100° under reduced pressure (to convert any acetate salt of the product into the free base) and then recrystallized three times from benzene and heated at 100° for 48 hr under reduced pressure: mp 189–190° cor. *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.72; H, 4.55; N, 17.35.

Imidazole was obtained from the Aldrich Chemical Co., recrystallized three times from benzene and sublimed under reduced pressure: mp 88–89 cor (lit.[5] mp 90.2–90.6°).

Tris(hydroxymethyl)aminomethane (Tris, ultrapure) was obtained from Mann Research Laboratories.

Deuterium oxide and DCl in deuterium oxide were obtained from Biorad Laboratories.

The distilled water supplied to the laboratory was run through a demineralizer and redistilled in an all-glass still.

All other chemicals used were Mallinckrodt or Baker–Adamson analytical reagents.

Methods.—Measurements of pH and pD were made using a Radiometer Model 4b pH meter which was standardized with a 1:1 phosphate, NBS primary standard solution.[6] The response of the glass electrode was checked with another NBS primary standard solution (either borax or phthalate). Any nonideality in the glass electrode response was corrected with the temperature compensator. This correction never corresponded to more than 1°/pH unit difference between the primary standards. Measurements of pH and pD were made before and after each kinetic run, and the average value of pH was used. The total change in pH during a kinetic run in a buffered solution rarely exceeded 0.02 unit.

Hydrogen ion concentrations were estimated from the pH and the mean activity coefficient of hydrogen chloride in potassium chloride solutions. The mean activity coefficient used (0.75 at $\Gamma/2 = 0.20\ M$) was interpolated from the data listed by Harned and Owen.[7] The hydroxide ion concentration was estimated from the hydrogen ion concentration and the formal dissociation constant for water (K_W'), *i.e.*, $K_W\alpha_{H_2O}/\gamma_{H^+}\gamma_{OH^-}$ which was interpolated from data listed in ref 7. The formal dissociation constant used was $1.74 \times 10^{-14}\ M$ at $\Gamma/2 = 0.20\ M$.[8]

Rate Measurements.—The disappearance of imides was followed spectrophotometrically at 300 mμ using a Gilford Model 2000 multiple-sample absorbance recorder.

Reactions in buffered solutions were carried out in a cuvette equipped with a ground-glass stopper. The buffers used were KH_2PO_4–Na_2HPO_4, Tris HCl, and $NaHCO_3$–Na_2CO_3. The absorbance was monitored continuously, and the temperature was controlled (25° ± 0.05°) by circulating water from a thermostated bath through the thermospacers surrounding the cell compartment. The temperature of the reacting solution was determined with a NBS certified thermometer. The approach of the absorbance (A) to its final value (A_∞) was first order. Pseudo-first-order rate constants (k_{obsd}) were determined by the method of Guggenheim[9] or from the slopes of the linear plots of $-\ln(A - A_\infty)$ *vs.* time. The independence of the rate constants on the initial concentration of imide also established that the reaction was first order in imide.

Below pH values of 7.5, the hyrolysis of imide to amic acid does not go to completion,[2] and the concentration of imide in equilibrium with amic acid becomes significant. Therefore, below pH values of 7.5, k_{obsd} was determined from the initial rate of disappearance of imide (R) using relationship 1. The initial

$$R = -\frac{1}{E} \times \frac{dA}{dt} = k_{obsd}[I^0] \quad (1)$$

slope of the absorbance *vs.* time plot at 300 mμ is represented by dA/dt, while $[I^0]$ is the initial concentration of imide, and E is the extinction coefficient of the imide. All initial rates were obtained from measurements made before 6% of the final concentration of N-methylphthalamic acid was reached, and these initial absorbance *vs.* time plots were linear. For initial rate measurements, full scale on the recorder was set to 0.1 absorbance unit. For other measurements of absorbance, full scale on the recorder was set to 1.0 absorbance unit.

The products of the reactions were characterized by the identity of their ultraviolet spectra taken at the end of the kinetic runs with the spectra of the amic acids. When the reaction did not go to completion, the final spectrum could be rationalized by assuming a mixture of imide and amic acid.[10] Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer. The formal acid dissociation constant (K_D) for **1a** was determined by dissolving **1** in acid and back titrating with base to pH 6. (Above pH 6, the hydrolysis of **1** interferes with the determination of the titration curve.) Values of K were calculated from the relationship $K_D = [H^+][\mathbf{1b}]/[\mathbf{1a}]$ at several points in the titration curve. The average value of K_D was $2.0 \times 10^{-7}\ M$ in water and $0.62 \times 10^{-7}\ M$ in deuterium oxide.

Results

Equation 2 should describe the observed depencence (Table I) on the hydroxide ion and the buffer ([B]) concentration of the pseudo-first-order rate constant for the hydrolysis of N-[2-(4-imidazolyl)ethyl]phthalimide (**1**), where α is the fraction of imide with an

$$k_{obsd} = \alpha(k_0 + k_1[OH^-] + k_2[B]) + (1 - \alpha)(k_0' + k_1'[OH^-] + k_2'[B]) \quad (2)$$

unprotonated imidazole residue. The two terms on the right side of eq 2 represent the contribution to k_{obsd} made by the hydrolysis of **1b** and **1a**, respectively. Since

$$\alpha = \frac{K_D}{[H^+] + K_D} \quad (3)$$

$$k_{obsd}/\alpha = k_0 + k_1'K_W'/K_D + k_1[OH^-] + k_2[B] + k_0'[H^+]/K_D + k_2'[B][H^+]/K_D \quad (4)$$

The ratio, k_{obsd}/α was evaluated using values of $2.0 \times 10^{-7}\ M$ and $0.62 \times 10^{-7}\ M$ for the formal acid dissociation constant (K_D) of N-[2-(4-imidazolyl)ethyl]phthalimide in water and deuterium oxide (see Experimental Section).

For the concentrations of buffer used, catalysis by buffer accounted for less than 15% of the observed rate. At pH 9.8, the $[OH^-]$-catalyzed reaction makes the predominant contribution to the observed rate constant, and a plot of $k_{obsd}/[OH]\alpha$ *vs.* $[B]/[OH^-]$ was extrapolated to $[B] = 0$ to obtain the value of $k_{obsd}/[OH^-]$ in the absence of buffer.[11] In the pH range of 5.2–8.2, values of k_{obsd}/α in the absence of buffer were determined by extrapolating plots[11] of k_{obsd}/α *vs.* [B] to [B] = 0. The effect of the small changes in $[OH^-]$ accompanying changes in the buffer concentra-

(5) F. Cramer, *Angew. Chem.*, **72**, 236 (1960).

(6) (a) R. G. Bates, "Determination of pH Theory and Practice," John Wiley & Sons, Inc., New York, N. Y., 1964, pp 62–94, 123–130. (b) pD = pH meter reading + 0.40: ref 6a, p 220.

(7) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, pp 638, 748, and 752.

(8) The effect of KCl on the activity coefficients in water and deuterium oxide were assumed to be equivalent, so that the value (6.5) given by R. W. Kingerly and V. K. La Mer [*J. Amer. Chem. Soc.*, **63**, 3256 (1941)] for the dissociation constant of water relative to the dissociation constant of deuterium oxide could be used to calculate $[OD^-]$.

(9) E. A. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

(10) J. Brown, S. C. K. Su, and J. A. Shafer, *J. Amer. Chem. Soc.*, **88**, 4468 (1966).

(11) At a constant ratio of the acidic to basic component of the buffer.

Table I

The Effect of pH and Buffers on the Hydrolysis of N-[2-(4-Imidazolyl)ethyl]phthalimide at 25° [a]

pH	Buffer	Buffer concn, M [b]	$10^5 k_{obsd}$, sec^{-1}	$10^5 k_{obsd}/\alpha$, sec^{-1} Obsd	$10^5 k_{obsd}/\alpha$, sec^{-1} Calcd [c]
5.28 [d]	1:5 NaAc–HAc			2.8 [e]	2.9
5.26		0.0277	0.157		
5.28		0.0462	0.168		
5.13		0.0924	0.187		
5.90 [d]	1:6 Na_2HPO_4–KH_2PO_4			3.0 [e]	2.9
5.89		0.0304	0.31		
5.90		0.0608	0.33		
5.91		0.122	0.34		
7.32 [d]	4:1 Na_2HPO_4–KH_2PO_4			3.2 [e]	3.2
7.28		0.0151	2.4		
7.32		0.0302	2.5		
7.36		0.0604	2.7		
7.57 [d]	7:1 Na_2HPO_4–KH_2PO_4			3.3 [e]	3.4
7.55		0.0284	3.1		
7.57		0.0428	3.3		
7.60		0.0572	3.3		
8.20 [d]	1:1 Tris–Tris HCl			5.2 [e]	5.2
8.19		0.0314	5.2		
8.20		0.0628	5.4		
8.20		0.0942	5.5		
9.81 [d]	10:11 Na_2CO_3–$NaHCO_3$			97 [f]	96
9.78		0.0206	94		
9.82		0.0412	106		
9.84		0.0618	111		

[a] $\Gamma/2 = 0.2$ maintained with KCl. [b] Acidic + basic component. [c] Calculated using the expression $k_{obsd}/\alpha = 2.9 \times 10^{-5} + 11$ [OH$^-$]. [d] Average pH for this buffer. [e] Evaluated by extrapolatng a plot of k_{obsd}/α *vs.* [B] to [B] = 0. [f] Evaluated by extrapolating a plot of $k_{obsd}/[OH^-]\alpha$ *vs.* [B]/[OH$^-$] to [B] = 0, and using this extrapolated value of $k_{obsd}/[OH^-]\alpha$ to calculate k_{obsd}/α at pH 9.81.

tion on the value of k_{obsd}/α was not significant, and, for the purposes of extrapolation, plots of k_{obsd}/α *vs.* [B] were assumed to be linear.

The depencence on the hydroxide ion concentration of the values of k_{obsd}/α at [B] = 0 should be described by eq 5.

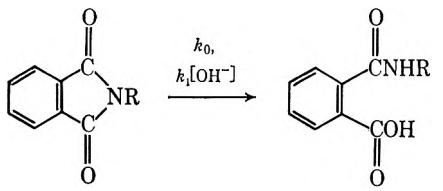
$$k_{obsd}/\alpha = k_0 + k_1K_W'/K_D + k_1[OH^-] + k_0'[H^+]/K_D \quad (5)$$

The data in Table I reveal that the contribution of the term $k_0'[H^+]/K_D$ to k_{obsd}/α is insignificant, since the dependence of k_{obsd}/α on the hydroxide ion concentration (at [B] = 0) may be represented by expression 6 where $k_0 + k_1'K_W'/K_D = 2.9 \times 10^{-5}$ sec^{-1}

$$k_{obsd}/\alpha = k_0 + k_1'K_W'/K_D + k_1[OH^-] \quad (6)$$

and $k_1 = 11$ sec^{-1} M^{-1}. In deuterium oxide, values of 1.4×10^{-5} sec^{-1} and 16 sec^{-1} M^{-1} were observed for $k_0 + k_1'K_W'/K_D$ and k_1, respectively.

Figure 1 compares the pH dependencies of the observed pseudo-first-order rate constants for the hydrolysis of imides **1**, **2**, **3**, and **4**, thereby illustrating the effect of the imidazole group on the hydrolysis of **1**. Values for k_0 and k_1 are listed in Table II.



2, R = $CH_2CH_2N^+(CH_3)_3Br^-$
3, R = $CH_2CH_2CH_2N^+(CH_3)_3Br^-$
4, R = CH_3

Table II

Rate Constants for the Hydrolysis of Some Phthalimides to Phthalamic Acids at 25°

Phthalimide	k_1, [a] sec^{-1} M^{-1}	$10^7 k_0$, [b] sec^{-1}
2	91	3.6
3	41	2.6
4	24	

[a] Obtained by extrapolating plots of $k_{obsd}/[OH^-]$ *vs.* [buffer]/[OH$^-$] to [buffer] = 0 at pH values above 7. [b] Obtained by extrapolating plots of $k_{obsd} - k_1[OH^-]$ *vs.* [buffer] to [buffer] = 0 at pH values below 7.

Examination of Table III reveals that the imidazole residue in **1** perturbs the ultraviolet absorption spectrum of the phthalimido group. Interestingly, concentrated solutions of imidazole cause similar perturbations in the ultraviolet spectrum of N-methylphthalimide. These results suggest that the imidazole residue in **1** is interacting with the phthalimido group.

Table III

The Effect of Imidazole on the Absorbance of Some Phthalimides

Phthalimide	Conditions	E_{300}/E_{250} [a]
1	0.025 M KH_2PO_4–0.025 M Na_2HPO_4	2.79 [b]
2		5.28
3		5.63
4		5.26
4	0.434 M imidazole–0.434 M imidazole HCl	3.43 [b]

[a] E_{250} and E_{300} represent the extinction coefficients of the imides. The extinction coefficients of these imides were independent of the imide concentration. [b] The low value for this ratio is mainly attributable to an increase in E_{250}.

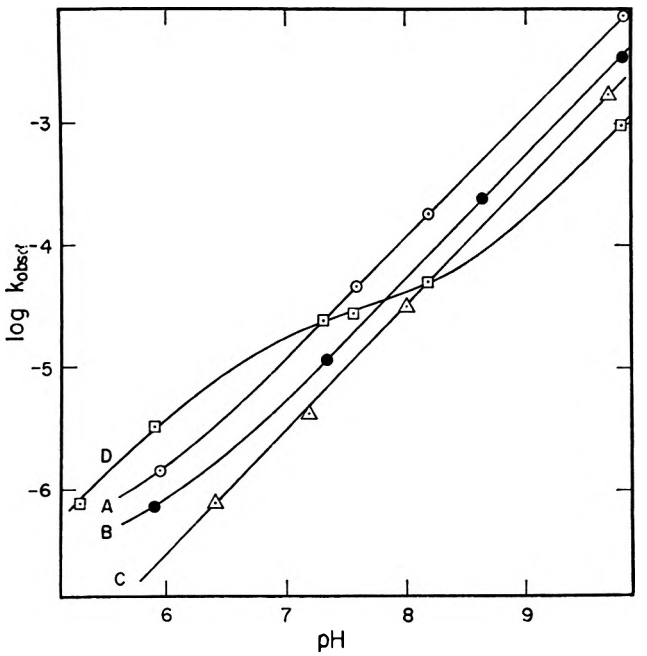


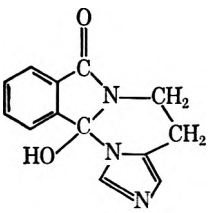
Figure 1.—The pH dependencies of the observed pseudo-first-order rate constant for the hydrolysis of some N-substituted phthalimides to the corresponding phthalamic acids at 25°: A, N-(2-trimethylaminoethyl)phthalimido bromide (2), ⊙ (solid line calculated from $k_{obsd} = 3.6 \times 10^{-7} + 91[OH^-]$); B, N-(3-trimethylaminopropyl)phthalimido bromide (3), ● (solid line calculated from $k_{obsd} = 2.6 \times 10^{-7} + 41[OH^-]$); C, N-methylphthalimide (4), △ (solid line calculated from $k_{obsd} = 24[OH^-]$); D, N-[2-(4-imidazolyl)ethyl]phthalimide (1), ⊡ {solid line calculated from $k_{obsd}/\alpha = 2.9 \times 10^{-5} + 11[OH^-]$ and $\alpha = (2.0 \times 10^{-7})/([H^+] + 2.0 \times 10^{-7})$}.

Discussion

It is not surprising that in basic solution the cationic imides 2 and 3 are more susceptible to hydroxide ion catalyzed hydrolysis than imides 1 and 4. Similarly, the enhanced reactivity of 1 at pH values near neutrality might be attributed solely to electrostatic effects associated with the protonated form of 1. In terms of eq 4, this assumption means $k_1'K_W'/K_D \gg k_0$. Therefore, $k_1' = 333$ sec^{-1} M^{-1} (eq 6). It is unlikely, however, that 1a with its center of positive charge further removed from a carbonyl carbon atom would be more susceptible to hydroxide ion catalyzed hydrolysis than 2 and 3 (Table II). Also, if electrostatic effects were responsible for the enhanced reactivity of 1 in solutions near neutrality, the "spontaneous" or water-catalyzed hydrolysis of 1a would also be expected to be increased. In reality, the fit of eq 6 to the data in Table I requires that the term representing "spontaneous" hydrolysis of 1a (k_0') be less than the corresponding terms assigned to 2 and 3.[12] It is therefore more reasonable to assume that the imidazole residue in 1 catalyzes the hydrolysis of the phthalimido group.

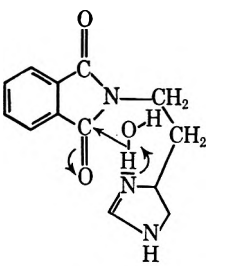
We have previously reported the catalysis and inhibition of the hydrolysis of 4 by imidazole.[2] Spectroscopic and kinetic evidence was presented in that report suggesting that imidazole acts as a general base in catalyzing the hydrolysis of 4, and that imidazole may form an unreactive tetrahedral addition compound with 4.

The increased absorbance of 1 at wavelengths below 300 mμ suggests that the interaction between the imidazole and phthalimido group in 1 is similar to the interaction between imidazole and N-methylphthalimide. Perhaps a fraction of 1 exists as the unreactive tetrahedral addition compound 5. The low value



5

observed for the second-order rate constant for hydroxide ion catalyzed hydrolysis of 1 (11 sec^{-1} M^{-1} *vs.* 24 sec^{-1} M^{-1} for 4) is also consistent with the existence of a substantial amount of 5. Expulsion of amide anion from 5 to form the acylimidazole seems unlikely, since the ability of imidazole to displace groups from a carbonyl carbon atom decreases sharply as the pK_a of the leaving group becomes larger than 10.[13] The observed deuterium isotope effect of 2.1 for k_0 also argues against nucleophilic displacement of an amide anion by a neighboring imidazole group. It is unlikely that imidazolium ion is functioning as a general acid in catalyzing attack by hydroxide ion, since the calculated rate constant for this process is not significantly lowered by deuterium oxide.[14] It therefore seems reasonable to assume that imidazole is functioning as a general base in catalyzing attack by water on imide 1.



6

The first-order rate constant (k_0) for the intramolecularly catalyzed hydrolysis of 1 by imidazole is estimated as 2.9×10^{-5} sec^{-1}, while the second-order rate constant for the imidazole-catalyzed hydrolysis of N-methylphthalimide is 2.0×10^{-5} sec^{-1} M^{-1}. The ratio of these two rate constants, 1.5 M, gives the effective local concentration of imidazole in 6.

This ratio can be compared with the value of 13 M estimated by Ferscht and Kirby[15] for the effective

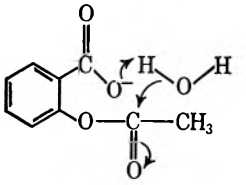
(12) If the value of k_{obsd} were in error by 10% at pH 5.28, then the maximum value of k_0' $[H^+]/K_D$ would be $1.1 \times 2.8 \times 10^{-8} - 2.9 \times 10^{-8}$ and the upper limit of k_0' would be 0.52×10^{-7} sec^{-1}. This value is less than the corresponding values (k_0) assigned to 2 (3.6×10^{-7} sec^{-1}) and 3 (2.6×10^{-7} sec^{-1}).

(13) J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 837 (1964).

(14) Assuming that general acid catalysis by the neighboring imidazolium ion is important, $k_1' = [K_D/K_W']_{H_2O} \times 2.9 \times 10^{-5}$ or 333 sec^{-1} M^{-1} in water and $k_1' = [K_D/K_W']_{D_2O} \times 1.4 \times 10^{-5}$ or 324 sec^{-1} M^{-1} in deuterium oxide.

(15) A. R. Ferscht and A. J. Kirby, *ibid.*, **89**, 4857 (1967).

concentration of carboxylate in the hydrolysis of aspirin.



7

A difference in the relative orientation of the catalytic residue and the carbonyl carbon atom in **6** and **7** is probably responsible for the difference in the efficiencies of the two catalysts. Also, if a significant fraction of **1** exists, in the unreactive tetrahedral form **5**, the estimate of the effective concentration of the imidazole residue in **6** would be too low.

Registry No.—**1**, 5959-80-8; **2**, 20452-82-8; **3**, 20452-83-9; **4**, 550-44-7.

Stereochemistry of Flexuosin A and Related Compounds[1,2]

WERNER HERZ, P. S. SUBRAMANIAM, AND N. DENNIS

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

Received March 6, 1969

2-Acetylflexuosin A and autumnolide, two new sesquiterpene lactones, were isolated from an Alabama collection of *Helenium autumnale* L. Correlation of the former with linifolin A led to the elucidation of the complete stereochemistry of flexuosin A and its congeners.

Helenium autumnale L. collections of unspecified provenance are reported[3] to serve as sources of the pseudoguaianolide helenalin (**1**), but more recent extractions of plant material from North Carolina[4] and Pennsylvania[5] yielded other sesquiterpene lactones and no helenalin.[6] In an effort to shed light on these variations we have examined several southeastern collections of *H. autumnale*. Material from northwestern Florida and southern Georgia gave respectable yields of helenalin, as claimed in the early[3] literature. On the other hand material from Greene County, Ala., gave instead of helenalin two previously unreported sesquiterpene lactones. The study of these compounds allowed us to clarify the structure of flexuosin A[10] and is described in this paper.

The substance obtained in larger yield (0.3%), $C_{19}H_{26}O_7$, mp 124–126°, exhibited ir bands (see Experimental Section) which indicated the presence of one hydroxyl group, two esters, and an α,β-unsaturated γ-lactone. That the ester bands were derived from two secondary acetates as suggested by the empirical formula was verified by the nmr spectrum, which had two singlets at 1.98 and 2.00, a doublet at 5.36, and a triplet of doublets at 4.52 ppm. The nmr spectrum also had the signals characteristic of the usual α,β-unsaturated γ-lactone function associated with pseudoguaianolides of the helenalin series (two narrowly split doublets at 6.18 and 5.97 and a complex triplet at 4.9 ppm), one secondary hydroxyl group (broadened doublet at 3.8 ppm), a methyl singlet, and a methyl doublet.

Acetylation of the new lactone afforded diacetylflexuosin A (**2d** devoid of stereochemistry) of known structure and uncertain configuration.[10] Comparison of the nmr spectra of the new lactone, flexuosin A (gross structure **2a**),[10,11] alternilin (gross structure **2b**),[11] and **2d** gave clear evidence for its formulation as 2-acetylflexuosin A (gross structure **2c**). The broadened doublet associated with H-4 exhibited the same chemical shift in the nmr spectra of **2a**, **2b**, and the new lactone, but moved downfield on acetylation to **2d**. On the other hand, **2d** and the new lactone displayed identical chemical shifts for the triplet of doublets associated with H-2 and the doublet associated with H-6.[12]

Oxidation of the new sesquiterpene lactone gave the cyclopentanone derivative **3** (new carbonyl band at 1750 cm^{-1}) whose nmr spectrum (absence of 3.8-ppm signal) confirmed the assignments of the previous paragraph. Pyrolysis of **3** in a nitrogen atmosphere afforded a crystalline substance identical in all respects with linifolin A, whose absolute configuration has been shown[11] to be **4**. This result defined the previously unknown asymmetric centers C-1, C-5, C-6, C-7, and C-8 of flexuosin A, alternilin, and their congeners.

There remained the problem of determining the configuration at C-2 and C-4. Unlike pulchellin,[13] flexuosin A could not be induced to form a carbonate or a sulfite. Hence, the hydroxyl groups were *trans*. The nature of the five-membered ring is such that this information, even with knowledge of the absolute configuration at C-1 and C-5 and of the coupling constants $J_{H\text{-}1,H\text{-}2}$, $J_{H\text{-}2,H\text{-}3a}$, $J_{H\text{-}2,H\text{-}3b}$, $J_{H\text{-}3a,H\text{-}4}$, and $J_{H\text{-}3b,H\text{-}4}$, does not permit an unambiguous assignment of stereochemistry to C-2 and C-4. However, the configura-

(1) Constituents of *Helenium* Species. XXIII. Previous paper, L. Tsai, R. J. Highet, and W. Herz, *J. Org. Chem.*, **34**, 945 (1969).

(2) Supported in part by grants from the National Science Foundation (GP-6362) and the National Institutes of Health (GM-05814).

(3) For leading references see W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Amer. Chem. Soc.*, **85**, 19 (1963); W. Herz and P. S. Santhanam, *J. Org. Chem.*, **32**, 507 (1967).

(4) R. A. Lucas, R. G. Smith, and L. Dorfman, *ibid.* **29**, 2101 (1964).

(5) W. Herz and P. S. Subramaniam, unpublished results.

(6) The existence of subspecies or varieties may be responsible for these differences. A collection labeled *H. autumnale* var. *canaliculatum* (Lam.) T. and G. (equivalent to *H. latifolium* Mill. according to Rydberg,[7] but not according to Gleason and Cronquist[8] where *H. latifolium* is absorbed in *H. autumnale* var. *autumnale*) furnished[9] tenulin and no helenalin.

(7) P. A. Rydberg, *North American Flora*, **34**, part 2, 119(1915).

(8) H. A. Gleason and A. Cronquist, "Manual of Vascular Plants of the Northeastern United States and Adjacent Canada," D. Van Nostrand Company, Princeton, N. J., 1963.

(9) Unpublished work by B. F. Aycock and A. E. Senear, cited by R. Adams and W. Herz, *J. Amer. Chem. Soc.*, **71**, 2546 (1949).

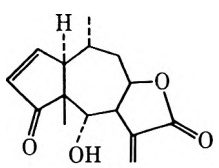
(10) W. Herz, Y. Kishida, and M. V. Lakshmikantham, *Tetrahedron*, **20**, 979 (1964).

(11) W. Herz, C. M. Gast, and P. S. Subramaniam, *J. Org. Chem.*, **33**, 2780 (1968).

(12) The isolation of authentic **2c** requires that the monoacetylflexuosin A, mp 158–160°, obtained previously[10] in low yield by treatment of flexuosin A with isopropenyl acetate–toluenesulfonic acid be formulated as **2c** (4-acetylflexuosin A).

(13) W. Herz, K. Ueda, and S. Inayama, *Tetrahedron*, **19**, 483 (1963).

tion at C-4 of dehydroflexuosin A (**5**)[10] has already been deduced as R by application of the Horeau method.[14] Hence the configuration at C-2 of flexuosin A and its derivative must be R also, and the complete formulas of the naturally occurring compounds flexuosin A, 2-acetylflexuosin A, and alternilin are **2a**, **2c**, and **2b**. A



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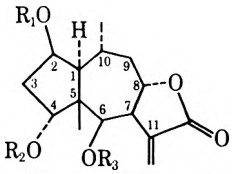
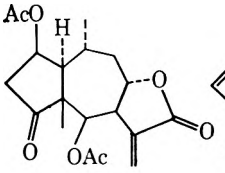


2a, R_1, R_2 = H; R_3 = Ac
b, R_2, R_3 = H; R_1 = Ac
c, R_2 = H; R_1, R_3 = Ac
d, R_1, R_2, R_3 = Ac
e, R_1 = H; R_2, R_3 = Ac



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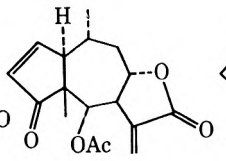

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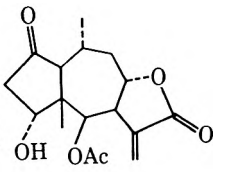

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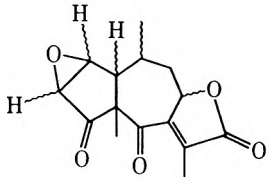

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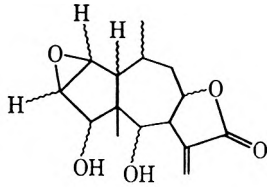

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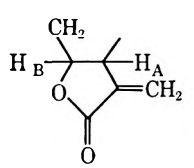
comparison of the molecular rotations of **2a**, **2c**, **2d**, and **2e** (Table I) independently indicates that the stereochemistry at C-2 and C-4 is identical (both atoms R).

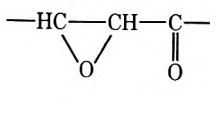
TABLE I
$[M]^{CHCl_3}$ OF FLEXUOSIN A DERIVATIVES

Flexuosin A (2a)	40°		
2-Acetylflexuosin A (2c)	1°	Δ[M]	−39°
4-Acetylflexuosin A (2e)	−0.2°	Δ[M]	−40°
Diacetylflexuosin A (2d)	−46°	Δ[M]	−86°

The minor constituent of *H. autumnale* from Alabama, $C_{15}H_{20}O_5$, mp 188–190°, $[\alpha]^{25}D$ 20.6°, has been named autumnolide. The nmr spectrum of this substance (DMSO-d_6) exhibited two doublets associated with the hydroxylic protons of two secondary hydroxyl groups, signals characteristic of partial structure A



A



B

(narrowly split doublets at 6.02 and 5.81, multiplet of H_B at 4.8 ppm), a five-proton multiplet in the range 3.3–3.8 ppm, a methyl doublet, and a methyl singlet. Hence, four of the five oxygen atoms were accounted for.

(14) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).

On conversion of autumnolide into a diacetate, two of the five protons in the 3.3–3.8-ppm cluster experienced a downfield shift and now appeared as doublets at 4.70 and 4.63 ppm, thus establishing the presence of two hydroxyl groups of the type $R_2CH-CH(OH)R_3$. The remaining three low-field protons were assigned to H_A of partial structure A, generally found in the range of 2.9–3.4 ppm, and, because of the presence of a fifth oxygen atom, to two protons on carbon carrying an ethereal oxygen.

Oxidation of autumnolide furnished in very low yield a crystalline diketone which gave a positive KI test for the presence of partial structure B. The nmr spectrum was consonant with formula **6** (disappearance of H_A signal and downfield shift of H_B signal of A, disappearance of all other low-field signals with the exception of a two-proton multiplet near 3.75 ppm, presence of a vinyl methyl resonance) arising from migration of the exocyclic double bond into conjugation with one of the carbonyl groups. This would lead to structure **7** for autumnolide, but the amount of material on hand was not sufficient to establish this unambiguously.

Experimental Section[15]

Extraction of *Helenium autumnale* L.—(A) Powdered *H. autumnale* L., (1.55 kg), collected by Dr. S. McDaniel on Sept 30, 1967, 1 mile north of Pleasant Ridge, Greene County, Ala. (McDaniel voucher 9867 on deposit in herbarium of Mississippi State University), was extracted with chloroform and worked up in the usual manner.[16] The crude gum (26.0 g) was dissolved in the minimum amount of benzene (no tenulin crystallized out on being left overnight) and was chromatographed over 420 g of silicic acid (Mallinckrodt 100 mesh), 400-ml fractions being collected. Fractions 1–6 (benzene), 7–16 (benzene–chloroform 4:1), 17–25 (benzene–chloroform 3:2), and 26–28 (benzene–chloroform 1:1) eluted practically nothing. Fractions 29–31 (benzene–chloroform 1:1) eluted a small amount of gum which showed several spots on tlc and was discarded. Fractions 32–33 (benzene–chloroform 1:1) also eluted a small amount of gum which showed two major spots, one of which corresponded to 2-acetylflexuosin A. Fractions 34–37 (benzene–chloroform 1:1) and 38–49 (benzene–chloroform 2:3) eluted gums showing essentially one spot. Combination and purification by preparative tlc (developer chloroform–methanol 24:1) gave 3.6 g of 2-acetylflexuosin A. The colorless stout needles melted at 124–126° after recrystallization from ether–petroleum ether: ir 3525 (OH), 1765, 1668 (α,β-unsaturated lactone), and 1730 cm^{-1} (double strength, two acetates); nmr 6.18 and 5.97 (d, 3.5, $=CH_2$), 5.36 (d, 3, H-6), 4.9 (td, 7.5, 2, H-8), 4.52 (td, 9, 2.5, H-2), 3.8 (br, sharpens to doublet, J = 4.5 Hz, on addition of D_2O, H-4) 3.15 (m, H-7), 2.0 and 1.98 (acetates), 1.03 (d, 6, C-10 methyl), and 0.79 ppm (C-5 methyl).

Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15; O, 30.57. Found: C, 62.27; H, 7.16; O, 30.57.

Fractions 50–53 (benzene–chloroform 1:3) eluted 1.0 g of gum containing 2-acetylflexuosin and impurities which required double preparative tlc before 0.24 g of pure 2c could be isolated. Fractions 63–69 (benzene–chloroform 1:3) and 57–62 (benzene–chloroform 1:4) eluted complex mixtures. Fractions 63–69 (chloroform) eluted solid material. Two recrystallizations from ethyl acetate–hexane afforded 0.48 g of autumnolide which had mp 188–190°; $[\alpha]^{25}D$ 20.6° *c* 1.84, ($CHCl_3$); ir (Nujol) 3520, 3400 (OH), 1760, and 1660 cm^{-1} (conjugated lactone); nmr DMSO-d_6) 6.02 (d, 2) and 5.61 (d, 1.5, $=CH_2$), 5.15 (d), and

(15) Melting points are uncorrected. Rotations were run in chloroform, ultraviolet spectra in 95% ethanol, infrared spectra in chloroform. Nmr spectra were determined in deuteriochloroform unless specified otherwise on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are quoted in parts per million, line separations in hertz. Signals are denoted in the usual manner: d, doublet; t, triplet; c, complex signal whose center is given; m, multiplet; br, somewhat broadened singlet. Singlets are unmarked. Analyses were by Dr. F. Pascher, Bonn, Germany.

(16) W. Herz and G. Högenauer, *Ibid.*, **27**, 905 (1962).

4.8 (d, 4, two OH, disappears on exchange with D_2O), the latter superimposed on a one-proton multiplet near 4.75 (H-8), 3.3–3.8 (five-proton multiplet), 1.08 (d, 5, C-10 methyl), and 0.74 ppm (C-5 methyl).

Anal. Calcd for $C_{15}H_{20}O_6$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.43; H, 7.23; O, 28.88.

(B) Powdered *H. autumnale* L. (5.4 kg), collected by Mr. Robert R. Lazor at the east end of the bridge on Florida Route 20 over the Apalachicola River near Bristol, Liberty County, Fla., in Sept 1968 (Lazor voucher no. 1306 on deposit in the herbarium at Florida State University), was extracted with chloroform and worked up in the usual way. Chromatography of the crude gum (79 g) over 800 g of silicic acid gave in the benzene eluates a small amount of a triterpene mixture. Benzene–chloroform (2:1 and 1:1) gave mixtures. Elution with chloroform gave 20 g of helenalin. Elution with chloroform–ether (9:1 and 8:2) gave mixtures which were not separated satisfactorily on rechromatography.

Extraction of *H. autumnale* L., collected by Mr. R. Lazor and Dr. R. K. Godfrey on Sept 9, 1968, 13 miles south of Moultrie, Ga. (Lazor–Godfrey voucher no. 1185 on deposit in the herbarium of Florida State University), gave results which did not differ significantly from the ones described in the preceding paragraph.

Linifolin A.—Dehydro-2-acetylflexuosin A (**3**) (100 mg) was heated at 180° under nitrogen for 1 hr. The straw-colored solid which formed on cooling was dissolved in benzene and recrystallized to give 95 mg of linifolin A, mp 202–203° (lit. mp 202–204°), mixture melting point with authentic material, undepressed, and nmr and ir spectra superimposable.

Reaction of Flexuosin A with Thionyl Chloride.—A solution of 0.15 g of flexuosin A in 3 ml of dry pyridine was mixed with 10 drops of thionyl chloride at 0°, left at room temperature for 4 hr, and then poured on ice. The product was extracted with ether. The ether extract was washed, dried, and evaporated. The amorphous residue which could not be recrystallized satisfactorily exhibited ir bands at 1770 (γ-lactone), 1745, and 1200 cm^{-1} (acetate), but had no bands characteristic of hydroxyl or sulfite functions. The product gave a positive test for chlorine.

Reactions of 2-Acetylflexuosin.—Acetylation of 120 mg of 2-acetylflexuosin A with acetic anhydride–pyridine in the usual manner afforded, after recrystallization from ether–petroleum ether, 102 mg of material, mp 130–131°, which was identical in all respects (tlc, mixture melting point, and ir and nmr spectrum) with authentic diacetylflexuosin A.

To a solution of 150 mg at 2-acetylflexuosin A in 6 ml of acetone was added dropwise 0.5 ml of Jones reagent[17] with stirring at 0°. After 20 min at room temperature, excess oxidant was destroyed by adding a few drops of methanol. The solution was diluted with water and extracted with ether. Removal of ether followed by recrystallization from acetone–isopropyl ether afforded 114 mg of dehydro-2-acetylflexuosin A (**3**), which had mp 168–170°; ir 1765 and 1670 (unsaturated lactone), 1750 (cyclopentanone), 1740 (esters), and 1410 cm^{-1} (CH_2CO); nmr 6.18 (d, 3.5) and 5.61 (d, 3, $=CH_2$), 5.95 (d, 3.5, H-6), 5.12 (dq, 12, 7, 3, H-2), 4.51 (td 10, 3, H-8), 3.2 (m, three protons, H-3 and H-7), 2.03 and 1.97 (acetates), 1.09 (C-10 methyl), and 1.06 ppm (C-5 methyl); ORD (*c* 0.083, methanol) $[\Phi]_{600}$ 397°, $[\Phi]_{589}$ 442°, $[\Phi]_{310}$ 4575°, $[\Phi]_{276}$ −485°, $[\Phi]_{230}$ 3170°.

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.60; O, 30.28. Found: C, 62.70; H, 6.67; O, 30.35.

Diacetylautumnolide.—A mixture of 100 mg of autumnolide, 1 ml of pyridine, and 1 ml of acetic anhydride was heated at 80° for 2 hr. After the usual work-up the crude product was chromatographed over 2 g of silicic acid. Chloroform eluted a product (single spot on tlc) which was recrystallized from ether: yield 52 mg; mp 101–103°; $[\alpha]^{26}D$ −14.6° (*c* 0.835, $CHCl_3$); nmr 6.24 (d) and 5.71 (d, 2, $=CH_2$), 4.70 (d, 6, H-6), and 4.63 (H-4) superimposed on 4.65 (m, H-8), 3.3 (two protons, H-2 and H-3) superimposed on 3.3 (m, H-7), 2.04 and 2.02 (acetates), 1.18 (d, 6, C-10 methyl), and 1.09 ppm C-5 methyl).

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64; O, 30.73. Found: C, 62.48; H, 6.75; O, 30.88.

Attempts to prepose a monoacetyl derivative by acetylation at room temperature resulted in the formation of a glass which appeared to polymerize on standing.

Oxidation of Autumnolide.—Oxidation of 50 mg of autumnolide in 3 ml of acetone with 0.2 ml of Jones reagent in the usual manner afforded a colorless solid mixture (tlc). Preparative tlc over silica gel (developer 6% methanolic chloroform) and recrystallization from acetone–ether permitted isolation of 8 mg of the compound responsible for the major spot. It gave a positive 2-epoxy ketone test with potassium iodide and negative ferric chloride and Zimmermann tests. The poorly resolved nmr spectrum exhibited signals at 5.5 (m, H-8), 3.75 (m, two protons, H-2 and H-3), 1.83 (br, C-11 methyl), and 1.30 (d, 6, C-10 methyl).

Registry No.—**2c**, 20483-26-5; **3**, 20505-31-1; **7**, 20505-32-2; diacetyl **7**, 20483-27-6.

(17) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 142.

Cleavage of α-Nitro Ketones

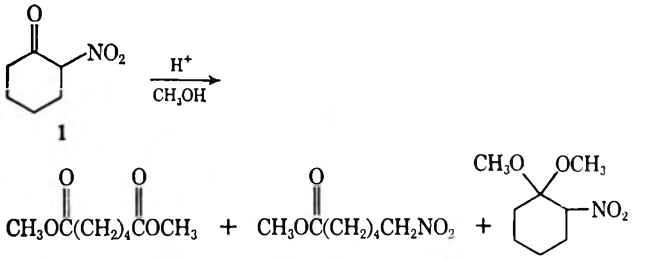
H. FEUER AND P. M. PIVAWER[1]

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received January 17, 1969

The cleavage of α-nitro ketones has been recently the subject of several investigations.[2-7] In a previous publication we noted that in refluxing methanolic acetic acid 2-nitrocyclohexanone (**1**) and 2-nitro-3,5,5-trimethylcyclopentanone (**2**) were converted into methyl 6-nitrohexanoate (**3**) and methyl 2,2,4-trimethyl-5-nitropentanoate, respectively, while under similar conditions 2-nitrocycloheptanone (**4**) and 2-nitrocyclooctanone failed to react.

In continuation of our work we have found that cleavage in methanol containing a catalytic amount of concentrated sulfuric acid at room temperature led to different products. As shown in Table I, **1** was converted into dimethyl adipate, 2,2-dimethoxynitrocyclohexane (**5**), and **3** (eq 1). Nitro ketone **4** behaved similarly.



(1)

The respective α-nitro ketals were prepared directly from **1** and **4** in high yield by an acid-catalyzed reaction

(1) Dow Chemical Corp. Fellow, 1963–1964.
(2) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, **31**, 3152 (1966).
(3) A. S. Matlack and D. S. Breslow, *ibid.*, **32**, 1995 (1967).
(4) R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Amer. Chem. Soc.*, **77**, 527 (1955).
(5) H. O. Larson and E. K. Wat, *ibid.*, **85**, 827 (1963).
(6) A. Hassner and J. Larkin, *ibid.*, **85**, 2181 (1963).
(7) T. Simmons and K. L. Kreuz, *J. Org. Chem.*, **33**, 836 (1968).

TABLE I

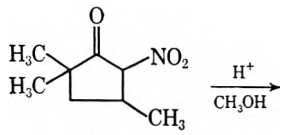
PRODUCTS OF THE ACID-CATALYZED CLEAVAGE OF α-NITRO KETONES

α-Nitro ketone	Registry no.	Products (yield, %)
α-Nitrocyclohexanone[a-c]	4883-67-4	Dimethyl adipate (53), methyl 6-nitrohexanoate (3), 2,2-dimethoxynitrocyclohexane (14)
α-Nitrocycloheptanone[d,e]	13154-27-3	Dimethyl pimelate (28), methyl 7-nitroheptanoate (12), 2,2-dimethoxynitrocycloheptane (4)
α-Nitrocycloheptanone[f]		Diethyl pimelate (65)
α-Nitrocyclooctanone[f]	13154-28-4	Diethyl suberate (55)
3-Nitro-4-heptanone[f]	13154-33-1	Ethyl butyrate, ethyl propionate
3-Nitro-3-methyl-2-butanone[f-i]	13292-96-1	Ethyl acetate, 2-nitropropane (12)
2-Bromo-2-nitrocyclooctanone[f]	20642-74-4	Diethyl suberate (60), ethyl 8-bromo-8-nitrooctanoate (17)
2-Nitro-1-tetralone[f]		No reaction

[a] The reaction was carried out in methanol at room temperature for 3 hr in the presence of catalytic amounts of concentrated sulfuric acid. [b] According to ref 3, in aqueous sodium bicarbonate the product was 6-nitrohexanoic acid. [c] According to ref 7, in concentrated sulfuric acid adipic acid was the product. [d] Reaction condition as in footnote *a* except that the reaction time was 4 hr. [e] 50% of ketone was recovered. [f] The reaction was carried out in absolute ethanol and concentrated sulfuric acid at reflux temperature for 3 hr. [g] 88% of ketone was recovered after a reaction time of 16 hr. [h] The experiment was performed by M. Auerbach. [i] According to ref 7, no reaction occurred in concentrated sulfuric acid.

with methyl orthoformate.[8] Very little ring cleavage occurred during this transformation.

On the other hand, 2 reacted differently from the other nitro ketones, giving rise to N-hydroximide 6 and to a small amount of dimethyl 2,2,4-trimethylglutarate (eq 2).



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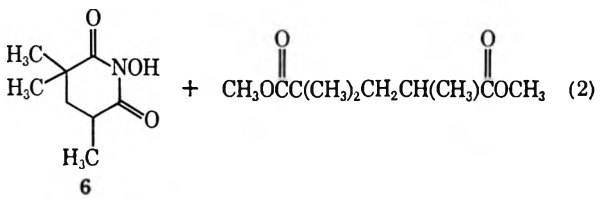


6 (2)

Both Larson[5] and Hassner[6] reported that this unusual ring expansion with cyclic five-membered-ring α-nitro ketones proceeded in the presence of hydrochloric acid and acetic anhydride. Compound 2 was converted on treatment with hydrochloric acid into 6 (70% yield), but did not react with acetic anhydride.

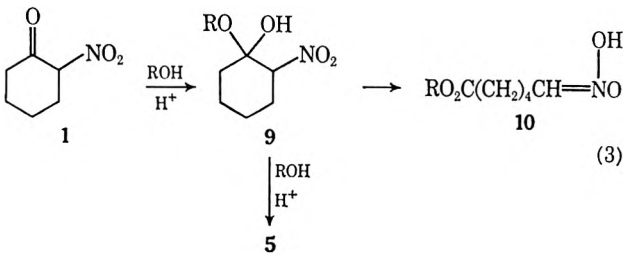
2-Bromo-2-nitro-3,5,5-trimethylcyclopentanone (7) and 2-bromo-2-nitrocyclooctanone (8) did not react with concentrated hydrochloric acid at 40°. Nevertheless 8 was cleaved readily in refluxing ethanol in the presence of catalytic amounts of sulfuric acid (Table I).

Discussion

In 1957, Feuer, *et al.*,[9] proposed that cleavage of 2,5-dibromo-2,5-dinitrocyclopentanone which proceeded readily in methanol and dry hydrogen chloride to yield methyl 2-bromo-2-nitroglutarate and methyl 2,5-dibromo-2,5-dinitropentanoate involved formation of a hemiketal. We suggest a similar mechanism to explain the cleavage of α-nitro ketones (eq 3). The important step in this mechanism is the formation of hemiketal 9 with subsequent cleavage to an *aci*-nitro intermediate 10. Formation of 9 during the reaction was clearly indicated by the fact that α-nitro ketals were isolated from the acidic cleavage of 1 and 4. Intermediate 10 is preferentially converted into an ω-nitrocarboxylic ester (or acid) in weakly acidic[2] or basic[3] media, and to a dicarboxylic ester (or acid), possibly *via* a modified Nef reaction,[10] in strongly acid solutions.

As suggested by Simmons and Kreuz,[7] the conversion of α-nitro ketones into carboxylic acids in strong acidic media could involve the direct conversion of a protonated form of 1 into a nitrile oxide, but this reaction path does not explain the ready cleavage of compounds 7, 8, and 3-nitro-3-methyl-2-butanone (11) containing *t*-nitro groups. In fact, it was reported that 11 did not undergo cleavage when treated with excess 96% sulfuric acid.[7] On the other hand, the formation of hemiketals as intermediates explains the facile cleavage of α-nitro ketones in alcohol in the presence of catalytic amounts of acid.

A possible explanation for the failure of α-nitrotetralone (12) to cleave in the acid-catalyzed reaction with methanol might be its failure to form a hemiketal. This could also account for our observation that 12 did not give a ketal on treatment with methyl orthoformate. It is of interest that Pearson[4] observed that ω-nitroacetophenone did not cleave in aqueous hydrochloric acid.



1 9 10 5 (3)

Experimental Section

Gas chromatographic analysis was performed on an Aerograph A903 at 135° using a 4-ft SF-96 on Chromosorb column.

Reaction of α-Nitro Ketones in Refluxing Absolute Ethanol.—The following experiment is typical of the procedure employed. 2-Nitrocycloheptanone (4, 2.0 g, 0.012 mol) and 3 drops of concentrated sulfuric acid were added to 25 ml of absolute ethanol and the reaction mixture was refluxed until 4 could no longer be detected by glpc (3 hr). Sodium acetate was added to neutralize the acid followed by 100 ml of ether to precipitate inorganic salts. After filtration and evaporation of solvents, the residue was distilled to give 1.8 g (65%) of diethyl pimelate, bp 65–66° (0.05 mm), n^{20}D 1.4301 (lit.[11] n^{20}D 1.4299).

(8) L. Claisen, *Chem. Ber.*, **29**, 1007 (1896).

(9) H. Feuer, J. W. Shepherd, and C. Savides, *J. Amer. Chem. Soc.*, **79**, 5768 (1957).

(10) W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

Reaction of 2-Nitro Ketones in Methanol at Room Temperature. A. 2-Nitrocycloheptanone (4).—Compound **4** (0.8 g, 0.005 mol) and 5 drops of concentrated sulfuric acid were added to 50 ml of absolute methanol and the mixture was allowed to stir for 20 hr. After neutralization with sodium acetate, 200 ml of ether was added to precipitate inorganic salts. The reaction mixture was filtered and the solvent evaporated. Distillation of the residue gave 0.9 g of material, bp 60–80° (0.2 mm). Glpc analysis revealed four components: **4** (50%), dimethyl pimelate (28%), methyl 7-nitroheptanoate (12%), and 2,2-dimethoxynitrocycloheptane (4%). The retention times of these compounds were identical with those of authentic samples.

B. 2-Nitro-3,5,5-trimethylcyclopentanone (2).—Compound **2** (1.5 g, 0.0088 mol) was added to 25 ml of absolute methanol followed by 5 drops of concentrated sulfuric acid. After being stirred for 96 hr the reaction mixture was worked up in the manner as described in experiment A. Distillation gave 0.8 g of material, bp 45–62° (0.5 mm), and 0.5 g of a high boiling material which solidified in the distilling head.

Glpc analysis of the fraction, bp 45–62°, revealed two components, unreacted **2** (46%) and dimethyl 2,2,4-trimethylglutarate (5%). The ester was purified by glpc: n^{20}D 1.4305 (lit.[12] $n^{21.5}$D 1.4309).

Recrystallizing the high boiling material from *n*-heptane gave 0.4 g (33%) of 2,6-dioxo-3,3,5-trimethyl-1-hydroxy-1-azacyclohexane (**6**): mp 118–119.5°; ir (Nujol) 3350 (OH) and 1740 and 1665 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.32 [t, 9, $C(CH_3)_2$ and $C(CH_3)$], 1.69 (d, 1, J = 3 Hz, H, equatorial in CH_2), 1.83 (s, 1, H axial in CH_2), 2.80 (m, 1, CH), and 7.60 (s, 1, OH).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.18. Found: C, 56.35; H, 7.68; N, 8.19.

When the reaction was carried out in refluxing methanol for 20 hr, 1.0 g of **2** yielded 0.7 g (58%) of diester and 0.25 g (25%) of **6**.

When 0.5 g of **2** was allowed to stir at room temperature for 12 hr in 10 ml of concentrated hydrochloric acid, 0.35 g (70%) of **6**, mp 118–119°, was obtained after evaporation of the aqueous solution and sublimation of the residue at 40° (0.05 mm).

(11) E. Huntress and S. Mulliken, "Identification of Pure Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1941, Order I.

(12) G. R. Enser and W. Wilson, *J. Chem. Soc.*, 4068 (1956).

Acetate of 6.—To 10 ml of acetic anhydride was added 0.1 g of **6** and, after the mixture stirred for 24 hr, excess acetic anhydride was removed *in vacuo*. The residue, 0.11 g (100%) was purified by glpc: n^{20}D 1.4680.

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.34; H, 7.04; N, 6.57. Found: C, 56.44; H, 7.08; N, 6.33.

2,2-Dimethoxynitrocycloheptane.—To a mixture of 10 g of absolute methanol, 7.0 g of methyl orthoformate, and 3 drops of concentrated sulfuric acid was added 1.0 g (0.0062 mol) of **4**. After 12 hr at room temperature sodium bicarbonate was added to neutralize the acid, the reaction mixture filtered, and the solvent was evaporated. Distillation gave 1.2 g of material, bp 55–62° (0.4 mm). Glpc analysis revealed the presence of three components: **4** (10%), dimethyl pimelate (18%), and 2,2-dimethoxynitrocycloheptane (72%). Dimethyl pimelate and **4** were identified by comparison of their retention times with those of authentic samples. 2,2-Dimethoxynitrocycloheptane was purified by glpc: n^{20}D 1.4760; ir (neat) 1550 and 1370 (NO_2) and 1110 cm^{-1} (OCH_3).

Anal. Calcd for $C_9H_{17}NO_4$: C, 53.20; H, 8.37; N, 6.90. Found: C, 53.34; H, 8.21; N, 6.83.

Similarly was prepared **2,2-dimethoxynitrocyclohexane** (83%), mp 53–54° after recrystallization from methanol.

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.79; H, 7.94; N, 7.41. Found: C, 50.74; H, 8.08; N, 7.20.

2-Bromo-2-nitro-3,5,5-trimethylcyclopentanone (7).—Potassium 2-keto-3,3,5-trimethylcyclopentanenitronate[2] (2.1 g 0.01 mol) was placed in 25 ml of carbon tetrachloride and bromine was added until a faint yellow color persisted. The mixture was filtered and the filtrate was evaporated. The residual solid was recrystallized from hexane to give 2.0 g (67%) of compound **7**: mp 49–51°; ir (melt) 1515 and 1350 (NO_2) and 1755 cm^{-1} (C=O).

Anal. Calcd for $C_8H_{12}BrNO_3$: C, 38.40; H, 4.80; N, 5.60; Br, 32.00. Found: C, 38.44; H, 4.91; N, 5.63; Br, 32.40.

Registry No.—2,2-Dimethoxynitrocycloheptane, 20642-76-6; 2,2-dimethoxynitrocyclohexane, 20642-78-8; **6**, 20642-75-5; **7**, 20642-77-7.

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of this work.

Carbonium-Ion Behavior in Aluminum Bromide–1,2,4-Trichlorobenzene

G. M. KRAMER

Central Basic Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey 07036

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Nmr spectroscopy was used to monitor the catalytic activity of the aluminum bromide–1,2,4-trichlorobenzene system and to study long-chain hydride-transfer reactions between paraffins and cations. Compounds containing tertiary C–H bonds generally participate in extremely rapid reactions converting all the paraffins into ions in moments. Rearrangement of the intermediates to ions with a different number of branches is slower and usually rate determining. Ionic rearrangements leading to similarly branched species, however, are fast and these studies do not distinguish between these rates and those of hydride transfer. Normal paraffins appear to react much more slowly, probably because both the rates of forming and rearranging secondary ions are slow.

Aluminum bromide has a long history as an exceedingly active Friedel–Crafts catalyst. It is able to support the formation of alkyl cations which undergo extensive intramolecular isomerization and intermolecular reactions. The intermolecular reactions are generally of two types depending on the presence of unsaturated reactants in the system. When olefinic compounds are present, polymerization usually predominates, although cracking of high molecular weight ions and hydride abstraction reactions from the olefin also are often observed.

In the absence of olefins or other bases the alkyl ions enter into hydride abstraction reactions with paraffins.[1] This reaction is often considered the rate-determining step in the isomerization of paraffins, particularly when a normal paraffin is the hydride donor. Alkyl cations formed over $AlBr_3$ are known to be efficient at abstracting either tertiary or secondary hydride ions and thus participating in long-chain isomerization processes.

A major result of earlier work with this system was the finding that nmr spectroscopy could be used to study long-chain intermolecular hydride-transfer processes between isobutane and low concentrations of *t*-butyl cations,[2] eq 1. It can be shown that the doublet of

$$i\text{-}C_4H_{10} + t\text{-}C_4H_9^+ \rightleftharpoons t\text{-}C_4H_9^+ + i\text{-}C_4H_{10} \quad (1)$$

(1) P. D. Bartlett, F. E. Condon, and A. Schneider, *J. Amer. Chem. Soc.*, **66**, 1531 (1944).

(2) G. M. Kramer, B. E. Hudson, and M. T. Melchior, *J. Phys. Chem.*, **71**, 1525 (1967).

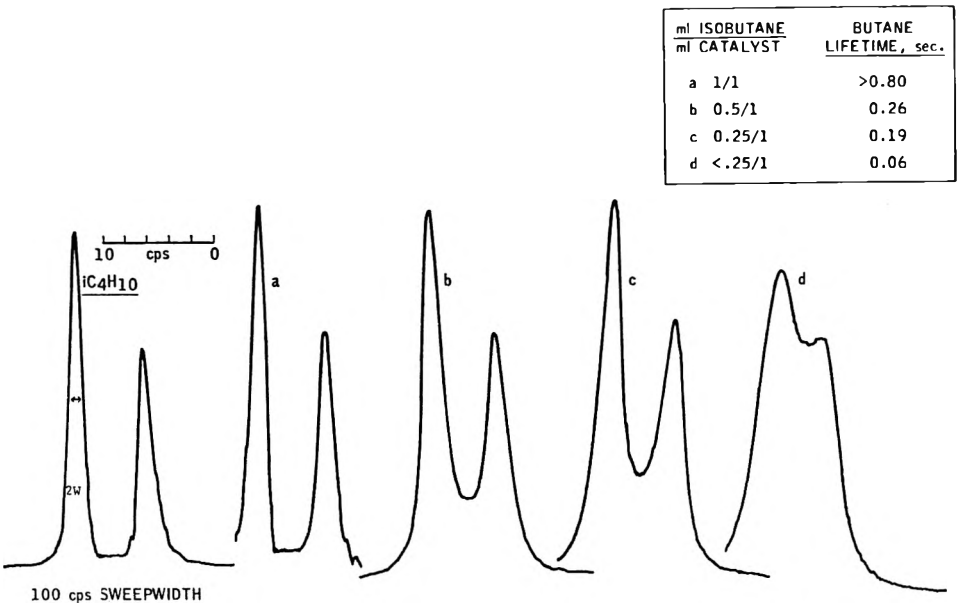


Figure 1.—Nmr spectra of isobutane reacting in 0.5 *M* aluminum bromide–1,2,4-trichlorobenzene; 0.1 *M* water. The effect of lowering the isobutane/catalyst ratio upon the methyl resonance.

isobutane's methyl resonance will coalesce to a singlet when the average lifetime of isobutane molecules is about 0.06 sec. This condition can be approached with about 3.0 *M* solutions of isobutane in 1,2,4-trichlorobenzene containing 0.5 *M* aluminum bromide and about 0.1 *M* water. When the singlet is obtained all isobutane molecules on the average are converted into ions in this time. The lifetime of the ions is much below 0.06 sec and could be calculated if their steady-state concentration was known, *i.e.*, $\tau_{ion} = 0.06 \times [ions]/[i\text{-}C_4H_{10}]$. In any event an active $AlBr_3$ catalyst will convert isobutane into an ion at a high rate and for exceedingly long periods of time, one sample maintaining activity for more than 1 month.

The *t*-butyl cations show little evidence of isomerizing to *s*-butyl ions and isobutane is not isomerized to *n*-butane at any significant rate with this catalyst. This is probably related to a sizable energy difference between *t*-butyl and isobutyl cations which are the likely intermediates in the isomerization.

The present work is mainly concerned with the problems of preparing reproducibly active catalysts and of establishing the scope of the long-lived hydride-transfer reaction. In addition, some information concerning the fate of cations which can isomerize by energetically feasible paths will be discussed.

Preparing "Reproducibly Active Aluminum Bromide–Trichlorobenzene."—A major difficulty with utilizing aluminum bromide–1,2,4-trichlorobenzene for nmr studies has been that of preparing catalysts of essentially equivalent reactivity. This problem has in great part been solved by preparing large quantities of aluminum bromide and trichlorobenzene solutions, promoting with different amounts of water, and utilizing the behavior of isobutane as a barometer of catalyst activity. The test is simply to prepare a standard solution of isobutane in the catalyst system and then to examine the nmr spectrum for evidence of exchange. Any solution exhibiting detectable line broadening is an active catalyst, and an estimate of the activity can easily be made.

Suitable catalysts have been prepared by slowly adding water to a vigorously stirred solution of 30 g of aluminum bromide in 225 ml of 1,2,4-trichlorobenzene. The preparation is done in an otherwise inert atmosphere and any hydrogen bromide evolved is allowed to weather off. Redistilled aluminum bromide and various commercial reagents were all inactive until promoted in this way. Catalysts containing about 0.1 *M* water and 0.5 *M* aluminum bromide exhibit sufficient activity to substantially broaden isobutane's nmr spectrum and this composition was used in most of the subsequent work. An indication of the effect of water upon the reaction is given in Table I.

TABLE I
EFFECT OF WATER PROMOTION ON THE SPECTRUM OF ISOBUTANE

	1:1[a]		0.25:1[a]	
$[H_2O]$, *M*	Doublet separation, cps	Butane lifetime, sec	Doublet separation, cps	Butane lifetime, sec
Blank	5.96	∞	5.96	∞
0.0494	5.82	≫0.8	5.76	0.8
0.0988	5.76	⩾0.8	5.50	0.19

[a] Volume ratio of isobutane/catalyst.

The main factor affecting isobutane's broadened spectra with a given catalyst appears to be the isobutane/catalyst ratio. Lowering the ratio results in broader spectra which is consistent with a decreased lifetime for the butane molecules, Figure 1.

It thus becomes possible to study the behavior of a series of hydrocarbons over an essentially uniformly active catalyst containing aluminum bromide. The catalyst yielding a minimum activity when employed with isobutane was arbitrarily chosen for this purpose.

The Behavior of Alkanes Containing Tertiary C–H Bonds.—The existence of a long-chain hydride-transfer process between isobutane and *t*-butyl ions appears to be a single example of a general reaction between paraffins containing tertiary C–H bonds and their corresponding cations. Eight C_5 through C_8 paraffins, meth-

ylcyclopentane, and methylcyclohexane all gave evidence of participating in the hydride-transfer process.

Some spectral changes were induced in all of the compounds upon contact with the catalyst. Isomerization is often found to accompany the hydride-transfer reaction and affect the nmr spectrum. The extent of isomerization over the water-promoted catalyst during the nmr scan often appears to be somewhat restricted to simple carbonium-ion rearrangements involving hydride and methide shifts along a chain. Processes leading to a change in branching appear to be slower and of minor importance with respect to influencing signal shape in the spectrometer. These interpretations are in accord with established cation behavior.

Spectral observations were made on mixtures of the catalyst and paraffin prepared in an inert atmosphere. The catalyst, 0.5 ml, was first added to an nmr tube and frozen at −80°. Then 0.5 ml of paraffin was added and the mixture was kept cold until the spectrometer was tuned. The contents of the tube were then thawed and shaken once or twice and the spectrum was recorded within several minutes.

Estimates of the lifetimes of the paraffins were made by comparing their spectra with calculated line shapes of exchanged broadened multiplets.[3]

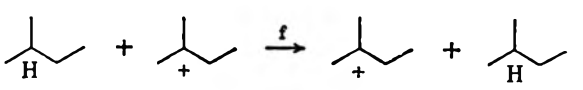
These estimates are tabulated in Table II and the behavior of the hydrocarbons is discussed below.

TABLE II

LIFETIME OF HYDROCARBONS IN 0.5 *M* ALUMINUM BROMIDE–1,2,4-TRICHLOROBENZENE, 0.1 *M* WATER

Compound	Registry no.	Lifetime, sec
Isobutane	75-28-5	>0.8
Isopentane	78-78-4	>0.8
2,3-Dimethylbutane	79-29-8	0.7
3-Methylpentane	96-14-0	0.7
2-Methylpentane	107-83-5	
2,4-Dimethylpentane	108-08-7	>0.7
2,2,3-Trimethylbutane	464-06-2	>0.7
2,2,4-Trimethylpentane	540-84-1	0.5
2,3,4-Trimethylpentane	565-75-3	?
Methylcyclopentane	96-37-7	0.13
Methylcyclohexane	108-8 2	?

Isopentane.—Isopentane gave a slightly broadened spectra. The half-widths of the methyl doublet increased about 10% while the doublet separation decreased very slightly. The lifetime of isopentane is roughly about 0.8 sec. Broadening of the spectrum is postulated as due to intermolecular hydride transfer, eq 2.



(2)

It is also assumed that the spectrum of isopentane is unaffected by the presence of a low concentration of reactive *t*-amyl ions. Any intramolecular rearrangements which the ion may undergo before being trapped as isopentane should have no sensible effect on the spectrum. Isopentane slowly isomerizes to *n*-pentane with this catalyst but the *n*-pentane concentration is negligible during the nmr scan.

(3) Tables of Exchange Broadened NMR Multiplets, Technical Note 2, Contract No. AF 61 (052)-03, Weizmann Institute, Rehovoth, Israel, 1961.

2,3-Dimethylbutane.—The spectrum of this hexane is substantially broadened and some isomerization is noticeable. Isomerization appears to be considerably slower than hydride transfer because the lifetime of 2,3-dimethylbutane is short and it would be expected to reach at least a pseudoequilibrium with the methylpentanes in moments if ionic rearrangements were facile. The average lifetime of 2,3-dimethylbutane is estimated as ~0.7 sec.

2-Methylpentane and 3-Methylpentane.—2-Methylpentane's spectrum undergoes moderate change. There is some broadening and a decided shift in the intensity of the alkyl bands upon reaction of 3-methylpentane with the catalyst. It is apparent that 2- and 3-methylpentane are rapidly interconverting so that one observes the spectra of an equilibrating system containing predominantly 2-methylpentane.

It does not seem possible to decide upon the relative rates of the intermolecular hydride transfer and the intramolecular isomerization paths from this spectrum as both processes are fast on the nmr time scale. It is interesting to note that isomerization to 2,3-dimethylbutane does not occur so rapidly as the methylpentane equilibration. Thus there must be substantial barrier to rearrangement to the 2,3-dimethylbutyl cation.

2,3,3-Trimethylbutane.—Triptane's nmr spectrum broadens upon contact with the aluminum bromide–1,2,4-trichlorobenzene catalyst. Isomerization is difficult to detect and the spectrum gives little evidence of reactions other than hydride transfer. Rearrangement of the ion, if it were occurring, would not affect the spectra. The observed broadening is interesting because it suggests that steric barriers to the hydride-transfer reaction are not prohibitive in what might have been expected to be a rather strained transition state.

2,4-Dimethylpentane.—This paraffin appears to isomerize rapidly upon contact with the catalyst. As with the methylpentanes it is not possible to decide which reaction may be rate determining.

2,2,4-Trimethylpentane and 2,3,4-Trimethylpentane.—Both octanes undergo immediate reaction with the aluminum bromide–1,2,4-trichlorobenzene catalyst. The nmr spectrum changes rapidly upon contact of the reactants and products recovered from the solution indicated that extensive isomerization and cracking had occurred.

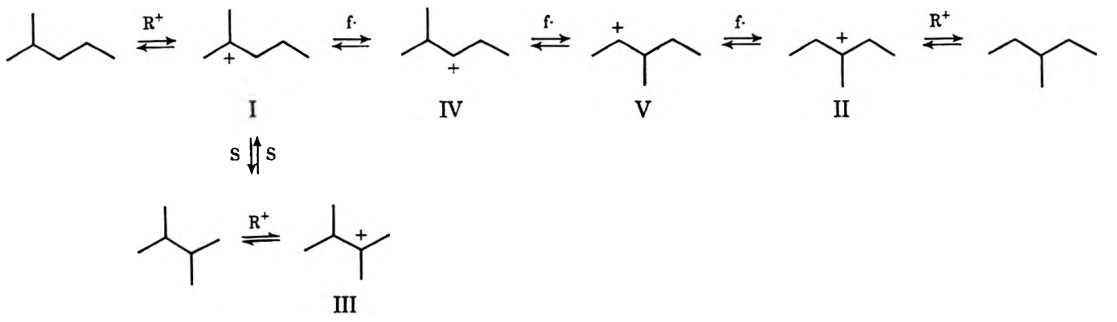
Methylcyclopentane.—The methyl doublet of methylcyclopentane broadens substantially and hydride transfer is clearly faster than rearrangement to a cyclohexyl ion. Cyclohexane is the favored isomer at equilibrium but rearrangement to the secondary ion is evidently slow. The lifetime of methylcyclopentane is estimated at 0.13 sec.

Methylcyclohexane.—The spectrum of this compound is very slightly altered. The main changes appear to be shifts in the relative intensities of the methylene proton bands, although some broadening of the methyl doublet can also be seen.

Discussion

Hydride transfer between tertiary cations and paraffins containing tertiary C–H bonds thus appears to be a generally rapid reaction leading to the nearly instantaneous conversion of paraffins into ions. Many of the

SCHEME I



cations recapture hydride ions before rearranging but those which can isomerize by simple 1,2-hydride and alkyl shifts to other tertiary cations without undergoing a change in branching do so with surprising ease. In the latter case it is not possible to decide if hydride transfer or the rearrangement is rate determining as both reactions are rapid on the nmr time scale and one observes an equilibrium mixture of the participating isomers.

These observations lead to Scheme I for the interconversion of hexanes over the water-promoted aluminum bromide–1,2,4-trichlorobenzene system. Either 2- or 3-methylpentane may be converted into a tertiary cation *via* a rapid bimolecular hydride transfer to another ion in the system. The newly formed ion may isomerize by rapid intramolecular hydride and methide shifts to an equilibrium mixture of secondary and tertiary cations.

Conversion of the methylpentyl cations into the 2,3-dimethylbutyl cation or the reverse, however, is slower than either of the previous reactions. Thus the rate-determining process in isomerizing methylpentanes to 2,3-dimethylbutane is the rearrangement of the methylpentyl cations, not their formation. The slow step in the reverse reaction must necessarily lie in the isomerization of the 2,3-dimethylbutyl cation to the same transition state reached in the forward reaction and thus it is not surprising that this rearrangement is also more difficult than intermolecular hydride transfer.

It should be noted that the solutions studied contained equal volumes of the hydrocarbons and the catalyst. These solutions lead to the nearly instantaneous equilibration of 2-methylpentane and 3-methylpentane at ambient conditions. Isomerizations requiring more involved skeletal rearrangements are much slower. Thus, isobutane, isopentane, and the methylpentanes do not readily isomerize to *n*-paraffins, although there is no difficulty in forming the tertiary cations. The problem with isobutane may be that a primary isobutyl cation is too highly energetic relative to *t*-butyl but the *t*-amyl and methylpentyl ions should have little difficulty on energetic grounds of forming secondary *n*-alkyl cations. That these rearrangements are slow implies the existence of an energy barrier between the tertiary and secondary ions substantially exceeding the difference in stability of the product ions.

Secondary Ion Sources.—All of the paraffins containing tertiary C–H bonds thus appear readily to undergo reactions leading to the formation of cations and to participate in rapid long-term intermolecular hydride-transfer reactions with them. Hydrocarbons which are secondary ion precursors, however, generally appear to react more slowly with the same catalyst, Table III. Thus normal butane, pentane, and hexane show few spectral changes. The latter compounds undergo a slow isomerization, but *n*-butane does not form isobutane at a significant rate. It would be interesting to see if *n*-butane-1-^{13}C isomerizes to *n*-butane-2-^{13}C, but this has not been investigated in trichlorobenzene. In other systems this isomerization proceeds faster than the conversion of *n*-butane into isobutane.[4-6] The apparent reluctance of *n*-paraffins to react more readily is probably due to both the difficulty of generating a sufficiently high concentration of secondary ions and the existence of barriers to their rearrangement.

TABLE III

BEHAVIOR OF SECONDARY ION PRECURSORS

Compound	Observation
n-C_4H_{10}	Relative changes in CH_2 fine structure and the chemical shift
n-C_5H_{12}	Difficult to see a change initially. Sample is heavily isomerized to *i*-C_5H_{12} after 72 hr
n-C_6H_{14}	Spectra may be sharper initially, but after 72 hr *n*-hexane is heavily reacted
$C_yC_5H_{10}$	Little change is seen
$C_yC_6H_{12}$	Little change in initial sample. Some isomerization in 72 hr
$C_yC_7H_{14}$	Considerable isomerization to MC_yC_6 upon mixing
$C_yC_8H_{16}$	Isomerizes upon contact
Norbornane	No detectable change
Bicyclo[2.2.2]octane	Extremely reactive. An equilibrium product composition seems to be present upon contact

Cyclic compounds show more signs of reaction, particularly large-ring compounds which can undergo exothermic rearrangements to alkylcyclohexanes. Thus, while cyclopentane appears unreactive and cyclohexane slowly isomerizes to methylcyclopentane, cycloheptane and cyclooctane react and isomerize upon contact with the catalyst. Bicyclo[2.2.2]octane which also ought to generate a secondary ion capable of isomerizing to a more stable tertiary structure undergoes immediate isomerization at a rapid rate. The half-lives of the latter compounds appear to be on the order of minutes

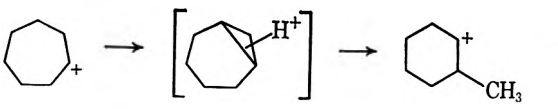
(4) D. M. Brouwer and J. M. Oelderik, *Rec. Trav. Chim. Pays-Bas*, **87**, 732 (1968).

(5) J. W. Otvos, D. P. Stevenson, C. D. Wagner, and O. Beeck, *J. Chem. Phys.*, **16**, 745 (1948).

(6) M. Saunders, E. L. Hagen, and J. Rosenfeld, *J. Amer. Chem. Soc.*, **90**, 6882 (1968).

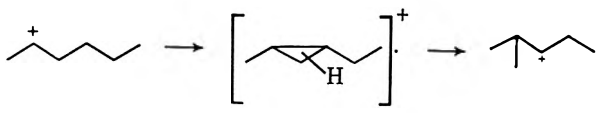
or less which suggests that hydride transfer from the naphthene to either secondary or tertiary ions is facile. It should be noted that, if the *n*-paraffins also had half-lives of this magnitude, essentially no broadening would have been detected with them.

Rearrangement of cycloheptane presumably occurs through a protonated cyclopropane intermediate or transition state without the formation of a primary ion (eq 3). A similar mechanism can be written for sec-



(3)

ondary hexyl ions but rearrangement in this case is relatively slow (eq 4). It is not clear if the apparent



(4)

difference in reactivity of cycloheptane and the *n*-paraffins is due primarily to a difference in ease of ion formation or in behavior of the ion once formed.

There is no obvious reason why hydride transfer from cyclopentane to cyclopentyl ions should be any more difficult than transfer from cycloheptane to a cycloheptyl or methylcyclohexyl ion. Similarly there is no reason why *n*-butane or *n*-hexane should be reacting at much different rates than the cycloparaffins. Thus it is likely that the half-lives for all of these compounds are similar and of the order of minutes. If this is so, then the slow isomerization of *n*-butane, *n*-pentane, and *n*-hexane ought to be attributed to a relatively high activation energy for rearrangement of the secondary ion.

The behavior of secondary ion precursors may consequently be explained by assuming that (a) it is difficult to generate secondary cations whose steady-state concentration is appreciably lower than that of tertiary ions obtained from branched paraffins and that (b) branching of the secondary ion has a high energy barrier. The intermediacy of secondary ions is best seen by examining systems where rearrangement to a tertiary cation can take place easily. Such systems are found with large cycloparaffins. It is not obvious why larger barriers exist for the rearrangement of *s*-alkyl ions but the rearrangement of *n*-paraffins is generally slow. A tentative reason for this may be that the alkyl cations rearrange through the intermediacy of protonated cyclopropanes whose formation requires a relatively free cation. The cation–anion interaction in this solvent may be sufficiently strong to prevent the rearrangement unless the cation is predisposed to cyclize. Such a situation is favored where a secondary ion is generated on a naphthene since cyclization is favored by the relatively rigid framework and is subject to little steric interference by either an anion or solvent.

In summary it has been found that long-chain hydride-transfer reactions between paraffins containing tertiary C–H bonds and tertiary cations occur readily over a water-promoted aluminum bromide catalyst in 1,2,4-trichlorobenzene. The ions may undergo rapid intramolecular rearrangements which do not lead to a change in the degree of branching. Normal paraffins and naphthenes generally react more slowly, although naphthenes which can rearrange to more stable products do so easily.

Registry No.—Aluminum bromide, 7727-15-3; 1,2,4-trichlorobenzene, 120-82-1.

Anodic Oxidations. V. The Kolbe Oxidation of Phenylacetic Acid and 1-Methylcyclohexaneacetic Acid at Platinum and at Carbon

SIDNEY D. ROSS AND MANUEL FINKELSTEIN

Sprague Research and Development Center, North Adams, Massachusetts 02147

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The Kolbe oxidations of phenylacetic acid and 1-methylcyclohexaneacetic acid have been studied at both platinum and carbon anodes. At platinum, the products are derived from both free-radical and cationic intermediates, with products resulting from free radicals predominating. At a carbon anode, almost all of the products result from the generation of carbonium ions at the electrode. It is suggested that this unique ability of a carbon anode to promote the generation of carbonium ions is due to the presence within carbon of paramagnetic centers which bind the initially formed radicals, impede their desorption, and, therefore, promote a second electron transfer.

The remarkable effect on the product composition in the Kolbe reaction that results from substituting a carbon anode for the usual platinum electrode was first reported by Koehl.[1] In the case of acetate oxidation, for example, the anodic products are ethane and carbon dioxide on platinum, but almost entirely methyl acetate on carbon. The product composition in this Kolbe oxidation, as well as in others that have been studied,[1] has been rationalized by assuming that, except for special substrates where the greater stability of the carbonium ion compared with its related free radical affords driving force for a second electron transfer,[2] the predominant reaction mode on platinum is a one-electron transfer to give free-radical, product-forming intermediates. On carbon, on the other hand, the preferred reaction path appears to be a two-electron transfer at the anode to give cationic, product-forming intermediates.

(1) W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **86**, 4686 (1964).

(2) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanora, Jr., and E. J. Kaiser, *ibid.*, **82**, 2645 (1960); E. J. Corey and J. Casanova, Jr., *ibid.*, **85**, 165 (1963).

This distinction between carbon and platinum electrodes is also observed in more complex anodic oxidations. In the oxidation of cyclooctatetraene in acetic acid containing acetate ion,[3] the methyl-substituted products, which are obtained on platinum and which must result from methyl radicals generated at the anode, are not found with a carbon electrode. We have previously suggested[4] that the significant difference between platinum and carbon anodes may reside principally in the fact that the latter contain numerous paramagnetic centers which strongly attach any radicals formed, present a barrier to their desorption, and thus promote further oxidation to carbonium ions.

In the present investigation, evidence in support of this hypothesis has been sought by studying the Kolbe oxidation of phenylacetic acid and 1-methylcyclohexaneacetic acid on both platinum and carbon anodes. As will be elaborated subsequently, the results also have some bearing on the still controversial question of whether the free radicals generated at the anode are transformed into products while still adsorbed on the electrode[5] or after desorption from the electrode into the solution.[6]

Results

The Kolbe reactions of the two acids chosen for investigation, phenylacetic acid and 1-methylcyclohexaneacetic acid, have both been studied previously, but only with platinum anodes. Phenylacetic acid was oxidized electrochemically, first in methanol and pyridine by Fichter and Stenzl,[7] and later in methanol alone by Linstead, Shephard, and Weedon.[8] In both studies, the major product, formed in yields of approximately 50%, was bibenzyl, the normal Kolbe product resulting from coupling of benzyl radicals. This reaction is of particular interest because the intermediate benzyl radical has a relatively low ionization potential (7.76 eV),[9] and it seems relatively certain that the potential required to oxidize phenylacetic acid would be more than high enough to effect the further oxidation of a benzyl radical to a benzyl cation.

The anodic oxidation of 1-methylcyclohexaneacetic acid was first studied in methanol solution by Muhs.[10] The major product was the Kolbe dimer, 1,2-bis(1-methylcyclohexyl)ethane, obtained in 58% yield. Also obtained were 1-methylcycloheptene (11%) and 1-methyl-1-methoxycycloheptane (13%), two products in which the carbon skeleton has been rearranged and which almost certainly involve cationic precursors.

In the present investigation, the anodic oxidation of phenylacetic acid was studied in methanol, in 67% methanol–33% pyridine (by volume), and in 67% water–33% pyridine (by volume). In each experiment, 0.1 mol of substrate in 150 ml of solvent was oxidized, and 2 ± 0.2 equiv of charge/mol of phenylacetic acid was passed through the solution. In the oxidations in methanol and 67% methanol–33% pyridine, 0.5 g of sodium was used to partially convert the acid to its sodium salt, and the current was maintained at 2.0 A in methanol and at 1.0 A in 67% methanol–33% pyridine during the electrolysis. In 67% water–33% pyridine, it was not necessary to partially convert the acid to its sodium salt to obtain sufficient conductivity, and these solutions were electrolyzed at 2.0 A. In the absence of pyridine, the anode becomes coated and must be cleaned periodically. The addition of pyridine obviates this difficulty and permits the entire electrolysis to be run without interruption for electrode cleaning.

The products obtained in these oxidations are listed in Tables I–III. Only bibenzyl and toluene are clearly formed from benzyl radicals generated at the anode. The origin of methyl phenylacetate is uncertain. In a control experiment, an electrolysis solution in methanol left standing at room temperature for 24 hr without voltage applied was found to contain 0.094 g (0.00063 mol) of the ester by vpc. Such esterification would only account for a small part of the methyl phenylacetate found on electrolysis in methanol and is a much less probable reaction in 67% methanol–33% pyridine. It is an intriguing but unproven possibility that the ester arises, at least in part, from anodic oxidation of molecu-

Table I

Products Obtained on Anodic Oxidation of 0.1 Mol of Phenylacetic Acid in Methanol

Product	Moles at Pt	Moles at C
Bibenzyl	0.0132	0.0047
Benzyl methyl ether	0.0151	0.0278
Toluene	0.00065	0.00033
Benzaldehyde dimethylacetal	0.00066	0.0014
Methyl phenylacetate	0.0028	0.0048
Benzyl alcohol	0.0024	0.0041

Table II

Products Obtained on Anodic Oxidation of 0.1 Mol of Phenylacetic Acid in 67% Methanol–3% Pyridine

Product	Moles at Pt	Moles at C
Bibenzyl	0.0162	0.0000
Benzyl methyl ether	0.0135	0.0405
Toluene	0.00044	0.00040
Methyl phenylacetate	0.0036	0.0050
Benzyl alcohol	0.0036	0.0060
Phenylacetic acid (recovered)	0.0022	0.0012

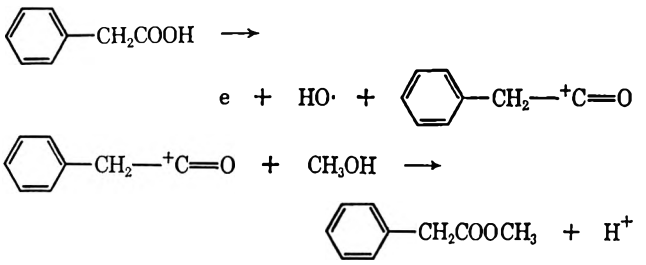
Table III

Products Obtained on Anodic Oxidation of 0.1 Mol of Phenylacetic Acid in 67% Water–33% Pyridine

Product	Moles at Pt	Moles at C
Bibenzyl	0.0068	0.0000
Benzyl alcohol	0.0104	0.0240
Benzaldehyde	0.0075	0.0018
Toluene	0.0004	0.0000

(3) L. Eberson, K. Nyberg, M. Finkelstein, R. C. Petersen, S. D. Ross, and J. J. Uebel, *J. Org. Chem.*, **32**, 16 (1967).
(4) S. D. Ross, *Trans. N. Y. Acad. Sci.*, **30**, 901 (1968).
(5) B. E. Conway and A. K. Vijh, *Electrochim. Acta*, **12**, 102 (1967); *Z. Anal. Chem.*, **224**, 149, 160 (1967).
(6) L. Eberson, *Acta Chem. Scand.*, **17**, 2004 (1963); *Electrochim. Acta.*, **12**, 1473 (1967).
(7) Fr. Fichter and H. Stenzl, *Helv. Chim. Acta*, **22**, 976 (1939).
(8) R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, *J. Chem. Soc.*, 3624 (1952).
(9) A. G. Harrison, P. Kebarle and F. P. Lossing, *J. Amer. Chem. Soc.*, **83**, 777 (1961).
(10) M. A. Muhs, Ph.D. Thesis, University of Washington, 1954; *Dissertation Abstr.*, **14**, 765 (1954).

lar phenylacetic acid and involves an acylium ion as an intermediate, as shown below. All other products are



best rationalized as primary products resulting from benzyl cations or as secondary products formed by further oxidation of these primary products.

In all three solvents, the anodic oxidations are accompanied by extensive tar formation. The products observed on both platinum and carbon anodes with methanol as solvent account for 48% of the starting acid. In 67% methanol–33% pyridine, 56% of the starting acid is accounted for with a platinum anode and 52% with the carbon electrode. In 67% water–33% pyridine, the conversion to identifiable products is very much lower, 32% on platinum and 26% on carbon.

A more significant distinction becomes apparent when the observed products are divided, in each case, into those resulting from free-radical intermediates and those derived from carbonium-ion intermediates. Table IV tabulates the ratios, moles of free-radical products/moles of ionic products, for each experiment. In this work, the observed number of moles of bibenzyl has in every case been multiplied by two, as this product results from the coupling of two benzyl radicals. It is clear from Table IV that, compared with a platinum anode, a carbon anode strongly suppresses or eliminates those products which result from radical intermediates.

TABLE IV

RELATIVE AMOUNTS OF FREE-RADICAL AND IONIC PRODUCTS ON THE ELECTROCHEMICAL OXIDATION OF PHENYLACETIC ACID

Solvent	Anode	Moles of free-radical products / moles of ionic products
Methanol	Pt	1.3
Methanol	C	0.26
67% Methanol–33% pyridine	Pt	1.4
67% Methanol–33% pyridine	C	0.0076
67% Water–33% pyridine	Pt	0.78
67% Water–33% pyridine	C	0.00

The Kolbe oxidation of 1-methylcyclohexaneacetic acid was studied in 67% methanol–33% pyridine at both platinum and carbon anodes. In these experiments, 0.1 mol of the acid in 150 ml of solvent was oxidized at a constant current of 1 A until 2 ± 0.1 equiv of charge had passed through the solution. Before electrolysis, the acid in these solutions was partially converted to its sodium salt with 0.5 g of sodium.

The availability of vpc has made it possible to determine some of the minor as well as the major products formed in these reactions. All of these products are shown in Table V. The 1,2-bis(1-methylcyclohexyl)-ethane and the 1,1-dimethylcyclohexane result from the generation of 1-methylcyclohexylmethyl radicals at the

TABLE V

PRODUCTS OBTAINED ON ANODIC OXIDATION OF 0.1 MOL OF 1-METHYLCYCLOHEXANEACETIC ACID IN 67% METHANOL–33% PYRIDINE

Product	Moles at Pt	Moles at C
1,2-Bis(1-methylcyclohexyl)ethane	0.0204	0.00067
1-Methylcycloheptene and/or 1-ethylcyclohexene[a]	0.00681	0.0276
1-Methyl-1-methoxycycloheptane	0.00474	0.0214
1-Ethyl-1-methoxycyclohexane	0.00294	0.0121
Methyl 1-methylcyclohexaneacetate	0.00025	0.0000
1,1-Dimethylcyclohexane	0.00062	0.00018
1-Methyl-1-methoxymethylcyclohexane	0.0000	0.00021
1-Methylcyclohexaneacetic acid (recovered)	0.0286	0.0069

[a] Not separated by vpc.

anode. Methyl 1-methylcyclohexaneacetate may, as in the formation of methyl phenylacetate from phenylacetic acid, be the result of anodic oxidation of the acid to give the corresponding acylium ion. The remaining observed products are best interpreted as resulting from the generation at the anode of the 1-methylcyclohexylmethyl cation, and the spectrum of the found products, both with rearranged and unrearranged carbon skeletons, is typical of carbonium-ion reactions. Since spiro[2.5]octane is a possible product from this carbonium ion, particularly if the ion is present in an unsolvated or "hot" state, it was prepared independently, and its presence was sought in the electrolysis product. However, it was not present in detectable amount.

In these reactions, tar formation was much less extensive, and it was possible to account for 77% of the starting acid with the platinum electrode and 67% of the starting acid with the carbon anode. At the platinum electrode, 74% of the observed products are formed from radical intermediates and 26% are from ionic precursors. At carbon, only 2% of the products result from free radicals, and 98% have their origin in carbonium ions. In this system, too, the carbon electrode shows a remarkable ability to divert the Kolbe reaction from its normal, preferred free-radical path and favors the generation of cationic intermediates.

Experimental Section

Materials and Reference Compounds.—The following compounds were prepared by procedures given by Muhs.[10]

1-Methylcyclohexaneacetic acid: bp 65–70° (0.04 mm); $n^{23}D$ 1.4682.

Methyl-1-methylcyclohexylmethyl ether: bp 39–40° (30 mm); $n^{23}D$ 1.4408.

Methyl-1-methylcyclohexaneacetate: bp 86–91° (13 mm); $n^{24}D$ 1.4507.

Methyl 1-ethylcyclohexyl ether: bp 72–80° (35 mm); $n^{25}D$ 1.4462.

Methyl 1-methylcycloheptyl ether: bp 60–61° (14 mm); $n^{26}D$ 1.4507. This structure was confirmed by nmr, which showed three peaks with area ratios of 3.06:12.4:2.99.

1,1-Dimethylcyclohexane and 1-methylcycloheptene were obtained from the Aldrich Chemical Co.

1,2-Bis(1-methylcyclohexyl)ethane was isolated by distillation from a Kolbe oxidation of 1-methylcyclohexaneacetic acid in methanol: bp 73–75° (0.06 mm); $n^{23}D$ 1.4796. The nmr spectrum showed three peaks with area ratios of 10.7:1.95:2.85.

1-Methylcyclohexanemethanol, bp 75–77° (14 mm), $n^{19}D$ 1.4683, was prepared by the lithium aluminum hydride reduction

of 1-methylcyclohexanecarboxylic acid, prepared according to Baumgarten, Bower, and Okamoto.[11]

Spiro[2.5]octane, n^{24}D 1.4458, was prepared from bis(bromomethyl)cyclohexane[12] by the procedure of Boord, *et al.*[13] The diol required for the above dibromide preparation was made by the method of Bergson and Biezais.[14]

Electrolyses.—The electrolysis cell and electrode assemblies are those previously described and used in the electrochemical oxidation of cyclooctatetraene at constant current.[3] The following two procedures, one with phenylacetic acid and one with 1-methylcyclohexaneacetic acid, are typical of those used.

Electrolysis of Phenylacetic Acid in 67% Methanol–33% Pyridine.—Sodium (0.5 g) was allowed to react with methanol (100 ml), and pyridine (50 ml) and phenylacetic acid (13.6 g, 0.1 mol) were added to this solution. The electrolysis, in this case with a platinum anode, was at a constant current of 1 A until 18,600 C of charge had passed through the solution. The crude electrolysis mixture was taken up in water (750 ml) and extracted with four 250-ml portions of ether. The combined ether extracts were extracted first with a solution of potassium hydroxide (6 g) in water (150 ml), then in three portions with a solution of concentrated hydrochloric acid (50 ml) in water (250 ml), and finally with water. The ether solution was dried over anhydrous magnesium sulfate and then concentrated to a volume of 50 ml for analysis by vpc.

The combined aqueous layers were made strongly acidic and extracted with two 250-ml portions of ether. The ether extract was dried over magnesium sulfate, the solvent was removed at the water pump, and the crude product was crystallized from hexane, yielding 0.3 g of recovered phenylacetic acid.

Electrolysis of 1-Methylcyclohexaneacetic Acid in 67% Methanol–33% Pyridine at a Platinum Anode.—Sodium (0.5 g) was allowed to react with methanol (100 ml). Pyridine (50 ml) and 1-methylcyclohexaneacetic acid (15.6 g, 0.1 mol) were added, and the solution was electrolyzed at 1.0 A until 21,400 C of charge had passed through the solution. The electrolysis mixture was poured into water (1 l.), and, after addition of salt, was extracted four times with a total of 1 l. of ether. The ether solution was extracted twice with 200-ml portions of hydrochloric acid (160 ml of concentrated acid in 250 ml of water), then with water, then with two 100-ml portions of 10% sodium hydroxide solution, and finally with water again. The ether solution was dried over anhydrous magnesium sulfate and concentrated to 50 ml for analysis by vpc.

All of the aqueous extracts were combined, giving a strongly acidic solution. This was extracted twice with 200-ml portions of benzene. The benzene solution was dried, and the benzene was removed at the water pump. The residue was converted to the methyl ester *via* the acid chloride, and this was analyzed by vpc as a measure of unreacted 1-methylcyclohexaneacetic acid.

Analysis by Vpc.—All of the vpc analyses were carried out with a Perkin-Elmer Model 154B vapor fractometer using helium as the carrier gas. All of the products formed in the oxidation of phenylacetic acid as well as the 1,2-bis(1-methylcyclohexyl)ethane and the methyl 1-methylcyclohexaneacetate were determined with a Perkin-Elmer large-diameter Golay column (0.06 in. × 300 ft) in which the stationary phase was Ucon polyglycol LB-550-X. The remaining products were determined on a Perkin-Elmer A column, 2 m in length, in which the solid support is diatomaceous earth and the liquid substrate is diisodecyl phthalate. In all cases, the unknown solutions were compared with standards prepared from the identified components.

Isolation of Bibenzyl.—The ether solution of the products from the oxidation of phenylacetic acid in 67% methanol–33% pyridine at a platinum anode was distilled at the water pump, with the heat supplied by a bath at 85°, to remove volatile substances. The residue was dissolved in hexane, and the bibenzyl was isolated by column chromatography. The yield was 2.51 g, mp 49–50.5° after crystallization from methanol. Analysis by vpc of this same ether solution had indicated the presence of 2.96 g of bibenzyl.

Isolation of Methyl 1-Ethylcyclohexyl Ether.—The ether solution of products from the electrolysis of 1-methylcyclohexaneacetic acid at a carbon anode was separated on a Model A-700 Aerograph Autoprep fitted with a column 20 ft × $^3/_8$ in., packed with 30% SE-30 on 45–60 Chromosorb W. The temperature was 200°. The substance separated had $n^{23.5}$D 1.4506 and was shown to be pure by analytical vpc on the Golay column, where it had the same retention time as authentic methyl 1-ethylcyclohexyl ether.

Discussion

The differences in the course of the Kolbe reaction on platinum and on carbon anodes are large and significant. At platinum, both free radicals and carbonium ions are generated, but the preferred reaction path is one in which the products result from the former type of intermediate. On a carbon anode, the latter type of intermediate is strongly favored, the formation of products attributable to free-radical intermediates is largely suppressed, and the yields of Kolbe coupling products are very low.

The present results with both phenylacetic acid and 1-methylcyclohexaneacetic acid are fully in accord with the above generalizations. They are also completely consistent with our previous suggestion[4] that the unique characteristic of a carbon electrode is the presence within it of numerous paramagnetic centers which bind anodically generated free radicals, impede their desorption into the solution, and, therefore, promote a second electron transfer to give a carbonium ion. The presence of such paramagnetic centers in carbons and graphites is well documented.[15] For an anodically formed radical, *e.g.*, $CH_3\cdot$, chemisorbed on the electrode, M, through an M–CH_3 bond, it can be shown that the M–CH_3 bond energy, as calculated by Pauling's procedure, is not significantly different when M is platinum or carbon, if one neglects the presence of paramagnetic centers on carbon.[16] It is, therefore, reasonable and even probable that the striking differences observed with carbon and platinum electrodes are due to the presence of paramagnetic centers in the former.

If one adopts Conway's hypothesis,[5] the first step in the reaction on platinum is a one-electron transfer at the anode to give a radical adsorbed on the electrode. The radical thus generated may react with another adsorbed radical to give the coupling product, or with another appropriate molecule in a hydrogen-transfer reaction (*e.g.*, to form toluene from the benzyl radical), with both reactions occurring while the radicals are still adsorbed on the electrode. Alternatively, the radical may transfer a second electron to the electrode to give a cation which will be driven from the anode by electrostatic forces and will react in the solution. The partitioning of the final products into free-radical products and carbonium-ion products will be determined by this competition, largely one of radical dimerization on the electrode surface *vs.* a second electron transfer. In accordance with the above, the different results observed on a carbon electrode might be attributed to the fact that the paramagnetic centers on carbon bind the initially generated radicals more strongly, make the radical dimerization reaction energetically more unfavorable, and, thus, promote carbonium-ion formation.

(11) H. E. Baumgarten, F. A. Bower, and T. T. Okamoto, *J. Amer. Chem. Soc.*, **79**, 3145 (1957).

(12) E. R. Buchman, D. H. Deutsch, and G. I. Fujimoto, *ibid.*, **75**, 6228 (1953).

(13) R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *ibid.*, **70**, 946 (1948).

(14) G. Bergson and A. Biezais, *Arkiv Kemi*, **22** (35) 475 (1964); *Chem. Abstr.*, **63**, 6996 (1965).

(15) See D. J. E. Ingram in "Chemisorption," W. E. Garner, Ed., Academic Press Inc., New York, N. Y., 1957, p 260, and references cited therein.

(16) Unpublished results by Dr. A. K. Vijh of these laboratories.

In Eberson's picture of the mechanism,[6] all of the product-forming reactions, both those involving free radicals and those involving ionic intermediates, occur in the solution. The initial step is, again, a one-electron transfer to give a radical, which may then either transfer a second electron or be desorbed from the anode surface. The product distribution will now be determined by this competition between radical desorption and electron transfer. If this view is correct, the carbon electrode favors carbonium-ion products, because the paramagnetic centers impede radical desorption and, therefore, favor electron transfer.

In the reactions now under consideration, it must be assumed that the applied potentials are sufficiently high to permit a second electron transfer from the initially generated radicals, since carbonium-ion products would not be observed on both platinum and carbon if this were not the case. If the radicals all react while adsorbed on the electrode and if the applied potential is supplying sufficient activation energy to permit a second electron transfer, it is difficult to see how radical dimerization can compete successfully with electron transfer, as it does at a platinum anode. The bimolecular, coupling reaction might be expected to have both an unfavorable enthalpy and entropy of activation. Even though the activation energy for radical dimerization in solution is normally low, in this case one must, in addition, overcome the energy by which the two radicals are held on the electrode surface. The entropy of activation might also be expected to be negative, since in addition to being detached from the electrode surface the two radicals will probably require a change in orientation with respect to the electrode before they will be able to attain a configuration suitable for coupling. The radical dimerization reaction is, moreover, a purely chemical process, and the necessary free energy of activation cannot be supplied electrochemically as it is for the electron-transfer reaction.

The Eberson picture of the Kolbe reaction obviates these difficulties. On platinum, the radicals generated are largely desorbed from the electrode, perhaps in a concerted process with elimination of carbon dioxide from an initially generated acyloxy radical. On carbon, the additional binding forces that are available attach the bulk of the radicals generated to the electrode surface, and these undergo a second electron transfer to give a cation. The present results afford some support for this interpretation even if they fall short of proving it.

Registry No.—Phenylacetic acid, 103-822; 1-methylcyclohexaneacetic acid, 14352-58-0.

Slow Rotations in Some Substituted Anilides[1]

T. H. SIDDALL, III, AND W. E. STEWART

Savannah River Laboratory, E. I. du Pont de Nemours and Company, Aiken, South Carolina 29801

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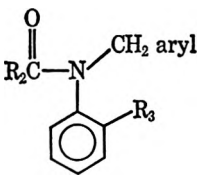
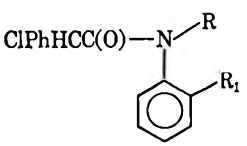
Barrier heights (kilocalories per mole) for rotation around the nitrogen–benzene bond are reported for 19 anilides of the type

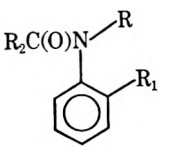


The only amide isomer observed is as shown, with the *ortho*-substituted benzene ring *trans* to oxygen (except for formanilides). However, rotation around the nitrogen–benzene bond is preceded by rotation around the carbonyl–nitrogen bond to give the activated state. Variations in barrier height from compound to compound are rationalized in terms of steric and electronic factors.

We have reported[2] the effects of various substituents, R and R_1, on the rate of rotation around the nitrogen–benzene bond in amides of the type



This paper reports a similar study of amides of the type



where R_2 and R_1 are varied and R is a benzyl (or closely related) group. Data are also included for two thioamides. The rotation rates were determined by signal shape analysis[3] of the nuclear magnetic resonance (nmr) signals (AB quartet) arising from the nonequivalent benzyl methylene protons. These protons are nonequivalent when rotation around the N–C (aromatic) bond is slow on the nmr time scale and give an AB quartet which coalesces into a singlet as rotation becomes rapid.[4–7]

(1) The information contained in this article was developed during the course of work under Contract AT(07-2)-1 with the U. S. Atomic Energy Commission.

(2) T. H. Siddall, III, and W. E. Stewart, *J. Phys. Chem.*, in press.

(3) J. Heidberg, J. A. Weil, G. A. Janusonis, and J. K. Anderson, *J. Chem. Phys.*, **41**, 1033 (1964).

(4) T. H. Siddall, III, and C. A. Prohaska, *J. Amer. Chem. Soc.*, **88**, 1172 (1966).

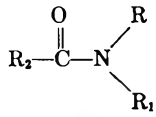
(5) T. H. Siddall, III, *J. Org. Chem.*, **31**, 3719 (1966).

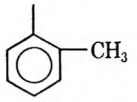
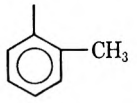
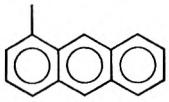
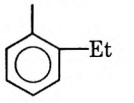
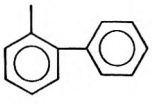
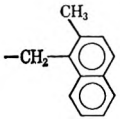
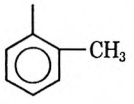
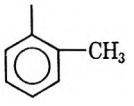
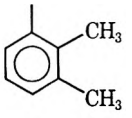
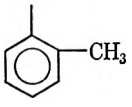
(6) B. J. Price, J. A. Eggleston, and I. O. Sutherland, *J. Chem. Soc., B* 922 (1967).

(7) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967)

TABLE IA

FREE ENERGIES OF ACTIVATION FOR ROTATION AROUND AMIDE BOND AND N—C (AROMATIC) BOND IN



Compd	R	R_1	R_2	ΔF^*, kcal/mol (°C) C(O)—N bond	ΔF^*, kcal/mol (°C) N—C (aromatic) bond	Chemical shift $\nu_A - \nu_B$, at 110°, cps (°C)
I	—CH_2Ph		H	20,[a] 19[b] (*endo* → *exo*) 21,[a] 20[b] (*exo* → *endo*)	13 (−25), *endo*[c] 10 (−80), *exo*[d] 18 (−58), *exo*[d]	11 (−25) 33 (−80)
II (thioamide)	—CH_2Ph		H	22 (*endo* → *exo*) 24 (*exo* → *endo*)	18 (100), *endo* 10 (−70), *exo* (d) 10 (−63), *exo* (d)	6 19 (−70)
III	—CH_2Ph		CH_3		22.6 (143) 22.2 (159)	70
IV	—CH_2Ph		*t*-Butyl		19.5 (110) 19.8 (121) 20.0 (134) 19.7 (144)	92
V	—CH_2Ph		*t*-Butyl		17.5 (80) 17.8 (90) 17.9 (110)	109
VI			CH_3		22.9 (159) 22.8 (168)	30
VII	—CH_2Ph		$(C_6H_5)_2(CH_3)C$—		20.6 (101) 20.0 (110) 20.1 (121) 19.8 (128)	74
VIII	—CH_2Ph		CH_3		23.0 (153) 22.7 (161) 22.9 (162) 22.8 (167) 22.7 (173)	43
IX	—CH_2Ph		$(C_2H_5)_3C$—		19.4 (103) 19.4 (110) 19.6 (117) 19.8 (132) 19.5 (142)	88

[a] Signal shape analysis at 100°. [b] Reequilibration at −13°. [c] In $CDCl_3$. [d] In 50:50 $CDCl_3$–"Freon"-11.

Experimental Section

The amides were prepared by the conventional procedures of (1) adding a mixture of the desired amine plus Et_3N (to combine with HCl) to the appropriate acyl chloride or (2) alkylating the unsubstituted anilide *via* its sodio derivative. The formamide was prepared by distilling a large excess of formic acid from an N-benzyltoluidine mixture. The thio compounds were prepared by refluxing the corresponding amide for about 1 hr with an equal weight of P_2S_5 suspended in toluene, then treating the resulting thioamide adduct with dilute Na_2CO_3 solution. All compounds were purified by distillation under high vacuum. Compounds were purified further in most cases by crystallization from various solvents. Samples were made up of 200 mg of amide plus 500 μl of *o*-dichlorobenzene. The *o*-dichlorobenzene had been freshly passed through a column of Linde 5A Molecular Sieve. The *o*-dichlorobenzene was chosen as a solvent because of its relative inertness, freedom from high field nuclear magnetic resonance signals, and its wide-liquid range. It was suggested to us by the work of Sandström.[8] The loaded nmr tubes were bubbled with and then sealed under nitrogen. For low-temperature work, $CDCl_3$ and a 50–50 mixture of $CDCl_3$ and "Freon-11"[9] were used. Nmr tubes containing these solvents were sealed *in vacuo*.

All nmr spectra were obtained with a Varian A-60 spectrometer that was equipped with the variable temperature accessory. Temperatures were measured with the conventional methanol and glycol "thermometers." These were calibrated against thermocouples. Nmr spectra were obtained at different scan rates and spectrometer settings to obtain the best signal-to-noise ratio, always taking care to avoid saturation.

Results and Discussion

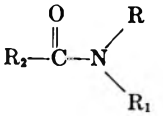
Calculation of Barriers.—The barriers to rotation around the aryl–nitrogen bond in the various com-

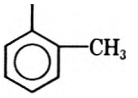
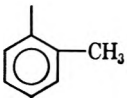
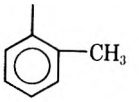
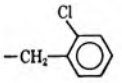
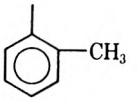
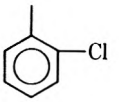
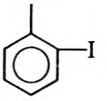
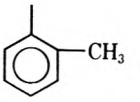
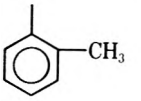
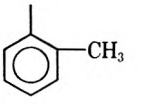
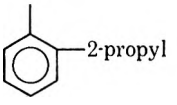
(8) J. Sandström, *J. Phys. Chem.*, **71**, 2318 (1967).

(9) Trademark of Du Pont for its fluorocarbon products.

TABLE IB

FREE ENERGIES OF ACTIVATION FOR ROTATION AROUND AMIDE BOND AND N—C (AROMATIC) BOND IN



Compd	R	R_1	R_2	$\Delta F^{\ddagger}$, kcal/mol (°C) C(O)—N bond	$\Delta F^{\ddagger}$, kcal/mol (°C) N—C (aromatic) bond	Chemical shift, $\nu_A - \nu_B$ at 110°, cps
X	—CH_2Ph		Cl		19.2 (101) 19.5 (110)	27
XI	—CH_2Ph		*t*-Butyl		18.9 (105) 19.1 (105), $CHCl_2CHCl_2$ 18.9 (110) 19.1 (110), $CHCl_2CHCl_2$	81 81, $CHCl_2CHCl_2$
	UO_2Cl_2 adduct of XI in $CHCl_2CHCl_2$				22.1 (123)	98
XII	—CH_2Ph		2-Propyl		20.6 (117) 20.6 (132) 20.7 (142)	52
XIII			CH_3		20.4 (101) 20.0 (110) 20.1 (128)	38
XIV	—CH_2Ph		2-Propyl		19.8 (105) 19.7 (117)	84
XV	—CH_2Ph		CH_3		21.4 (154) 21.5 (161) 21.3 (173)	94
XVI	—CH_2Ph		Cl_3C—		20.0 (105) 20.1 (130) 20.1 (117)	67
XVII (thioamide)	—CH_2Ph		CH_3		>23.5 (170)[a]	60
XVIII	—CH_2Ph		CH_3		20.5 (124) 20.2 (124)[b] 20.0[b] (135)[c] 20.1[d] (142)[e]	44 40
XIX	—CH_2Ph		CH_3		22.6 (172) 22.4 (176)	65

[a] T. H. Siddall, III, and W. E. Stewart, unpublished results. [b] Neat. [c] Reference 7. [d] In nitrobenzene. [e] Reference 6.

pounds were calculated by matching the experimental AB patterns with calculated patterns; the experimental pattern in all cases arose from the nonequivalent methylene protons of the benzyl radical. The calculated spectra were obtained by computer plots of the signal shape equation given by Heidberg, *et al.*[3] The matching of spectra (except in the two cases noted below) was done from plots of signal shape parameters. These parameters were (a) the ratio of signal breadth to chemical shift at 0.2 signal height; (b) the same ratio at 0.6 signal height; (c) the ratio of height of central minimum to signal height maximum (on partly coalesced signals); and (d) the ratio of height of side minima to signal height maxima. At least two parameters were used for each match. Direct visual inspection and matching were also used. A single value of 14.0 cps was used for the AB coupling constant (J), and a single value of $T_2 = 0.11$ was used throughout. All observed J values were within 0.3 cps of 14.0, and T_2 was always within 10% of 0.11, based on observation in the slow exchange region. Since, in all cases (except those noted in Table I), the chemical shift was ≥ 20 cps (in most cases ≥ 40 cps), minor variations in T_2 and J do not affect the results significantly.

The chemical shift decreased with temperature in all cases (up to 3 cps/10°). The chemical shifts used in the calculations were obtained by extrapolation of shifts obtained at low temperature in the slow exchange region. The values at 110° are listed in Tables IA and IB.

Measurements were obtained only over the center region of intermediate exchange. In this region, the experimental spectra are most sensitive to the exchange

TABLE II
PUBLISHED DATA FOR AMIDE BOND ROTATIONAL BARRIERS IN N,N-DIMETHYLAMIDES, $RC(O)NMe_2$

Reference	R	Solution	Method	ΔF^* (T_c, °C)
a	Me	Neat	s.s.	19 (73)
b	Me	Neat	a.s.s.	20.1 (87)
c	Me	Neat	a.s.s.	19 (52)
d	CD_3	Neat	s.s.	18.1 (*75*)
d	CD_3	0.095 mol fraction in $CD_3S(O)CD_3$		18.3 (*75*)
b	Et	Neat	a.s.s.	17.7 (61)
a	Et	Neat	s.s.	18 (54)
e	Et	Neat	a.s.s.	17.6 (62)
e	Et	0.4 mol fraction in CH_2Br_2	a.s.s.	17.7 (60)
		0.1 mol fraction in CH_2Br_2	a.s.s.	18.2 (66)
		0.4 mol fraction in CCl_4	a.s.s.	16.3 (39)
		0.1 mol fraction in CCl_4	a.s.s.	16.6 (44)
a	Pr	Neat	s.s.	18 (57)
f	2-Pr	0.33 mol fraction *o*-$C_6H_4Cl_2$	a.s.s.	16.2 (26)
g	Cl	Neat	s.s.	16.8 (*25*)
b	Cl	Neat	a.s.s.	17.4 (53)
h	Cl	Neat	a.s.s.	16.7 (*25*)
h	Cl	Neat	Spin echo	16.7 (*25*)
e	Cl	Neat	a.s.s.	17.3 (59)
g	Cl	0.1 mol fraction in CCl_4	s.s.	16.3 (*25*)
e	Cl	0.4 mol fraction in CH_2Br_2	a.s.s.	17.4 (59)
e	Cl	0.1 mol fraction in CH_2Br_2	a.s.s.	17.5 (59)
e	Cl	0.4 mol fraction in CCl_4	a.s.s.	15.6 (51)
e	Cl	0.1 mol fraction in CCl_4	a.s.s.	16.8 (51)
b	CCl_3	Neat	a.s.s.	14.7 (14)
a	CCl_3	Neat	s.s.	14 (19)
h	CCl_3	Neat	a.s.s.	15.0 (*25*)
h	CCl_3	Neat	Spin echo	15.0 (*25*)
c	H	Neat	a.s.s.	22 (99)
i	H	0.04 mol fraction in $CHCl_2CHCl_2$	a.s.s.	20.9 (115)
a	H	Neat	s.s.	20 (113)
b	H	Neat	a.s.s.	22.4 (149)
j	H	Neat	a.s.s.	20.8 (*123*)
k	H	In α-chloronaphthalene	a.s.s.	20.6 (128)
l	H	Neat	4 site s.s.	21.0 (118)
m	D	Neat	s.s.	21.8 (126)
n	*t*-Bu	100 λ/500 λ $CDCl_3$	s.s.	11.6 (−36)

[a] C. W. Fryer, F. Conti, and C. Franconi, *Ric. Sci.*, **35**, Series 2, 788 (1965). [b] M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962). [c] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956). [d] R. C. Neuman, Jr. and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968). [e] J. C. Woodbrey and M. T. Robers, *ibid.*, **84**, 13 (1962). [f] G. Isaksson and J. Sandström, *Acta Chem. Scand.*, **21**, 1605 (1967). [g] R. C. Neuman, Jr., D. N. Roark, and V. Jonas, *J. Amer. Chem. Soc.*, **89**, 3412 (1967). [h] A. Allerhand and H. S. Gutowsky, *J. Chem. Phys.*, **41**, 2115 (1964). [i] E. S. Gore, D. J. Blears, and S. S. Danyluk, *Can. J. Chem.*, **43**, 2135 (1965). [j] R. C. Neuman, Jr. and L. B. Young, *J. Phys. Chem.*, **69**, 2570 (1965). [k] A. Mannschreck, A. Mattheus, and G. Rissman, *J. Mol. Spectry.*, **23**, 15 (1967). [l] M. Rabinovitz and A. Pines, personal communication; *J. Amer. Chem. Soc.*, **91**, 1585 (1969). [m] F. Conti and W. Von Phillipsborn, *Helv. Chim. Acta*, **50**, 603 (1967). [n] T. H. Siddall, III, and W. E. Stewart, unpulished results.

rate and least sensitive to the other parameters (T_2, J, chemical shift) and to spectrometer performance. Most of the data were obtained where signal parameter (c) is applicable. For chemical shifts of 20 cps or more, this is the most sensitive and reliable matching parameter. The standard deviation in ΔF^* (the free energy of activation) determined in this region is routinely about ±0.2 kcal/mol.

Within this center span of intermediate exchange, ΔF^* is constant within experimental error. On that basis, and because of the extensive overlap of data for different molecules and the small temperature variation in ΔF^* in a similar situation,[2] ΔF^* values provide a valid comparison of the rotational barriers in these compounds. The close agreement of data for XVIII obtained in this laboratory with published data[6,7] is also encouraging.

Because the chemical shifts for the AB pattern of each of the minor isomers of the formanilides (I and II) are small, these two situations required special consideration. Accurate rates could not be determined, and ΔF^* values are considered to be in error by up to 1 kcal/mol. The chief difficulty is that small variations in chemical shift, J, and T_2 significantly affect the signal shape, even in the central region of intermediate exchange. Physically, this is understandable, because spacing between center peaks approaches $1/T_2$ rapidly as the chemical shift falls below about 12 cps. For small chemical shifts, the shape of the small, wing signals is more sensitive to exchange rate than the center peaks. However, as the shift decreases, the intensity of the wing peaks decreases, and signal-to-noise ratios are very poor. The possibility of extracting more information from the wing peaks is under continued study in this laboratory. The data for the minor isomers in Table I were obtained by moving the temperature control back and forth to locate the coalescence temperature and scanning calculated spectra for the exchange rate at which the signals coalesce.

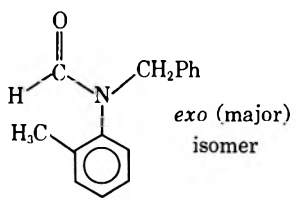
The data (Table II) for rotation around the carbonyl–nitrogen (amide) bond for I and II were obtained by direct, visual matching of computer plots (of Naka-

gawa's[10] formulation of the Gutowsky–Holm equation) with experimental spectra. Since the isomer population ratio, (minor isomer)/(major isomer), was as low as 0.07, these data were also obtained in unfavorable circumstances, causing errors of up to 1 kcal/mol. The signal from the major isomer, below coalescence, and the coalesced signal are both insensitive to the exchange rate. Only the shape of the minor isomer signal is responsive to exchange rate. This leads to unfavorable signal-to-noise ratios in the only part of the spectrum useful for exchange studies. It will also lead to a difficult statistical weighting problem in any computer program designed to match observed and calculated spectra. Both the computational and experimental problems are receiving further study in this laboratory. The barrier for I was also obtained by observing the growth of the methylene signal of the *endo* isomer at $-13°$ when crystalline *exo* isomer was dissolved.[2,11] This rate measurement also suffers from the adverse isomer ratio, but probably is more reliable than the value from signal shape analysis.

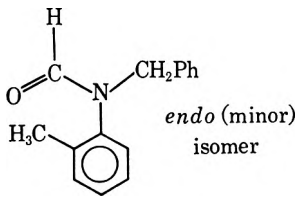
Results for rotation around the aryl–nitrogen bond are tabulated as ΔF^* (the free energy of activation) in Table I. Data for rotation around the carbonyl–nitrogen (amide) bond are given in Table II.

The Formamide (I) and Thioformamide (II).—The data for the formamide (I) and thioformamide (II) appear to be comparatively straightforward and will be discussed first. In both formamides, the minor amide isomer is assigned as the isomer with the benzene ring *cis* to the oxygen (or sulfur) atom (*endo* isomer). The benzene ring is held out of plane with respect to the amide framework. The proximity of the formyl proton to, and in a plane perpendicular to, the benzene ring in the major isomer (*exo* isomer, ring *trans* to the carbonyl oxygen) causes the relative upfield shift of the signal from the formyl proton in this isomer. This reasoning is justified in quantitative detail by Rae.[12]

This assignment is consistent with the observed rotational barriers. For I, the barrier is about 4 kcal/mol larger in the *endo* isomer. This is expected on simple steric grounds. The oxygen atom is "larger" than the formyl proton. The analogy with biphenyls[13] is seen when the activated states are shown. The trigonal amide framework replaces the second ring in a biphenyl. The effect is even more pronounced (8 kcal/

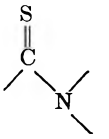


exo (major) isomer



endo (minor) isomer

mol) in the thioformamide. The increased barrier in the thioamide *endo* isomer, compared with the amide *endo* isomer, can probably also be rationalized on the steric grounds—the larger sulfur atom inhibits the rotation. However, in part, the increase may be due to the stiffer amide bond (see Table I) of the thio compound. The thioamide framework is less capable of



distortion to relieve strain in the activated state. The effect of sulfur vanishes in the case of *exo* isomers. Here the sulfur cannot have a direct steric effect, though it is surprising that it does not have at least small indirect steric effect through buttressing.[14] The increased barrier to rotation around the amide bond in the thio compound is expected from the literature.[15] For both I and II, the barrier to rotation around the C(O)–N (amide) bond is high compared with rotation around the aryl–nitrogen bond in both isomers.

The Route to Rotation in the Other Amides.—It is not so clear that the amide bond barrier is higher than the aryl–nitrogen bond barrier in the other amides, and this leads to doubt that rotation takes place directly around the aryl–nitrogen bond in the *exo* isomer. The chief experimental difficulty is that, for acetanilides and anilides with still larger carbonyl substituents (R_2), the *endo* isomer is generally not abundant enough to be observed. As a consequence, there is no way of directly observing the aryl–nitrogen barrier in the *endo* isomer or of observing the amide barrier. On steric grounds it is to be supposed that the aryl–nitrogen barrier would be smaller in the *endo* isomer. The R_2 groups will generally be much larger than the carbonyl oxygen atom. If this is true and the aryl–nitrogen barrier is greater than the amide bond barrier, the observations in Table I might apply to either (a) rotation around the amide bond or (b) rotation around the aryl–nitrogen bond in the *endo* isomer, depending on which of these, a or b, were larger. The barrier for the aryl–nitrogen bond in the *exo* isomer would not be observable. This situation has already been recognized for certain N-unsubstituted anilides.[16] In that case, rotation around the amide bond is larger, a is larger than b, and rotation around the aryl–nitrogen bond in the *exo* isomer is probably not observed.

There are certain exceptions to the rule that the *endo* isomer is not abundant enough in N-substituted anilides to be observable by nmr.[5] These are, first, the formanilides; and second, other anilides that have electronegative substituents on the α-carbon atom in the R group (carbonyl substituent). It was for that reason that compounds I, II, and XVI specifically were investigated. The significant amide-bond barrier is the barrier in passing from the major (*exo*) to the minor (*endo*) isomer, and not the reverse. For the formanilide, this barrier is 21 ± 1 kcal/mol (see Table I) or 20 ± 1 kcal if the reequilibration result is used. As discussed in the section on barrier calculations, the error here is large because of the disproportionate isomer ratio (*endo*/*exo* = 0.14 at 41°).

One way to estimate the barrier for anilides with other R groups is to extrapolate from the formamide. The barriers in a series of amides with varying R groups serve as the obvious (though not necessarily 100% reliable) means of making such an extrapolation.

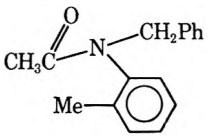
(10) T. Nakagawa, *Bull. Chem. Soc. Jap.*, **39**, 1006 (1966).
(11) H. S. Gutowsky, J. Jonas, and T. H. Siddall, III, *J. Amer. Chem. Soc.*, **89**, 4300 (1967).
(12) I. D. Rae, *Can. J. Chem.*, **44**, 1334 (1966).
(13) R. Adams, *Rec. Chem. Progr.*, **10**, 91 (1949).
(14) For a discussion of buttressing, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Co., Inc., New York, N. Y., 1962.
(15) G. Schwenker and H. Rosswag, *Tetrahedron Lett.*, 4237 (1967), and references therein.
(16) H. Kessler, *Tetrahedron*, **24**, 1857 (1968).

Published data for N,N-dimethylamides are collected in Table II. The values of ΔF^* were either taken directly from the original articles or calculated from data given in these articles.

Unfortunately, published values sometimes show rather wide variations. The six determinations for dimethylformamide (DMF) average to $\Delta F^* = 21.3 \pm 0.8$ (mean deviation) kcal/mol. For comparison below the barrier, ΔF^* is taken as 21 kcal/mol. For the closely related N-benzyl-N-methylformamide, ΔF^* (*exo* → *endo*) is 21.6 kcal/mol at 0° by the equilibration technique and ΔF^* is 21 kcal/mol at 100° by signal shape analysis.[11] The amide barrier in these *o*-substituted anilides is not more than it is in N,N-dimethylamides.

When R = Me (dimethylacetamide), the barrier is 2 kcal/mol lower than the barrier for DMF. The average value of the barrier (neat) is 19 kcal/mol. If the value from ref *d* is accepted, the increment is 3 kcal. The value from ref *d* has the best credentials because it was done for $CD_3C(O)NMe_2$ with deuterium decoupling and very careful signal shape analysis.

From these data and the reasoning above, it is probable that the barrier to rotation around the nitrogen–benzene bond was observed in the *endo* isomer in

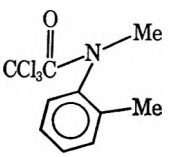


XVIII (and also XIII)

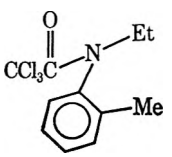
The indirect determination (19 kcal/mol) for rotation around the amide bond may be in error by 1.2 to 1.5 kcal/mol. In that case, the observed barrier would be the amide barrier.

In all other cases, the probable amide barrier is so low compared with our measurements that it seems certain that the barrier to rotation around the nitrogen–benzene bond in the *endo* isomer is being observed. For example, the calculated amide barrier where R = 2-propyl is 16 kcal/mol. For XII and for XIV the observed barriers are 4–5 kcal larger, and when R = *t*-butyl the observed barriers are about 7 kcal larger than the amide barrier.

With XVI (R = CCl_3), it was possible to verify the probable value of the amide barrier. In the closely related compound



two amide isomers are observable, in about equal abundance. In $CDCl_3$, the amide barrier is 15.3 kcal/mol (unpublished results, this laboratory). For $CCl_3C(O)NMe_2$, the average published value is 14.7 kcal/mol. In another related compound



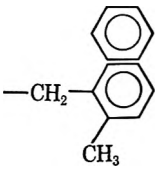
isomers were observed qualitatively, with coalescence of separate isomer signal sets occurring at about 10°. The 16-line pattern of the nonequivalent methylene protons of the ethyl group coalesces above 100°.

For reasons that are not clear to us, XVI itself gives no direct evidence for amide isomerism. The high field half of the AB pattern does become very broad at about 25°, while it is sharp below about 0° and above about 60°. However, two separate signal sets never emerge. The lack of two *o*-methyl signals may be due to degeneracy rather than to lack of amide isomerism. Only one *o*-methyl signal is observable in I even at low temperature, when two formyl signals and two methylene quartets are clearly observable.

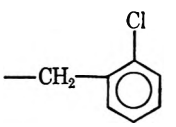
Effects of Various Substituents on the Barrier to Rotation around the Benzene–Nitrogen Bond.—Since rotation around the nitrogen–benzene bond is observed only for the *endo* isomer (except for I and II), the R_2 group (carbonyl substituent) cannot have a direct effect. However, there are some fairly large indirect effects. For example, the order of barrier heights is (for different R_2) Me = 2-propyl > *t*-butyl < CEt_3. The decrease with *t*-butyl may be due to the low amide barrier. The amide bond can be distorted easily, in a cooperative manner, to allow rotation around the benzene–nitrogen bond. However, another effect operates in the opposite direction—the buttressing effect.[13] For that reason, when $R_2 = Et_3C$, the barrier around the benzene–nitrogen bond increases again. In similar manner, the two effects operate in opposite directions to make Me = 2-Pr. The effect of the group $(C_6H_5)_2CH_3C$ (VII) to increase the barrier over that in XI and IX has no ready explanation at our hands. We can only assume that this group achieves some small interlocking effect.

The size and nature of the R_1 (aryl) group appear to have straightforward effects, in close analogy to rotation in biphenyls. Increased size or rigidity for the *ortho* substituent increases the barrier significantly. Compare IV with XI; XV with XIV; and XIV, XIX, and III with XVIII. It is not obvious, however, that the benzene ring should be "smaller" than the methyl group —compare V with XI. The data for VIII provides a clear case of buttressing.[12,13]

A size effect is noted when the other nitrogen substituent (R) is



rather than simple $PhCH_2$–. However, the modest increase of size of the group



has no observable effect.

The oxygen atom can be "made larger." A 3-kcal increase in barrier is observed when the uranyl ion is attached to the oxygen atom of XI. There is probably

also some electronic contribution to the increase in barrier. The exact nature of bonding of such molecules as amides to the uranyl group is subject to discussion.[14] However, whatever the exact nature of the bond, there must be a shift in electron density toward the oxygen atom. This requires an increased double-bond character and greater stiffness in the amide bond. To a much smaller extent, the oxygen atom is "made larger," presumably by hydrogen bonding to $CHCl_2CHCl_2$. The small increase in barrier (0.2 kcal) with this solvent compared with *o*-dichlorobenzene is at least qualitatively real. Very careful experiments were performed in which samples of XI in the two solvents were alternated in the spectrometer at 110°. In the latter solvent, the signals were definitely more nearly coalesced.

Registry No.—I, 17372-54-2; II, 20678-83-5; III, 13936-76-0; IV, 13936-78-2; V, 13936-77-1; VI, 20643-10-1; VII, 20643-11-2; VIII, 20643-12-3; IX, 13936-74-8; X, 20643-14-5; XI, 17372-56-4; XII, 17372-55-3; XIII, 13936-79-3; XIV, 20643-18-9; XV, 20633-57-2; XVI, 20633-58-3; XVII, 20633-59-4; XVIII, 6840-46-6; XIX, 20633-61-8.

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A Study of the Photoaddition Reactions of Norbornadiene with 2-Cyclohexenones[1]

J. J. MCCULLOUGH,[2] J. M. KELLY, AND P. W. W. RASMUSSEN

Chemistry Department, McMaster University, Hamilton, Ontario, Canada

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To gain mechanistic information on photoaddition reactions of 2-cyclohexenones, the additions of 2- and 3-methyl-2-cyclohexenone and 2-cyclohexenone to bicyclo[2.2.1]heptadiene have been studied. The products are of the following types: (i) cyclobutane derivatives (*cis*- and *trans*-fused structures are formed); (ii) α- and β-nortricyclyl-2-cyclohexenones; and (iii) α- and β-(7-*anti*-norbornenyl)-2-cyclohexenones. The nortricyclyl compounds were prepared by independent routes, and one of the norbornene derivatives was degraded to 7-norbornanecarboxylic acid. Other structure assignments rest on infrared and nmr spectra. In the reaction of 3-methyl-2-cyclohexenone and norbornadiene a 16% yield of 9-methyl pentacyclo[7.4.0.$0^{2,7}$.$0^{3,6}$.$0^{4,8}$]tridecan-13-one (9) is obtained. It is proposed that this and the cyclohexenone derivatives are formed *via* biradical intermediates. Hydrogen shifts are involved in the formation of the latter products, and a deuterium-labeling experiment showed that one such shift is intramolecular and stereospecific. Naphthalene quenching experiments imply that the cyclohexenone derivatives are formed by a triplet-state reaction.

The chemistry of bicyclo[2.2.1]hepta-2,5-diene (norbornadiene) is rich in reactions, in which both double bonds of the diene are involved. Such reactions include ionic[3] and free-radical[4] additions, photoisomerization,[5] and the 2,6 cycloaddition known as the homo Diels–Alder reaction.[6] Nortricyclene derivatives and 7-substituted norbornenes are oft-encountered products of these reactions.

In this paper we describe some photoadditions of norbornadiene with simple[7] 2-cyclohexenones, which are of particular interest for the following reasons. First, although photoadditions of alicyclic enones and unsaturated esters have long been known[8,9a] and have been extensively studied,[9,10] attention has been focussed on dimerizations of the carbonyl compounds or cross additions with uncomplicated alkenes. No work prior to our communication[1] had been reported in which a homoconjugated diene was employed as the substrate in a cross addition. It was, therefore, of interest to see to what extent the spatial relationship of the double bonds in norbornadiene modified the course of enone photoadditions to this diene. Such modification might result, for example, if biradical species were discrete intermediates in the addition reaction.[9a]

A further interesting aspect of photoadditions with this diene was the question of whether the symmetry-forbidden 2,6 cycloaddition[6] would occur. This is symmetry allowed,[11] and well known,[6] in ground-state chemistry.

To determine whether homoconjugated dienes do differ from alkenes in their photoaddition behavior, a study of the photoreactions of 2-cyclohexenone,

(1) For preliminary reports, see J. J. McCullough and J. M. Kelly, *J. Amer. Chem. Soc.*, **88**, 5935 (1966); J. J. McCullough and P. W. W. Rasmussen, *Chem. Commun.*, 387 (1969).

(2) Author to whom requests for reprints should be addressed.

(3) See J. A. Berson, "Molecular Rearrangements," Part I, Interscience, New York, N. Y., 1963, p 198.

(4) (a) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Amer. Chem. Soc.*, **80**, 635 (1958); (b) D. J. Trecker and P. Henry, *ibid.*, **85**, 3204 (1963); (c) N. O. Brace, *J. Org. Chem.*, **27**, 3027 (1962); (d) S. J. Cristol and D. J. Davies, *ibid.*, **29**, 1282 (1964); (e) T. V. Van Auken and E. A. Rick, *Tetrahedron Lett.*, 2709 (1968).

(5) (a) S. J. Cristol and R. L. Snell, *J. Amer. Chem. Soc.*, **76**, 5600 (1954); (b) W. G. Dauben and R. L. Cargill, *Tetrahedron Lett.*, **15**, 197 (1961); (c) G. S. Hammond, N. J. Turro, and A. Fischer, *J. Amer. Chem. Soc.*, **83**, 4674 (1961).

(6) (a) A. T. Blomquist and Y. C. Meinwald, *ibid.*, **81**, 667 (1959); (b) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962); (c) H. K. Hall, *J. Org. Chem.*, **42**, 215 (1960); (d) S. J. Cristol, E. L. Alfred and D. L. Wetzel, *ibid.*, **27**, 4058 (1962).

(7) "Simple" is taken here to mean derivatives whose π system is similar to 2-cyclohexenone—*i.e.*, alkyl derivatives.

(8) Early examples are W. Treibs, *Chem. Ber.*, **63**, 2738 (1930); *J. Prakt. Chem.*, **138**, 299 (1933). A. Butenandt, L. K. Poschmann, G. Failer, U. Siebert, and E. Biekert, *Ann.*, **575**, 123 (1952).

(9) (a) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); a summary of early examples is given here. (b) Y. Yamada, E. Uda, and K. Nakanishi, *Chem. Commun.*, 423 (1966). (c) M. Brown, *ibid.*, 340 (1965). (d) R. A. Schneider and J. Meinwald. *J. Amer. Chem. Soc.*, **89**, 2023 (1967). (e) P. Yates, S. N. Eğe, G. Büchi, and D. Knutsen, *Can. J. Chem.*, **45**, 2927 (1967). (f) S. N. Eğe and P. Yates, *ibid.*, **45**, 2933 (1967). (g) R. L. Cargill, M. E. Beckham, A. E. Sibert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965).

(10) (a) O. L. Chapman, "Photocycloaddition Processes," Abstracts of the 20th National Organic Symposium, Burlington, Vt., June 1967, p 127; (b) P. E. Eaton, *Accounts Chem. Research*, **1**, 50 (1968); (c) A. Cox, P. de Mayo, and R. W. Yip, *J. Amer. Chem. Soc.*, **88**, 1043 (1966); (d) H. D. Scharf and F. Korte, *Ber.*, **99**, 1299 (1966); (e) R. L. Cargill and M. R. Willcott, III, *J. Org. Chem.*, **31**, 3938 (1966).

(11) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

Table I

Effect of Solvent and Added Naphthalene on the Product Composition in 2-Cyclohexenone–Norbornadiene Additions

Run	Solvent	Reactants, molar concn: 2-Cyclohexenone	Norbornadiene	Naphthalene	Product composn, %[a]: Cyclobutanes	α-Substituted cyclohexenones	β-Substituted cyclohexenones
1[b]	Hexane	0.025	0.25		55.0	13.3	31.7
2	Hexane	0.025	0.25		53.3	15.9	30.8
3	*t*-Butyl alcohol	0.025	0.25		52.5	15.4	32.1
4	*t*-Butyl alcohol	0.025	0.25		52.3	16.3	31.4
5[c]	Hexane	0.0248	0.28	0.0492	50.8	15.7	33.5
6	*t*-Butyl alcohol[d]	0.0246	0.28	0.0492	59	14	27

[a] All ratios were by vpc, column B. [b] Runs 1 and 3 had 70% residual 2-cyclohexenone; 2 and 4 had 30%. [c] No light was absorbed by naphthalene. Bismuth trichloride–cupric sulfate filter[13a] solution was used. [d] Contained 7.5% methanol.

2-methyl-2-cyclohexenone, and 3-methyl-2-cyclohexenone, with norbornadiene, was undertaken.

Results

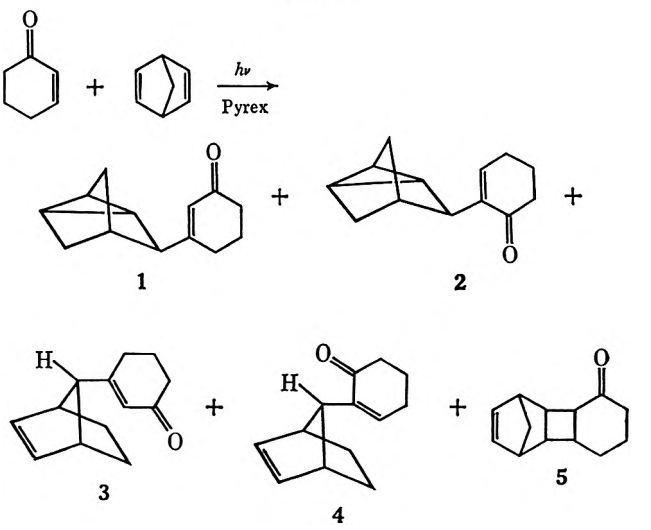
The light source used in all of the photolyses was a Hanovia, Type L, 450-W mercury lamp, contained in the usual water-cooled immersion apparatus. A Pyrex sleeve, 1 mm thick having 0% transmission at 280 mμ, was used in all runs. The reactions were run in hexane, *t*-butyl alcohol, or *t*-butyl alcohol containing 10% methanol, and no solvent effect was observed (Table I). Typically, 400 ml of solution containing 4.0 g of cyclohexenone and 40.0 g of norbornadiene (tenfold molar excess of diene) were irradiated under nitrogen until monitoring of aliquots by gas or thin layer chromatography or infrared or nmr analysis showed that the reaction was complete (2–8 hr, depending on the cyclohexenone used and the conversion desired). The residue obtained after solvent distillation was chromatographed on silica gel, and the fractions eluted by benzene–ethyl acetate, which were enriched in the various product types, were subjected to preparative gas chromatography.[12] The pure products thus isolated were examined by spectroscopic methods, and the purity was checked by gas chromatography and elemental analysis.

The system **2-cyclohexenone** and **norbornadiene** was the first to be investigated and will be considered first. Photolysis of 2-cyclohexenone and norbornadiene as described in the Experimental Section, in *t*-butyl alcohol or in hexane, resulted in the formation of adducts, as shown by vpc, thin layer chromatography, and infrared monitoring. These compounds were all shown to be 1:1 adducts of cyclohexenone and norbornadiene by their mass spectra which had molecular ions of *m/e* 188. They were separated by silica gel column and gas chromatography, and have been assigned the structures shown in Chart I, which are 3-(3-tricyclo[2.2.1.$0^{2,6}$]-heptyl)-2-cyclohexenone (**1**, 20%), 2-(3-tricyclo[2.2.-1.$0^{2,6}$]heptyl)-2-cyclohexenone (**2**, 8%), 3-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexenone (**3**, 9%), 2-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexenone (**4**, 8%), and a mixture of cyclobutanes (**5**, 55%).

The cyclobutanes, of which there are at least three stereoisomers, showed infrared peaks at 5.82 and 5.88 μ (*trans*- and *cis*-fused bicyclo[4.2.0]octan-2-ones, respectively).[9a] The compounds having absorption at 5.82 μ did not survive gas chromatography or treatment with alumina, but could be chromatographed without isomerization on silica gel. This behavior is as expected

(12) For details of gas chromatography, see Experimental Section.

Chart I



for *trans*-fused cyclobutanes (**5**) from the work of Corey, *et al.*[9a] These compounds also had infrared absorption at 14.2 μ (norbornene double bond[13]) and resonance at 6.00 ppm (2 H, vinyl protons) in the nmr. No attempts have been made to establish precisely the stereochemistry of any of these cyclobutanes.

The minor but more interesting products, the substituted cyclohexenones **1**–**4**, all had infrared bands at 5.99 μ (α,β-unsaturated ketone). The nortricyclyl products **1** and **2** had strong bands at 12.42 and 12.35 μ, typical of nortricyclene derivatives,[14] while norbornenes **3** and **4** had absorption at 14.20 μ.

3-Nortricyclylcyclohexenone (**1**) showed a resonance at 5.81 ppm (1 H, vinyl, α to carbonyl) in the nmr, and also a sharp signal at 1.16 ppm, attributed to the nortricyclene system. Structure **1** was confirmed by independent synthesis from 3-ethoxycyclohexenone and nortricyclylmagnesium bromide using the general procedure of Woods, *et al.*[15] 2-Nortricyclylcyclohexenone had a similar nmr spectrum to **1**, except that the vinyl resonance (1 H) was at 6.63 ppm showing that the cyclohexenone was α substituted.

Structure **3** for one of the norbornenyl cyclohexenones was derived by nmr spectroscopy. The low-field part of this spectrum showed signals at 5.70 (1 H, singlet, α to carbonyl) and at 6.11 ppm (2 H, triplet, norbornene

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, p 48; (b) L. Kaplan, H. Kwart, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **82**, 2341 (1960).

(14) G. E. Pollard, *Spectrochim. Acta*, **18**, 837 (1962).

(15) G. F. Woods, P. H. Griswald, Jr., B. H. Armbrecht, D. I. Blumenthal, and R. Plapinger, *J. Amer. Chem. Soc.*, **71**, 2028 (1949).

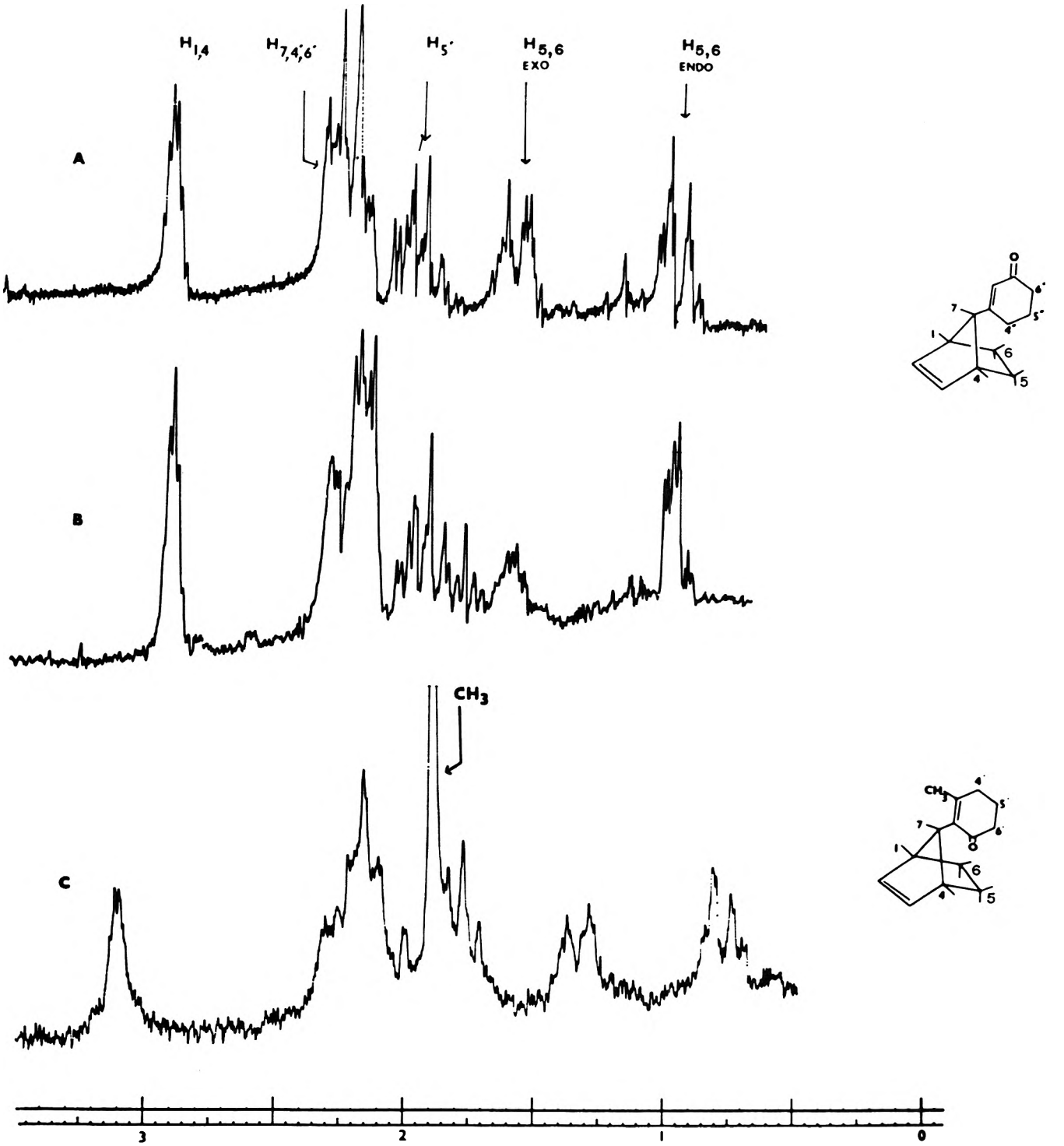


Figure 1.—100-Mcps nmr spectra: A, spectrum of **3**; B, spectrum of **3** showing one dueterium in the *exo* position; C, spectrum of **4**.

vinyl). The high-field region is shown in Figure 1A, and this is in accord with the substituent being at C_7 of the norbornene system. Thus, the *exo* and *endo* pairs of protons show as two pairs of multiplets of an AA'XX' system, the *endo* multiplet being at higher field.[16] Irradiation of the multiplet at 2.21 ppm, which includes the resonance of the allylic C_7 proton, caused the *endo* multiplet to simplify to a quartet. This shows that H_7 is coupled to the *endo* protons and therefore must be *syn* to the norbornene double bond.[17] The assignments of the remaining protons are shown in Figure 1.

Compound **4** had a similar nmr spectrum to that of **3** except that a resonance appeared at 6.63 ppm (1 H, singlet, β to carbonyl) again showing that the norbornene substituent was at the α carbon of the cyclohexenone.

Since some of the products are conjugated enones, and consequently would absorb light in the reaction, it was important to check their photostability. It was noted that the product ratio did not change detectably as the reaction proceeded. Also, 3-nortricyclylcyclohexenone (**1**), the major enone product, was irradiated

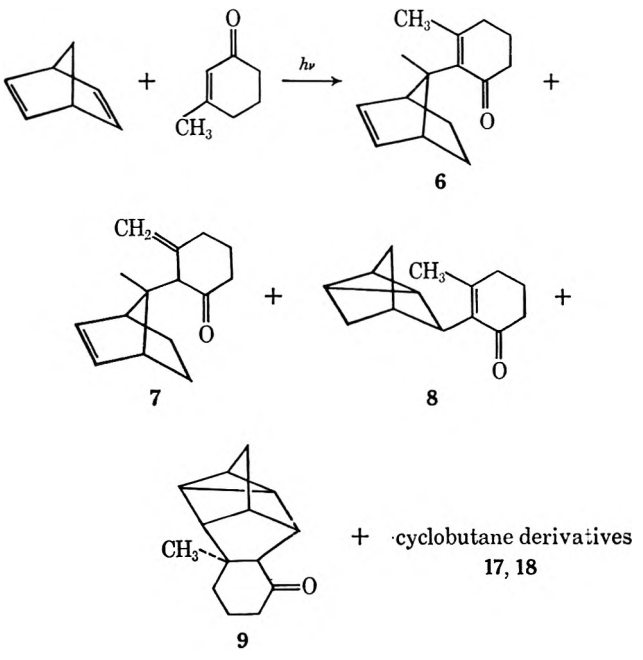
(16) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962); R. G. Foster and M. C. McIvor, *Chem. Commun.*, 280 (1967).

(17) J. Meinwald and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **85**, 2514 (1963).

separately and did not change on a 6-hr peroid of photolysis.

Photoaddition of **3-methyl-2-cyclohexenone** and **norbornadiene** in hexane or *t*-butyl alcohol gave rise to products to which the structures shown in Chart II

Chart II

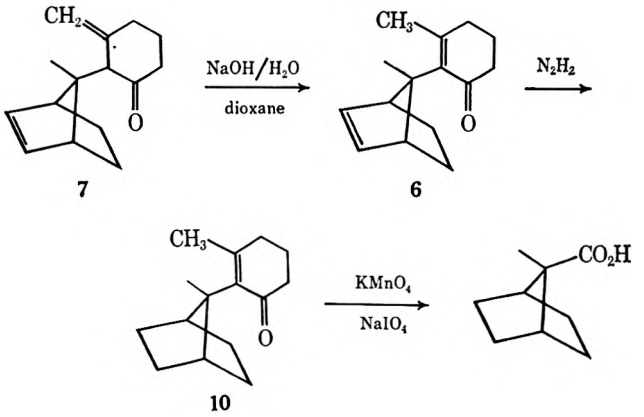


have been assigned. These structures are 3-methyl-2-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexenone (**6**, 2%), 3-methylene-2-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)cyclohexanone (**7**, 15%), 3-methyl-2(3-tricyclo[2.2.1.$0^{2,6}$]-heptyl)-2-cyclohexenone (**8**, 8%), 9-methylpentacyclo-[7.4.0.0.^{2,7}0.^{3,5}0.^{4,8}]tridecan-13-one (**9**, 16%), and cyclobutane derivatives (59%).

This mixture was also resolved by silica gel column and gas chromatography, as detailed in the Experimental Section. The compounds all had molecular ions at *m/e* 202. The structures assigned to enones **6** and **7** are based on spectroscopic evidence and a chemical degradation. In the infrared, both compounds had bands at 14.2 μ (norbornene).[13] The carbonyl absorption was at 5.99 (α,β unsaturated) for **6**, and at 5.83 μ (cyclohexanone) for **7**; the latter also had a strong band at 11.2 μ (*exo*-methylene group). Enones **6** and **7** were shown to be tautomers, since mild treatment of **7** with base caused clean isomerization to **6**. Diimide reduction[18] of **6** gave the corresponding norbornane **10** in quantitative yield. Oxidation of the latter with aqueous permanganate–periodate[19a] gave 7-norbornanecarboxylic acid, mp 74–75° (lit.[19b] mp 75–76.5°), identified by comparison with an authentic sample.[20] The degradation scheme is shown in Chart III.

The detailed nmr analysis and the unambiguous degradation show that all of the norbornenyl derivatives are 7-substituted compounds. Therefore the structures assigned earlier[1] (5-substituted norbornenes) are

Chart III



incorrect; no 5-substituted norbornenes were isolated from these reactions.

The nmr of **6** appears in Figure 1C, and its relationship with that of **3** is evident. Spin decoupling by irradiation of the multiplet centered at 2.30 ppm (which includes H_7) caused the resonance of the *endo* protons to simplify, showing that the 7 substituent is *anti* to the norbornene double bond (*cf.* nmr of **3**). The nmr of **7** is quite different in appearance from those of **3** and **6**. Resonances do appear at 4.60 and 4.70 ppm, which are attributed to the methylene group, and a triplet appears at 6.11 ppm due to the norbornene vinyl protons. The *endo* protons give rise to a multiplet (2 H) centered at 0.9 ppm; the remaining protons are all included in a wide multiplet bounded by 1.5 and 2.6 ppm.

Inspection of space-filling models[21] of **7** reveals that there is severe steric hindrance to rotation of the methylenecyclohexanone substituent, and this would create an anisotropic environment for the *exo* and the bridgehead protons, which may result in the unique nmr spectrum.

A further interesting type of product, isolated only from the reaction of 3-methyl-2-cyclohexenone and norbornadiene, is **9**, the product of formal homo Diels–Alder addition of these molecules. This product was always contaminated with unsaturated compounds whenever purification was by chromatography. The latter contaminants were removed by oxidation with permanganate/periodate reagent.[19a] This product had infrared absorption at 5.90 and at 12.37 μ (doublet, nortricyclene). The nmr showed no signals in the vinyl region, but had a methyl resonance at 1.02 ppm; structure **9** is assigned on the basis of these spectra and the resistance of the compound to oxidation. The stereochemistry shown for **9** in Chart II should be preferred if steric effects are important in the addition reaction.

Photolysis of **2-methylcyclohexenone** and **norbornadiene** gave a mixture of adducts which consisted of 2-methyl-3-(3-tricyclo[2.2.1.$0^{2,6}$]heptyl)-2-cyclohexenone (**11**, 14%), 2-methyl-3-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexenone (**12**, 10%), and cyclobutane adducts (**13**, 76%) (Chart IV).

Separation of these was achieved by the usual chromatographic methods (see Experimental Section). The adducts had molecular ions of *m/e* 202. As in the first reactions described, the cyclobutanes were not thor-

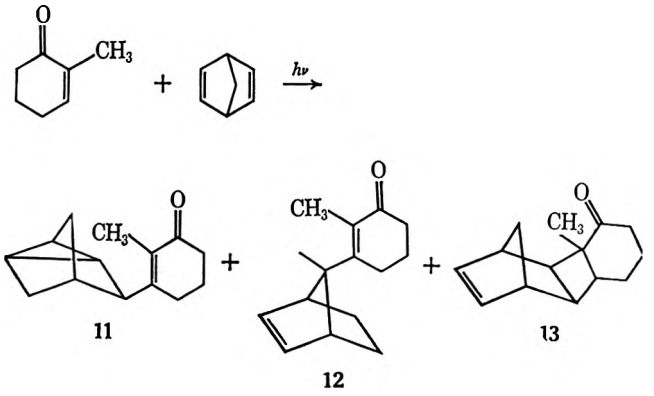
(18) W. C. Baird, B. Franzus and J. H. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).

(19) (a) J. T. Edward, D. Holder, W. H. Lunn, and I. Puskas, *Can. J. Chem.*, **39**, 599 (1961). (b) P. Yates and R. J. Crawford, *J. Amer. Chem. Soc.*, **88**, 1562 (1966).

(20) Kindly supplied by Dr. J. Warkentin of this department.

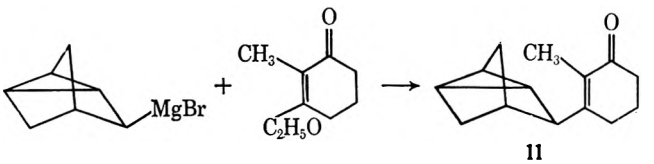
(21) Models used were Courtauld's Atomic Models, available from Griffin and George Ltd., Wembley, Middlesex, England.

CHART IV



oughly investigated. The presence of *cis*- and *trans*-fused bicyclo[4.2.0]octan-2-ones was inferred from the carbonyl region in the infrared, where bands appeared at 5.90 and 5.80 μ. It will be noted that enolization leading to isomerization is blocked by a methyl group in these adducts, and it was possible to isolate one of the *trans*-fused adducts by preparative gas chromatography, as described in the Experimental Section.

The substituted cyclohexenones **11** and **12** both had infrared bands at 5.98 μ (α,β-unsaturated carbonyl). The nortricyclene absorption[14] of **11** appeared at 12.37, and **12** had the band at 14.2 μ attributed to the norbornene double bond.[13] In the nmr, 2-methyl-3-nortricyclylcyclohenenone **11** showed signals consistent with the proposed structure, having narrow peaks at 1.15 and 1.25 ppm attributed to the nortricyclyl system, and a peak at 1.65 ppm due to the allylic protons of the methyl group. Product **11** was synthesized by reaction of 3-ethoxy-2-methyl-2-cyclohexenone with nortricyclylmagnesium bromide.



The structure of the norbornenylcyclohexenone **12** was assigned from its nmr spectrum, which is shown in Figure 2. The high-field region had the following signals: a multiplet at 0.97 (2 H, *endo* protons); a complex multiplet centered at 1.70 (7 H), which included resonances of the methyl group, the *exo* protons, and the pair of protons at C_5 of the cyclohexenone ring; a multiplet centered at 2.20 (4 H), assigned to the methylene groups at C_4 and C_6 of the cyclohexenone ring; and a broad peak (1 H) at 2.52 ppm assigned to the C_7 proton of the norbornene moiety. Also observed were resonances at 2.95 (2 H, bridgehead protons) and at 6.11 ppm (2 H, norbornene vinyl protons).

Irradiation of the single proton peak at 2.52 ppm resulted in simplification of the two-proton multiplet at 0.97 ppm (Figure 2) confirming the *anti* stereochemistry of this compound. This irradiation also revealed that the methyl protons are coupled to H_7, as the methyl resonance was also simplified by irradiation at 2.52 ppm.

To test the multiplicity of the cyclohexenone excited state which gives rise to these products, the photolysis of 2-cyclohexenone and norbornadiene was run with naphthalene (0.0492 *M*) present. The product ratio was examined by vpc (column B, 240°), and the results are given in Table I. Although this concentration of naphthalene caused a threefold retardation in reaction rate, the product distribution was not altered significantly from the reactions without naphthalene. The interpretation of this result is to be found in the Discussion.

A second experiment of mechanistic importance was the photoaddition of 3-deuterio-2-cyclohexenone[22] and norbornadiene, and examination of the 3-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexenone (**3**) which was formed. The mass spectrum had a molecular ion of *m/e* 189 ($C_{13}H_{15}DO$). The nmr (100 Mcps) is shown in Figure 1. It can be seen that the deuterium label in this product is located in the *exo* position of the ethano bridge of the norbornene moiety, since the *exo* multiplet has area one-half of its value for the protio compound, whose nmr is also shown in Figure 1. The conclusions from this observation are also presented in the Discussion.

Discussion

The products of photoaddition of 2-cyclohexenone and 2- and 3-methyl-2-cyclohexenones with norbornadiene are shown in Charts I, II, and IV. It will be noted that three types of products are obtained in each case: (i) cyclobutane derivatives (*cis*- and *trans*-fused bicyclo[4.2.0]octan-2-ones are formed; these were expected products, and will not be considered in any detail); (ii) α-substituted 2-cyclohexenone (except from 2-methyl-2-cyclohexenone); (iii) β-substituted 2-cyclohexenones (except from 3-methyl-2-cyclohexenone). For mechanistic reasons which will become apparent later, products **7** and **9** in Chart II are considered with groups ii and iii, respectively.

Excepting the cyclobutane adducts (group i), all of these products arise by novel photochemical pathways. Our work on these structures is primarily of mechanistic interest, and this discussion will be concerned with the mechanisms of their formation.

We will deal first with the question of the multiplicity of the enone excited state which gives rise to the substituted cyclohexenones. Photochemical reactions of cyclic enones in solution, including rearrangements,[23] photoreduction,[23a] and cycloadditions[24] generally proceed *via* triplet states. Therefore, a quenching experiment was performed to determine whether all of the products in the reaction of 2-cyclohexenone and norbornadiene arise from a triplet state. This photoaddition was run in the presence of 0.0449 *M* naphthalene, a

(22) (a) The 3-deuterio-2-cyclohexenone was prepared by $LiAlD_4$ reduction of 3-ethoxy-2-cyclohexenone by the method of W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 148 (1960); (b) *ibid.*, **40**, 41 (1960). (c) Deuterio **1** was also isolated. The nmr and mass spectra showed the presence of one deuterium atom in **1**, which appeared to be on a methylene bridge of the nortricyclyl moiety.

(23) (a) H. E. Zimmerman, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley, and M. Semmelback, *J. Amer. Chem. Soc.*, **88**, 1965 (1966); (b) H. E. Zimmerman and K. G. Hancock, *ibid.*, **90**, 3749 (1968).

(24) (a) P. E. Eaton and W. S. Hurt, *ibid.*, **88**, 5038 (1966). (b) J. L. Ruhlen and P. A. Leermakers, *ibid.*, **88**, 5671 (1966); **89**, 4944 (1967). (c) E. Y. Y. Lam, D. Valentine, and G. S. Hammond, *ibid.*, **89**, 3482 (1967). (d) P. de Mayo, J.-P. Pete, and M. Tchir, *ibid.*, **89**, 5712 (1967). (e) P. de Mayo, J.-P. Pete, and M. Tchir, *Can. J. Chem.*, **46**, 2535 (1968). (f) O. L. Chapman, J. H. Koch, F. Klein, P. J. Nelson, and E. L. Brown, *J. Amer. Chem. Soc.*, **90**, 1657 (1968).

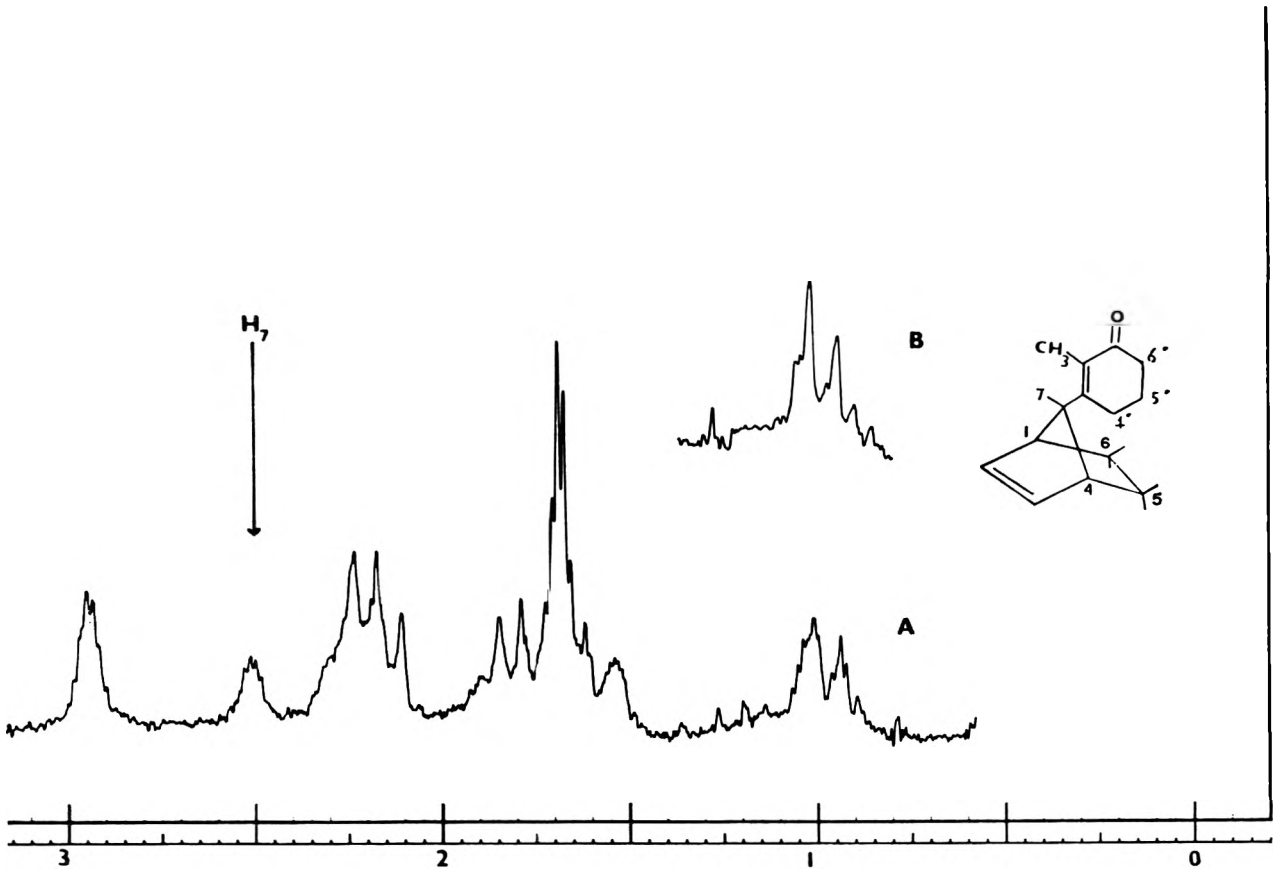


Figure 2.—Nmr spectrum of 2-methyl-3-(7-*anti*-norbornenyl)-2-cyclohexenone (12): A, normal spectrum; B, *endo*-proton multiplet when H_7 peak is irradiated.

quencher of 2-cyclohexenone triplets.[23,25] This naphthalene concentration caused a threefold retardation in rate, but no significant change in the product distribution, according to gas chromatography.[26] Since cycloadditions of 2-cyclohexenones and 2-cyclopentenone involve triplet states, our result[25] shows that the substituted cyclohexenones arise from a triplet[27] also. This might be the same species (or combination of species) which leads to the cyclobutane products, or two triplets could be involved which transfer energy to naphthalene at similar rates.

The second step in the formation of the 2-cyclohexenones and related products must involve bonding of norbornadiene to the α- and β-carbon atoms of the reacting cyclohexenone triplet. In the case of 2-cyclohexenone, which has the same substituent (hydrogen) at the α and β positions, the ratio of α- to β-substituted cyclohexenones in this addition is 4:9. It is tempting to try to correlate the predominance of β substitution with some property of the enone triplet. For example, the Hückel coefficients of π_3 (the lower antibonding MO) are -0.228 for the α and 0.657 for the β position of acroleinlike systems.[28] This orbital is singly occupied in the $n-\pi^*$ and $\pi-\pi^*$ triplets, and the larger coefficient of π_3 at the β position would give the higher odd-electron density there. If the triplet then reacts faster at the position of greater odd-electron density, the higher β coefficient is in accord with the higher amount of β-substituted products. Such interpretations are risky, however, on account of the large amount of cyclobutane adducts formed. Before the α/β ratios can be explained, it is necessary to know the relative amounts of cyclobutanes which arise from α and β bonding to the enone triplet, a figure which we cannot determine at present.

The structure of the substituent in the α- and β-substituted cyclohexenone products will now be discussed. The three addition reactions all give rise to compounds in which the substituent is either a nortricyclyl or a 7-

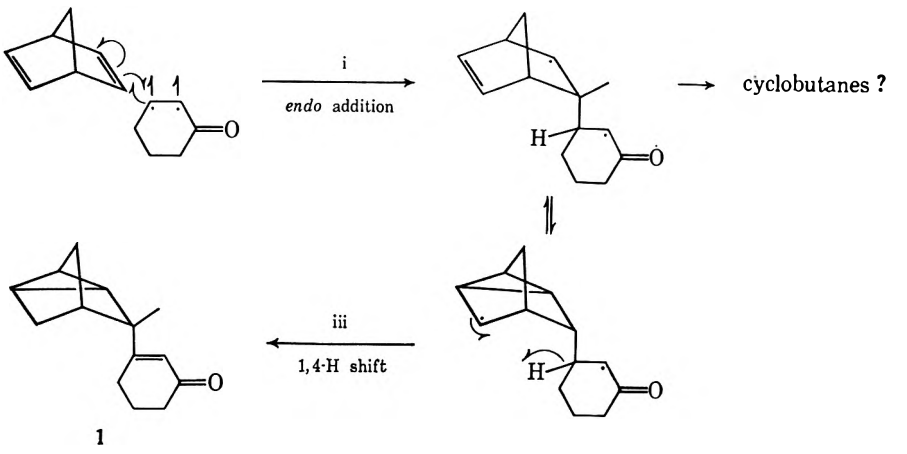
(25) Hammond, *et al.*,[24c] report that naphthalene *sensitizes* the dimerization of 2-cyclohexenone. This may be a result of singlet sensitization, since H. E. Zimmerman and J. S. Swenton [*J. Am. Chem. Soc.*, **89**, 906 (1967)] report quenching of naphthalene fluorescence by cyclohexenones.

(26) Although the product distribution was not significantly affected by naphthalene quenching according to vpc, infrared spectra showed that the *cis*- to *trans*-fused cyclobutane ratio was decreased in the quenched runs, in accord with the results of Chapman, *et al.*[24f] The change in the latter ratio on quenching may not be great enough to cause a significant difference in the enone/cyclobutane ratio, or the two proposed cyclohexenone triplets[24f] may both be involved in formation of the cyclohexenone derivatives.

(27) (a) The electronic configuration of the reacting triplet is not known at present. Excitation is to the $n-\pi^*$ singlet, since a Pyrex filter was used in the reactions. Recenty reported work by H. E. Zimmerman, R. W. Binkley, J. J. McCullough, and G. A. Zimmerman [*J. Amer. Chem. Soc.*, **89**, 6589 (1967)] has shown that, for ground-state geometry, the $n-\pi^*$ triplet is the lowest lying excited state of conjugated enones, and should be the reactive species in solution. See, however, ref 24d-f. (b) Since it is well known that norbornadiene and quadricyclane interconvert on sensitization [see, *e.g.*, G. S. Hammond, P. Wyatt, C. D. DeBoer, and N. J. Turro, *ibid.*, **86**, 2532 (1964)], the following possibilities for these reactions must be considered. (i) The adducts might arise by reaction of norbornadiene triplet with the enones. This seems unlikely, since the norbornadiene triplet would be required to react rapidly with the low concentration of enone, and not with the higher concentration of norbornadiene. The dimer of norbornadiene is not observed. We have quantitative results which suppport this conclusion, to be reported later. (ii) Some adducts might result from reaction of enone triplet with quadricyclane. Some of the latter is formed in the photolysis. However, when quadricyclane replaced norbornadiene in the photolysis, no adducts were formed.

(28) C. A. Coulson and A. Streitwieser, "Dictionary of π-Electron Calculations," W. H. Freeman and Co., San Francisco, Calif., 1965, p 227.

CHART V



anti-norbornenyl group. Our thesis is that the nortricyclylcyclohexenones (*e.g.*, **1** and **2**) are formed by initial attack of the cyclohexenone triplet from the *endo* side of the norbornadiene, while the 7-*anti*-norbornenyl derivatives (*e.g.*, **3** and **4**) arise from corresponding *exo* attack. It is helpful to have structures representing the proposed intermediates before us to discuss the mechanisms. The formation of a nortricyclyl derivative is depicted in Chart V.

This proposed mechanism consists of the following steps: (i) *endo* addition of the cyclohexenone triplet, with formation of a diradical species; (ii) a bridging process, leading to the nortricyclyl system; and (iii) a hydrogen transfer, forming the product **1**.

It is obvious that initial *endo* attack of the enone triplet is necessary for intramolecular hydrogen transfer to occur in step iii. We are committed to say, then, that (at least) 26% of the addition of 2-cyclohexenone to norbornadiene occurs from the *endo* side. By analogy with free-radical additions to this diene, 26% *endo* attack is a perfectly reasonable fraction.[29]

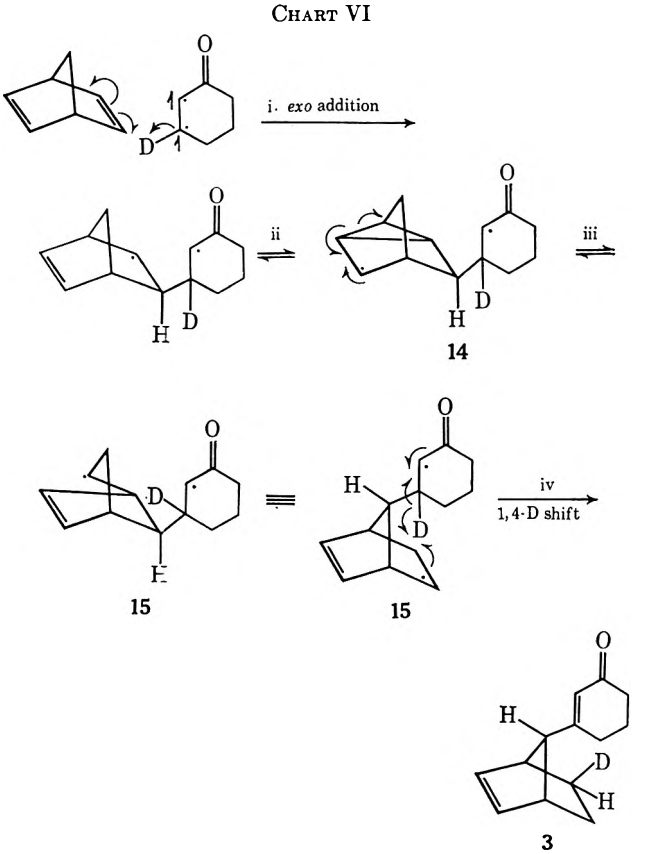
The first-formed intermediate is represented as a biradical species. An alternative zwitterionic intermediate seems unlikely since the product ratios in these additions are identical in hexane, cyclohexane, ethanol, and *t*-butyl alcohol (Table I). Also, work of Zimmerman and coworkers[30] using migratory aptitudes to probe the excited-state structure has shown that the β carbon is not electron deficient, making the zwitterion a less reasonable intermediate than the biradical species. This biradical may be analogous to the intermediates proposed by others[9a,d] as the species which cyclize to a four-membered ring.

Step ii has precedent in ground-state, free-radical chemistry in the norbornenyl–nortricyclyl radical equilibrium.[31] It is possible, however, that the bridging process, by which the nortricyclyl system is formed, and bonding to the enone triplet (*i.e.*, steps i and ii) are concerted.

The final step in the sequence leading to **1** is represented as a 1,4-hydrogen shift, which takes place from the biradical intermediate. While 1,2- and 1,3-hydrogen shifts do not occur readily in radical systems,[32] the corresponding 1,4[33] and 1,5[34] processes are known.

The proposed mechanism for the formation of a 7-*anti*-norbornenyl derivative (**3**) is shown in Chart VI.

CHART VI



exo addition of the enone triplet, followed (or accompanied) by bridging, gives an intermediate biradical (**14**) which cannot cyclize or migrate hydrogen to form a stable molecule. If, however, the three-membered ring opens as shown in step iii the intermediate **15** has a geometry which allows 1,4-hydrogen transfer with production of **3**. The effect of these transformations is to

(29) T. V. van Auken and E. A. Rick[4e] report 17–20% *endo* attack of thiol radicals to norbornadiene. H. Kwart and J. L. Nyce [*J. Amer. Chem. Soc.*, **86**, 2601 (1964)] report 20% *endo* addition of bromine radicals to norbornene.

(30) H. E. Zimmerman, R. D. Rieke, and J. R. Scheffer, *ibid.*, **89**, 2033 (1967).

(31) C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966); D. I. Davies, J. N. Done, and D. H. Hey, *Chem. Commun.*, 725 (1966).

(32) For discussions, see (a) R. Kh. Freidlina in *Advan. Free Radical Chem.*, **1**, 211 (1965); (b) C. Walling in "Molecular Rearrangements," Vol. I, Interscience, New York, N. Y., 1963, p 407.

(33) H. A. S. Gordon and J. R. McNesby, *J. Chem. Phys.*, **31**, 853 (1959).

(34) D. Helmlinger and G. Ourisson, *Ann.*, **686**, 19 (1965).

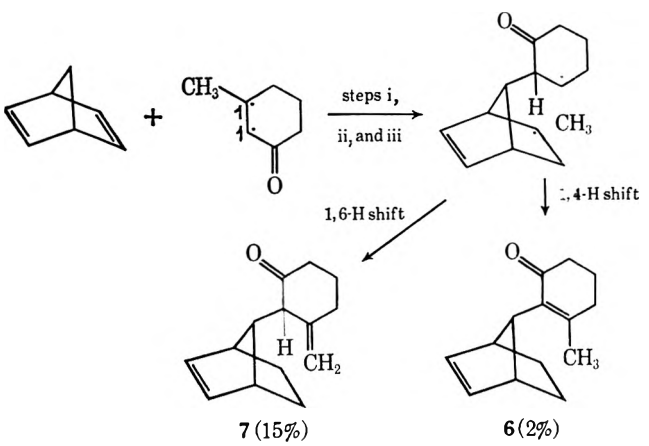
give a formal Wagner–Meerwein shift, affording the 7-*anti*-norbornenyl-2-cyclohexenones. These shifts are, of course, much better known in carbonium-ion chemistry, but at least one case of formation of 7-substituted norbornenes in a free-radical addition has been reported.[35]

The scheme of intramolecular processes shown in Chart VI predicts that the β hydrogen of reactant 2-cyclohexenone will be transferred to the *exo* side of the ethano bridge in **15**. To test this prediction, the photoaddition was carried out using 3-deuterio-2-cyclohexenone.[22a] The nmr (Figure 1) of deuterio **3** showed that the deuterium was exclusively in the *exo* position of the norbornene moiety, consistent with an intramolecular mechanism.[22c]

Sequences analogous to the mechanisms in Charts V and VI can, of course, be drawn to account for the α-nortricyclyl and α-norbornenylcyclohexenones. The reaction is initiated in these cases by attack with the α-carbon atom of the enone triplet.[36]

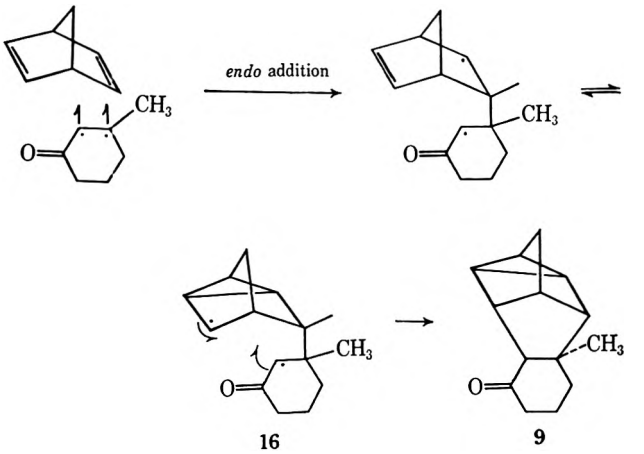
The unique products (**7** and **9**) (Chart II) which are formed in the addition of 3-methyl-2-cyclohexenone and norbornadiene are of interest. The methylenecyclohexanone (**7**) is a 7-*anti*-norbornene derivative and is almost certainly formed from the same intermediate as **6** (Chart VII). It is interesting that the 1,6 shift is apparently favored over the 1,4 process, although the transition state for the former appears less favorable in molecular models. In a control experiment, **6** was found to be quite stable to photolysis and certainly is not the precursor of **7** in the reaction.

CHART VII



Of considerable interest is the product of Diels–Alder-like addition[37] of 3-methyl-2-cyclohexenone and norbornadiene (**9**). This type of adduct was sought for but not found in the additions of 2-methyl-2-cyclohexenone and 2-cyclohexenone to norbornadiene. Its absence in the latter cases is also of interest. It probably arises in the reaction where formed by the route in Chart VIII.

CHART VIII



Attack of the enone triplet with the β-carbon atom from the *endo* side followed by bridging gives a diradical species **16** which cannot undergo the usual 1,4-hydrogen shift, but instead cyclizes to a five-membered ring.

The important question of whether or not the proposed initially formed 1,4 biradicals are intermediates[38] in the formation of the cyclobutane structures will now be considered. The possible processes which are available *a priori* to 1,4 and 1,5 biradicals are as shown in Chart IX.

Since nortricyclyl cyclohexenones are observed, and the product of cyclization to a five-membered ring is not (except in one special case), we must conclude that the 1,4-hydrogen shift is more rapid than this cyclization. In the reaction which does give rise to a cyclization product of the 1,5 biradical, formed from 3-methylcyclohexenone and norbornadiene, the 1,5 biradical is unable to undergo the 1,4-hydrogen shift (Chart VIII). If, then, 1,4 biradicals are precursors of the cyclobutane derivatives, clearly the cyclization reaction is sufficiently faster than a 1,3-hydrogen shift to exclude the latter completely; otherwise the formation of substituted 2-cyclohexenones would be common in many enone addition reactions, and 2-substituted norbornenes would be formed in the norbornadiene additions, neither of which is observed.[9]

Conclusions

The isolation of nortricyclyl- and 7-norbornenylcyclohexenones in the above addition reactions shows that the arrangement of double bonds in norbornadiene modifies the course of these reactions. The former products demand a mechanism in which one bond is formed between the reactants, followed by rearrangements and hydrogen shifts. The nortricyclyl and norbornenyl groups may be bonded to the α and β positions of the cyclohexenone. These products are best interpreted in terms of biradical-like intermediates, and the latter may be of the same type as gives rise to the well-known cyclobutane derivatives.

Experimental Section

Materials.—All solvents and reagents for photoaddition reactions were distilled before use. 2-Cyclohexenone (Aldrich

(35) J. A. Claisse and D. I. Davies, *Chem. Commun.*, 209 (1965).

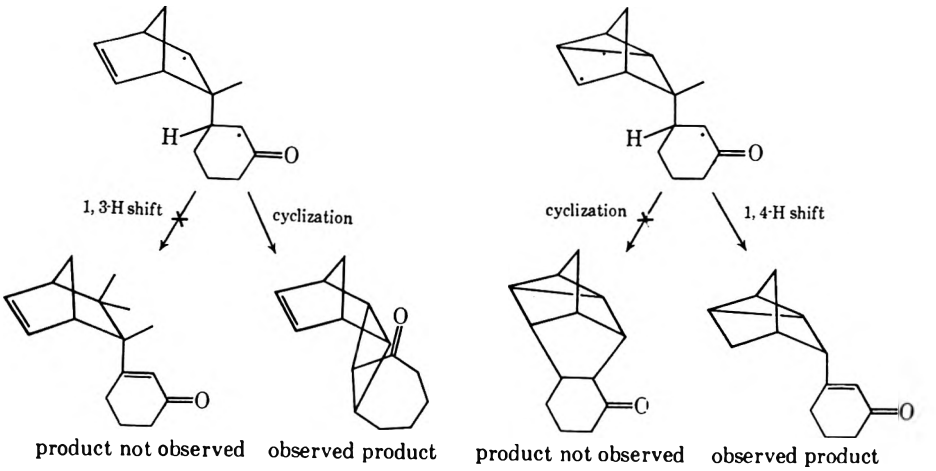
(36) The electronic structure drawn for the cyclohexenone triplet in Charts V and VI is not intended to imply that the excitation is localized in the carbon–carbon double bond; it is simply a convenient way of representing a species with "free valence" at the α- and β-carbon atoms, and has been used previously by Corey, *et al.*[9a]

(37) Orbital symmetry considerations[11] predict that a concerted photochemical addition of this type is forbidden. In view of the other structures isolated in our work, we favor a stepwise mechanism for the formation of **9**.

(38) Corey, *et al.*,[9a] and Schneider and Meinwald[9d] explained their results in terms of biradical intermediates.

CHART IX

POSSIBLE REACTIONS OF 1,4 AND 1,5 BIRADICALS



reagent) had bp 61–62° (16 mm), and 3-methyl-2-cyclohexenone (Aldrich reagent) had bp 58° (10 mm). 2-Methyl-2-cyclohexenone was prepared according to "Organic Syntheses" [39] and had bp 60–66° (20 mm). Bicyclo[2.2.1]hepta-2,5-diene (norbornadiene) (Aldrich reagent) was distilled at atmospheric pressure, bp 89–90°, and was used immediately as it polymerized on standing. Hexane (Eastman practical grade) was purified by successive shaking with concentrated sulfuric acid, water, aqueous potassium permanganate, and finally water. It was then dried over calcium chloride, filtered through a 34 × 4 cm column of silica gel, and distilled, bp 66.5–67.5°. The solvent thus purified had negligible absorption above 250 mμ. *t*-Butyl alcohol was Baker Analyzed reagent, bp 82°.

All photolyses were run under nitrogen, Canadian Liquid Air, certified grade, further purified by successive passage through vanadous sulfate[40] solution and concentrated sulfuric acid and over potassium hydroxide pellets.

Column chromatography was on silica gel, Grace, grade 923 (100–200 mesh). Both analytical and preparative gas chromatography (vpc) were employed. Analytical vpc was performed on a Varian Aerograph Model 204-B, dual-column instrument, with flame-ionization detectors. The following columns were used, with helium carrier gas at 27 ml/min: column A—0.125 in. × 5 ft 10% FFAP on Chromosorb W (60–80 mesh); column B—0.125 in. × 10 ft 12% FS 1265 on Chromosorb W (60–80 mesh); column C—0.125 in. × 5 ft 10% Ucon 300X on Chromosorb W (60–70 mesh). Preparative vpc was conducted on a Varian Aerograph Model 200 instrument with thermal conductivity detector. Helium gas at 60 ml/min was used with the following columns: column D—0.375 in. × 9 ft 20% FS 1265 on Chromosorb W (60–80 mesh); column E—0.375 in. × 4 ft 25% FFAP on Chromosorb W (45–60 mesh); column F—0.375 in. × 10 ft 15% SE-30 on Chromosorb W (60–80 mesh).

Nuclear magnetic resonance (nmr) spectra were routinely run on a Varian A-60 instrument in CCl_4 or CS_2, using tetramethylsilane as internal standard, and chemical shifts are given in parts per million downfield from this standard. Spectra in which spin decoupling was required were run at 100 Mcps on a Varian HA-100 instrument.

Infrared spectra were recorded with a Beckman IR-5 instrument, and for precise measurements a Perkin-Elmer 521 spectrometer was used. Spectral grade CCl_4 or CS_2 were the solvents, depending on the region of interest in the spectrum. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer, usually Fisher "spectranalyzed *n*-hexane" was the solvent.

Mass spectra were obtained using a Hitachi Perkin-Elmer MRU 6 mass spectrometer.

Elemental analyses were by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Photoaddition of 2-Cyclohexenone and Bicyclo[2.2.1]hepta-2,5-diene.—Irradiation of 2-cyclohexenone (8.06 g, 0.84 mol) and norbornadiene (68.8 g, 0.745 mol) in hexane (400 ml), with a Hanovia type L450W lamp fitted with a Pyrex sleeve, in the usual quartz immersion apparatus, under purified nitrogen, resulted in the disappearance of 2-cyclohexenone and the appearance of reaction products.

Progress of the reaction was followed by gas chromatography (column B, 240°) and by thin layer chromatography (tlc) on Eastman Kodak T.L.C. Kit, silica gel coated sheet, K301R developed with 3% ethyl acetate–benzene, of aliquots taken at 15-min intervals. After 7 hr, gas chromatography showed that nearly all of the 2-cyclohexenone had reacted, and the solvent was removed under vacuum. Gas chromatography (column B, 240°) showed components of retention times 4.0 min (**2** and **4**, mixture according to nmr and infrared), 4.5 min (**5**), 7.2 min (**3**), and 8.2 min (**1**), as well as 2-cyclohexenone (1.3 min).

Chromatography of Photolysate.—Since several spots corresponding to the products were obtained on silica gel thin layer chromatography, 2.467 g of the above photolysis mixture were chromatographed on a 64.0 × 4.0 cm column of silica gel, slurry packed in 4% ethyl acetate–benzene; the column was eluted with 6 l. of this solvent, followed by 5 l. of 20% ethyl acetate–benzene, and 125-ml fractions were collected. Fractions 1–3 contained unidentified nonketonic material (53 mg); fractions 4–6 contained **2** and **4** (627 mg); fractions 7–16 contained components **5** (982 mg); **3** and **1** were found in fractions 17–45 (517 mg). Recovery was 2.279 g (92%).

Identification of 2 and 4.—Fractions 4–6 from the column were combined and subjected to preparative vpc (column F, 200°). Two α,β-unsaturated cyclohexenones (infrared band at 5.99 μ) were obtained. Both cyclohexenones had a proton at the β carbon (nmr signal at 6.63 ppm). One was identified as a nortricyclene derivative by the doublet at 12.40 μ in the infrared; the other had a band at 14.20 μ (norbornene double bond).[13]

Identification of Components 5.—Fractions 7–16 contained components **5**; the two carbonyl bands in the infrared (5.82 and 5.88 μ) are characteristic of *cis*- and *trans*-fused isomers[9a] of **5**. The 5.82-μ band attributed to the *trans*-fused system disappeared on attempted separation by preparative vpc at 200°, or on treatment with alumina (*cf.* ref 9a). Also consistent with structure **5** were the infrared absorption at 14.2 μ (double bond) and nmr resonance at 6.00 ppm (2 H, vinylic protons).

Identification of 3.—Components **3** and **1** were found in fractions 17–45 and were separated by vpc (column E, 240°). Compound **3** was a 2-cyclohexenone (infrared band 5.99 μ, carbonyl) and also showed a band at 14.20 μ (double bond).[12] The structure was elucidated by nmr spectroscopy (see Results and Figure 1), and **3** was thus identified as 3-(7-*anti*-bicyclo[2.2.1]-hept-2-enyl)-2-cyclohexenone.

Anal. A satisfactory analysis was obtained for the monodeuterated derivative of **3**; see below.

Identification of 1.—This compound was also purified by vpc of column fractions 17–45. The significant infrared bands were at 5.99 (carbonyl) and 12.35 μ (doublet, nortricyclene).[14] This with the nmr spectrum pointed to 3-(3-tricyclo[2.2.1.$0^{2,6}$]heptyl)-2-cyclohexenone, which was confirmed by synthesis as described below.

(39) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 162.

(40) L. Meites and T. Meites, *Anal. Chem.*, **20**, 984 (1948).

Synthesis of 1.—Nortricyclylmagnesium bromide from nortricyclyl bromide (Aldrich reagent) (5.26 g, 0.030 mol) and magnesium (0.742 g, 0.03 g-atom) in ether (20 ml) was treated with 3-ethoxy-2-cyclohexenone[22b] (4.17 g, 0.029 mol) in ether (10 ml) at 0°, according to the general procedure of Woods, *et al.*[15] Addition was complete in 10 min, and the mixture was stirred for a further 20 min and decomposed with 5% sulfuric acid. The product was isolated with ether and dried with calcium chloride. After solvent removal *in vacuo*, the product was chromatographed on a 34 × 3 cm column of silica gel to remove 3-ethoxy-2-cyclohexenone. The column was eluted with 6% ethyl acetate–benzene, and 125-ml fractions were collected. Fractions 9–12 contained the 3-(3-tricyclo[2.2.1.0^{2,6}]heptyl)-2-cyclohexenone (1), 1.27 g, 23% based on nortricyclyl bromide. This material was identical with 1 from the photolysis, as shown by vpc behavior and infrared and nmr spectra.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.59. Found: C, 82.80; H, 8.72.

Photostability of 3-(3-Tricyclo[2.2.1.0^{2,6}]heptyl)-2-cyclohexenone (1).—A solution of 1 in cyclohexane (400 ml, 0.006 *M*) was photolyzed under reaction conditions for 14 hr, and the composition of the solution was monitored by vpc and infrared and ultraviolet spectroscopy. The absorption at 340 mμ had decreased slightly after this time, but no photolysis products appeared on vpc, and the infrared spectrum was unchanged.

Photoaddition of 3-Deuterio-2-cyclohexenone and Norbornadiene.—3-Deuterio-2-cyclohexenone[22a] (4.955 g, 0.0510 mol), judged 99% deuterated at the β position by nmr, and norbornadiene (36.72 g, 0.399 mol) in hexane (380 ml) were photolyzed for 5 hr through Pyrex with the Hanovia type L450W lamp. The photolysate (8.623 g) obtained on solvent evaporation was analyzed by vpc (column A, 228°) and showed the same products as the addition of 2-cyclohexenone and norbornadiene. 5-Deuterio-3-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexenone was isolated as described above for the protio compound. The mass spectrum had a molecular ion at *m/e* 189 ($C_{13}H_{15}DO$), and the nmr spectrum is shown in Figure 1.

Anal. Calcd for $C_{13}H_{15}DO$: C, 82.50; H + D, 9.05. Found: C, 82.53; H + D, 9.11.

Photoaddition of 3-Methyl-2-cyclohexenone and Norbornadiene.—Irradiation of 3-methyl-2-cyclohexenone (4.583 g, 0.0416 mol) and norbornadiene (50.0 g, 0.543 mol) in *t*-butyl alcohol (350 ml) and methanol (20 ml), for 3 hr as described for 2-cyclohexenone and norbornadiene, resulted in reaction of about 60% of the 3-methyl-2-cyclohexenone, estimated by infrared and vpc (column B, 231°) monitoring. After solvent distillation, the liquid residue (5.960 g) was chromatographed on a 36 × 4.0 cm column of silica gel, slurry packed in 3% ethyl acetate–benzene. The column was eluted with 5 l. of 3%, 6 l. of 5%, and 10 l. of 15% ethyl acetate–benzene, and 200-ml fractions were collected. The fractions were monitored by infrared and nmr spectra, and by vpc on the Ucon column C at 195°, on which all of the products of interest had different retention times. Fractions 10–12 contained a single product—7 (retention time 12.4 min) (688 mg); fractions 13–15 (1.045 g) contained five products—7 (12.4 min), 17 (18.0 min), 9 (19.6 min), 6 (21.4 min), and 8 (24.4 min). Fractions 16 and 17 were compound 18 (19.0 min, 474 mg). Fractions 18–60 were a mixture of *cis*- and *trans*-fused cyclobutanes (1.090 g) which were not investigated in detail, and 3-methyl-2-cyclohexenone (1.619 g) was eluted in the latter fractions). Recovery from the column was 4.916 g (84%). From the vpc analyses of these fractions, an estimate of the yields of products (6–9) could be made. These yields are given below for each component along with its characterization.

Isolation and Identification of 7.—The yield (15%) was also measured by vpc of the reaction mixture on column B at 230°. Preparative vpc of fractions 10–12 (column E, 245°) afforded pure 7, retention time 11 min. The spectral data showed that the compound was a cyclohexanone, and contained a vinyl methylene group and a norbornene double bond. The ultraviolet spectrum showed enhanced n–π* absorption, λ_{max}^{hexane} 300 mμ (ε 103), suggesting a β,γ-unsaturated ketone. The mass spectrum had a molecular ion of *m/e* 202, and all of the data pointed to 3-methylene-2-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)cyclohexanone.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.22; H, 8.86.

This structure was confirmed by the isomerization of 7 to 6, the conjugated isomer which was identified by degradation.

Base-Catalyzed Isomerization of 7 to 6.—The *exo*-methylene ketone 7 (0.786 g, 0.00388 mol) was stirred with sodium hydroxide (0.494 g, 0.0124 mol) in dioxane (150 ml) and water (60 ml) under nitrogen for 52 hr at 25°. The solution was ether extracted (four 50-ml portions); the extracts were washed with water (eight 50-ml portions) and dried ($MgSO_4$). Evaporation of the ether gave 0.500 g (64%) of a 2-cyclohexenone (infrared band at 5.99 μ), identified with component 6 of the photolysis by vpc on column C at 200°, retention time 19.6 min. The latter was not isolated from the photolysis, since it was only formed in 2% yield. The spectral data (see Results) were obtained on material from the isomerization of 7, and the structure assigned to 6 therefore that of is 3-methyl-2-(7-*anti*-bicyclo[2.2.1]hept-2-enyl-2-cyclohexenone.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.99; H, 8.97.

Photostability of 6.—The conjugated enone (6, 141 mg), from isomerization of the *exo*-methylene ketone 7 in hexane (54 ml), was irradiated with the Hanovia 450-W lamp for 5.5 hr. Gas chromatography (column C, 195°) did not show any peaks other than 6, retention time 23 min. Evaporation of the hexane afforded a quantitative recovery of 6, characterized by infrared and nmr spectroscopy.

Diimide Reduction[18] of 3-Methyl-2-(7-*anti*-bicyclo[2.2.1]hept-2-enyl-2-cyclohexenone (6).—Compound 6 (0.500 g, 0.00247 mol) and the dipotassium salt of azodicarboxylic acid (0.800 g, 0.00412 mol) in methanol (30 ml) were stirred under nitrogen while glacial acetic acid was added dropwise until all the solid salt had dissolved. Saturated $NaHCO_3$ solution (40 ml) was added, and the solution was extracted with ether (three 25-ml portions) and the extracts were dried ($MgSO_4$). Evaporation of the ether afforded 0.450 g (90%) of liquid which gave one peak on column B at 228°, was a cyclohexenone (infrared band at 5.99 μ), and had no vinylic protons (nmr spectrum). The mass spectrum had a molecular ion, *m/e* 204, consistent with the structure of 3-methyl-2-(7-bicyclo[2.2.1]heptyl)-2-cyclohexenone.

Oxidative Degradation of 3-Methyl-2-(7-bicyclo[2.2.1]heptyl)-2-cyclohexenone.—To a mixture of 7-norbornylcyclohexenone from the diimide reduction (0.450 g, 0.00221 mol), potassium carbonate (0.452 g, 0.00328 mol) dissolved in 13 ml of water, 48 ml of *t*-butyl alcohol–water azeotrope, 8 ml of a solution of sodium metaperiodate (3.23 g) in water (40 ml), and 8 ml of 0.8% aqueous potassium permanganate were added; then a further 33 ml of the above periodate solution was added at the rate of 1.8 ml/min for 10 min, then 0.5 ml/min for 30 min.

Sodium metabisulfite solution was then added, until the solution turned from red to brown, then a slight excess was added, and the solution was concentrated under reduced pressure to about 30 ml, cooled to 4°, and acidified with ice-cold 50% sulfuric acid (40 ml). The solution was ether extracted (four 25-ml portions); the extracts were washed with sodium metabisulfite, then with water, and dried ($MgSO_4$). The oily residue was subjected to liquid–liquid partition chromatography[41] on a column 3 × 55 cm slurry packed in pentane with 83.3 g of Mallinckrodt silicic acid and 16.7 g of Eagle–Picher Celatom, which had been coated with a mixture of 8.5 ml of water, 40 ml of methanol, 7.5 drops of 1 *N* ammonia, and 5 ml of bromocresol green solution (0.200 g/25 ml of methanol); 125-ml fractions were collected; and pentane eluted an acid, mp 56–64°, found in fractions 3 and 4. This was sublimed twice at atmospheric pressure to afford waxy white crystals, mp 74.0–75.0° (lit.[19b] mp 75–76.5°). The acid was identical with an authentic sample of 7-norbornanecarboxylic acid[20] by infrared, nmr, and mixture melting point.

Identification of 17.—Fraction 13 of the above column was subjected to vpc, column B at 245° (retention time 17 min). This infrared had bands at 5.90 and 14.20 μ (norbornene), consistent with a *cis*-fused cyclobutane adduct of norbornene and 3-methyl-2-cyclohexenone.

Identification of 9.—The infrared and nmr spectra of fractions 14 and 15 suggested that these might contain a nortricyclic adduct having a cyclohexanone carbonyl, which would correspond to structure 9, Chart II. The following oxidation procedure was employed to remove unsaturated compounds. A mixture containing 57% 9 (640 mg) in 30 ml of *t*-butyl alcohol–water azeotrope was added to K_2CO_3 (278 mg) in water (70 ml) with stirring. This was followed by the addition of 5 ml of a solution of sodium metaperiodate (2.0 g) in water (25 ml) and 2.0 ml of 0.8% aqueous potassium permanganate. A further 10 ml of periodate solution was added over 10 min, followed by 7.0 ml over 20 min.

(41) W. A. Neville, D. S. Frank, and R. D. Trepka, *J. Org. Chem.*, **27**, 422 (1962).

Further additions of the permanganate solution were made—1 ml was added after 2 min, then six 0.5-ml portions were added at 5 min intervals. Stirring was continued for 3 hr, excess bisulphite solution was added, and the solution was concentrated to half-volume *in vacuo;* it was cooled in ice, neutralized with cold 50% H_2SO_4, and extracted with ether. The extracts were washed with $NaHCO_3$ solution and water, then with 5% NaOH solution and again with water, and dried ($CaSO_4$). Evaporation of the ether gave 9 (160 mg), retention time 21 min on column C at 195°. The infrared had peaks at 5.90 (cyclohexanone carbonyl) and at 12.35 μ (nortricyclene doublet). The nmr showed a methyl signal at 1.02 ppm and no absorption downfield of 2.50 ppm. The mass spectrum had a molecular ion of *m/e* 202, and an analytical sample was obtained by preparative vpc (column E, 227°). The yield of 9 is estimated at 16%, and the assigned structure is that of 9-methylpentacyclo[7.4.0.$0^{2,7}$.$0^{3,5}$.$0^{4,8}$]tridecan-13-one.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.10; H, 8.87.

Identification of 8.—Fraction 13 from chromatography of the photolysis mixture was subjected to preparative vpc (column E, 235°). A peak (8) of retention time 18 min was collected and had a methyl peak at 2.07 ppm in the nmr and no vinylic protons. The infrared bands were at 6.00 (conjugated carbonyl) and 12.37 μ (nortricyclene). Product 8 is thus identified as **3-methyl-2-(3-tricyclo[2.2.1.0^{36}]heptyl)-2-cyclohexenone** and was formed in 8% yield in the photolysis.

Identification of 18.—Fractions 16 and 17 of the chromatography had *cis-* and *trans*-fused cyclobutanes with carbonyl bands at 5.86 and 5.91 μ and one of these was purified by gas chromatography. A peak of retention time 18 min on column E at 235° was collected. From the latter part of this peak an adduct was isolated which gave a molecular ion of *m/e* 202 and had infrared absorption at 5.91 (carbonyl, *cis*-fused system) and at 14.12 μ (norbornene). The adduct is identified as a *cis*-fused cyclobutane adduct of 3-methylcyclohexenone and norbornadiene and further stereochemical details are unspecified.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.19; H, 8.95.

Photoaddition of 2-Methyl-2-cyclohexenone and Norbornadiene.—2-Methyl-2-cyclohexenone (2.327 g, 0.0211 mol) and norbornadiene (19.854 g, 0.2155 mol) in *t*-butyl alcohol (375 ml) and methanol (20 ml) were photolyzed for 8 hr under the usual conditions. Monitoring by gas chromatography (column B, 245°) showed peaks of retention times 2.8 min (**13**), 6.9 min (**12**), and 7.9 min (**11**). Also observed were several peaks of retention times between 3.8 and 4.6 min and these components were not investigated in detail. The vpc analysis also showed that 75% of starting enone had reacted. The infrared spectra of aliquots had carbonyl bands at 5.80, 5.90, and 5.99 μ. The mixture remaining after solvent evaporation was chromatographed on a 36 × 4.0 cm column of silica gel, slurry packed in 2% ethyl acetate–benzene. The column was eluted with 6 l. of 2%, 1.5 l. of 3%, 2.5 l. of 4%, and 2 l. of 15% ethyl acetate–benzene, 200-ml fractions being collected. Fractions 12–17 (1.145 g) contained the components with retention times of 3.8–4.6 min, and these had infrared absorption at 5.90 μ (*cis*-fused cyclobutanes) except for fraction 12 which was mainly the 2.8-min compound (**13**). Fractions 18–60 (688 mg) contained **12** and **11**. Recovery from the column was 1.833 g.

Identification of 13.—Fraction 12 of the above column was separated by preparative vpc (column E, 245°) to afford **13**, which had infrared carbonyl absorption at 5.80, typical of *trans*-fused cyclobutane adducts of 2-cyclohexenones and alkenes, and absorption at 14.2 μ (norbornene double bond). This product was formed in 5% yield in the photolysis.

Identification of 12.—Fractions 20–28 were resolved by preparative vpc (column E, 245°). Compound **12** was collected (retention time 36 min); this had infrared bands at 5.99 (conjugated carbonyl) and at 14.20 μ (norbornene). The nmr spectrum is discussed in Results and is shown in Figure 2. From these spectra the structure assigned to **12** is that of **2-methyl-3-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexenone.**

Identification of 11.—Fractions 36–44 contained **11**, which was purified by preparative vpc on column A at 245° (retention time 40 min). The infrared showed unsaturated carbonyl absorption at 5.99 and a nortricyclene band at 12.37 μ. The nmr was similar to that of other nortricyclenes which we have characterized in this work. The spectra suggested that this product (**11**), which constituted 14% of the photolysis products, was **2-methyl-3-(3-tricyclo[2.2.1.$0^{2,6}$]heptyl)-2-cyclohexenone**, and this structure was confirmed by the synthesis outlined in Results.

2-Methyl-3-ethoxy-2-cyclohexenone.—This was prepared by a modification of the method of Gannon and House.[22b] A mixture of 2-methyl-1,3-cyclohexanedione (Aldrich) (24.82 g, 0.197 mol), *p*-toluenesulfonic acid monohydrate (1.035 g, 0.00544 mol), absolute ethanol (115 ml), and benzene (400 ml) were heated for 10 hr so that the benzene–water–ethanol azeotrope distilled at 67–70° during this time. The volume of the mixture was half of the original volume after 10 hr, and the mixture was extracted as described for 3-ethoxy-2-cyclohexenone.[22b] The dried ether solution was evaporated, and the following crystallization procedure was conducted in a drybox, under dry nitrogen. To the solid residue from the ether evaporation was added hexane (300 ml), and the solid was dissolved by warming. The solution deposited white crystals on cooling which were filtered, mp 58.5–59.5°, 11.75 g. A second and third crop (total 6.85 g) of yellow crystals were obtained from the filtrate; these had mp 56–59°. The total yield was 18.60 g (61%). The infrared showed two peaks in the carbonyl region at 6.05 and 6.18 μ, which are also shown by 3-ethoxy-cyclohexanone. The nmr spectrum was also consistent with the structure of **2-methyl-3-ethoxy-2-cyclohexenone.**

Anal. Calcd for $C_9H_{12}O_2$: C, 70.10; H, 9.15. Found: C, 70.26; H, 9.25.

The crystals were very hygroscopic and liquified rapidly in the air of the laboratory.

Synthesis of 11.—The Grignard reagent from nortricyclyl bromide (Aldrich) (8.572 g, 0.0495 mol) and magnesium (1.227 g, 0.0505 g-atom) in ether (30 ml) was prepared by the procedure of Woods, *et al.*,[15] but the reaction was run in a drybox under nitrogen. To the Grignard reagent cooled to 0° was added 2-methyl-3-ethoxy-2-cyclohexenone (7.735 g, 0.0502 mol) in ether (45 ml); the addition required 15 min; and the mixture was stirred. The stirring was continued for a further 30 min, and the solution was allowed to reach ambient temperature. After decomposition with 5% H_2SO_4, the ether solution was separated, washed with water, and dried ($CaSO_4$). The ether was evaporated to yield 7.62 g of oil, which was chromatographed on a 3 × 44 cm column of silica gel, slurry packed in 6% ethyl acetate–benzene, and eluted with this solvent, and 200-ml fractions were collected. Fractions 3–7 contained **11**, 1.10 g (11%), judged pure by vpc on column C at 195°, and identical with the photolytic product **11** by infrared and nmr spectra. Product **11** is therefore identified as 2-methyl-3-(3-tricyclo[2.2.1.$0^{2,6}$]heptyl)-2-cyclohexenone.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.21; H, 8.90.

Registry No.—Norbornadiene, 121-46-0; **3**, 20678-85-7; **4**, 20678-86-8; **5**, 14478-12-7; **6**, 20678-87-9; **7**, 20678-89-1; **12**, 20678-90-4; 5-deuterio-3-(7-*anti*-bicyclo[2.2.1]hept-2-enyl)-2-cyclohexanone, 20678-88-0; 2-methyl-3-ethoxy-2-cyclohexenone, 20643-20-3.

Acknowledgments.—We are grateful to Dr. J. Warkentin for a sample of norbornane-7-carboxylic acid and to Dr. R. A. Bell and Mr. J. Saunders for help in obtaining the nmr spectra. We gratefully acknowledge a grant from the Uniroyal Co., Ltd., which was used to purchase a gas chromatograph, and thank the National Research Council of Canada for continued financial support.

Hydrogenation of *syn*- and *anti*-7-Acetoxynorbornenes and 7-Acetoxynorbornadiene over Platinum and Palladium Catalysts[1a]

WILLIAM C. BAIRD, JR., BORIS FRANZUS,[1b] AND JOHN H. SURRIDGE

Central Basic Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey 07036

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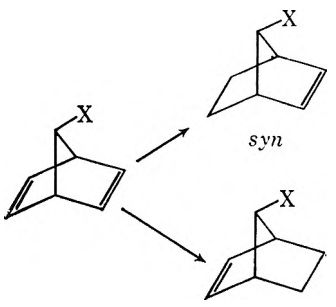
A study of the hydrogenation of *syn*- and *anti*-7-acetoxynorbornenes, 7-acetoxynorbornadiene, and related compounds over various platinum and palladium catalysts has been made. A marked sensitivity of these reductions to catalyst, catalyst prereduction, and the steric requirements of the 7 substituents has been observed. In addition to the anticipated reduction products, the hydrogenation of 7-acetoxynorbornadiene has yielded 3-acetoxynortricyclene in amounts ranging from 3–5% over platinum catalysts to 25–30% over prereduced palladium catalysts. Reductions utilizing deuterium have shown that the dienyl acetate and *syn*-7-acetoxynorbornene experience substantial *endo,cis* deuterium addition as well as the normally anticipated *exo,cis* addition. The *anti*-acetate reduces exclusively through *exo,cis* addition. The relative rates of *syn* and *anti* double-bond reduction, k_{anti}/k_{syn}, for *syn*- and *anti*-acetoxynorbornenes and for 7-acetoxynorbornadiene have shown that, while reduction of the monoolefins is largely controlled by steric effects, the reduction of the dienyl acetate is less sensitive to steric factors. A rationale for these observations is attributed to the direction of coordination of the olefinic substrates with the catalyst. The hydrogenation of norbornadiene and 7-acetoxynorbornadiene over prereduced palladium has revealed the anomalous behavior of the prereduced catalyst.

The preparation of *anti*-7-substituted norbornenes by the chemical reduction of readily available 7-substituted norbornadienes has been described in previous papers from this laboratory (eq 1).[2,3] Chemical reducing



(1)

X = OH, $OOCCH_3$, $OC(CH_3)_3$

agents have been found to be unsatisfactory for the synthesis of the corresponding *syn* isomers (eq 1) owing to the influence of electronic factors that direct such electrophilic additions preferentially to the *syn* double bond.[3,4] The argument was subsequently advanced that, in those reactions where electronic factors are nonoperative, then the steric shielding of the *syn* double bond of the diene by the 7 substituent should direct the reaction to the *anti* double bond.[4a] Consequently, catalytic hydrogenation of these dienes should occur primarily with the formation of *syn* product.[5] Experimental verification of this proposal resided in the reduction of 7-substituted norbornadienes over platinum and palladium catalysts to yield product mixtures enriched in the *syn* isomer.[4a,6]

Although these experimental results indicated a degree of steric control, close inspection of the details of these reductions revealed several peculiar features. First, when the 7 substituent was varied from hydroxy to acetoxy to *t*-butoxy, the observed *syn*/*anti* ratios corresponded to an order of steric requirement, $OOCCH_3 > OH > OC(CH_3)_3$, which was obviously illogical and demonstrated that the invocation of steric factors *per se* in these reductions did not account for the observed product distributions.

Secondly, it was noted that the use of the *syn*/*anti* ratio as an indicator for the true stereoselectivity of the hydrogenation reaction was misleading. This fact became apparent when the source of saturated compound (30–50% of the total) produced during these reductions was considered. The logical precursors of the saturated product were the isomeric *syn*- and *anti*-norbornenes. Since it had been qualitatively shown that the *anti* isomer is rapidly hydrogenated to saturated material,[4a] it was reasonable to expect that the reduction of the diene was producing substantially more *anti* compound than was ultimately detected in the reaction mixture.

Finally, it was apparent that the product distribution of reductions performed over prereduced palladium catalysts was completely different from those utilizing a nonprereduced catalyst. In contrast, platinum-catalyzed hydrogenations were independent of this variable.

In order to probe and define the chemistry of these reductions, a study of the hydrogenation of 7-acetoxynorbornadiene (**1**), *syn*- (**2**) and *anti*-7-acetoxynorbornenes (**3**), and related compounds over various palladium and platinum catalysts was undertaken. This report describes the results of these experiments and their implications.

Results

The hydrogenation of 7-acetoxynorbornadiene (**1**) over platinum and palladium catalysts proceeded as illustrated by eq 2; product distributions representative of these reductions are summarized in Table I.

(1) (a) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p 0–10. (b) Department of Chemistry, East Tennessee State University, Johnson City, Tenn.

(2) Lithium Aluminum Hydride. B. Franzus and E. I. Snyder, *J. Amer. Chem. Soc.*, **87**, 3423 (1965).

(3) Diimide. W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *ibid.*, **89**, 410 (1967).

(4) (a) B. Franzus, W. C. Baird, Jr., E. I. Snyder, and J. H. Surridge, *J. Org. Chem.*, **32**, 2845 (1967); (b) G. W. Klumpp, A. H. Veefkind, W. L. deGraaf, and F. Bickelhaupt, *Ann.*, **706**, 47 (1967); (c) J. Haywood-Farmer, R. E. Pincock, and J. I. Wells, *Tetrahedron*, **22**, 2007 (1966); (d) W. C. Baird, Jr., and M. Buza, *J. Org. Chem.*, **33**, 4105 (1968).

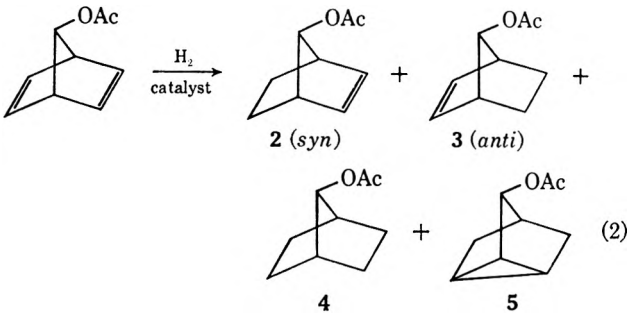
(5) (a) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Amer. Chem. Soc.*, **87**, 2596 (1965); (b) R. L. Burwell, Jr., *Chem. Rev.*, **57**, 895 (1957); (c) E. E. van Tamelen and R. J. Timmons, *J. Amer. Chem. Soc.*, **84**, 1867 (1962); (d) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *ibid.*, **64**, 1985 (1942).

(6) B. Franzus, W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **33**, 1288 (1968).

TABLE I

REDUCTION OF 7-ACETOXYNORBORNADIENE

Catalyst	Product composition, % *syn* 2	*anti* 3	Satd 4	Diene 1	Nortricyclene 5
Pd/C	46.1	9.0	21.6	18.3	5.0
HPd/C	28.8	26.6	14.1	8.9	21.7
PtO_2	37.2	3.2	27.1	32.5	4.6
HPt/C	44.2	4.0	21.3	23.3	7.2
Pt/C	35.8	3.0	29.3	25.6	6.3



A remarkable feature of these hydrogenations was the formation of 3-acetoxynortricyclene (**5**) in amounts ranging from 5–10% over platinum and nonprereduced palladium catalysts to 20–30% over prereduced palladium on charcoal. The formation of this nortricyclene derivative constituted the first occurrence of homoconjugative addition to a norbornadiene system during catalytic hydrogenation.[6-8] That the nortricyclic ester (**5**) is derived from 2,6 addition to the acetoxydiene (**1**) was apparent from the gradual increase of the nortricyclyl acetate content to the point at which no 7-acetoxynorbornadiene remained unreduced, and the production of the nortricyclic ceased. No 3-acetoxynortricyclene was formed during control reductions of *syn*- and *anti*-7-acetoxynorbornenes, a fact that revealed the dependence of the cyclization reaction on the presence of diene substrate. The nortricyclic acetate was stable under the reaction conditions, for the ester was not isomerized[9] or reduced by continued exposure to catalyst and hydrogen.

Table I reveals the sensitivity of the reduction to the choice of catalyst and in the case of palladium catalysts the effect of prereduction of the catalyst.[10] Product distributions obtained with platinum catalysts were essentially invariant and indicated independence of the catalyst source and its prereduced or nonprereduced state. A prereduced palladium catalyst produced *syn* (**2**), *anti* (**3**), and nortricyclic (**5**) esters in nearly equivalent amounts, but over a nonprereduced palladium catalyst the formation of *anti* isomer and nortricyclene was significantly diminished relative to *syn* compound. If the palladium-catalyzed reductions were performed at an initial hydrogen pressure of 2 atm, the relationship among *syn*, *anti*, and nortricyclic products was similar to that observed over a nonprereduced catalyst at atmospheric pressure.

The distinctive product distributions from the reduction of 7-acetoxynorbornadiene over these catalysts implied that the hydrogen addition reaction might not be occurring through *exo,cis* addition.[5] In order to explore this possibility, an examination of the direction of addition was undertaken by using deuterium as the reducing gas. This approach was not applicable to platinum-catalyzed reductions, for deuterium scrambling and/or deuterium–hydrogen exchange reactions precluded any accurate interpretation of the reduction path.[5b,11] Reductions over palladium catalysts, however, have been shown to be free of these complications,[5,6,12] and significant information was obtained from the palladium-catalyzed deuteriogenation of 7-acetoxynorbornadiene and *syn*- and *anti*-7-acetoxynorbornenes. The direction of deuterium addition to these compounds was ascertained by nmr analysis of the relative areas of the *endo* and *exo* hydrogens occurring at δ 0.80–1.30 and δ 1.50–1.85, respectively.[13,14]

Partial deuterium reduction (*ca.* 50% of theory) of 7-acetoxynorbornadiene (**1**) over palladium catalysts in ethanol proceeded in accord with Scheme I, yielding the products with the deuterium configurations illustrated. Table II summarizes the *exo,cis–endo,cis* deuterium distributions in the various products; the product compositions were comparable with those of Table I. The outstanding feature of these reactions was the significant degree of *endo,cis* deuterium addition that occurred in both steps of the reaction. The reduction of the *syn* double bond of the diene to yield *anti* isomer (**7**) involved 100% *endo,cis* addition; reduction of the *anti* double bond of **1** to *syn* product (**6**) exhibited *ca.* 15–30% *endo,cis* deuterium addition (**6b**) depending upon the reaction pressure and catalyst treatment. The formation of 3-acetoxynortricyclene (**9**) proceeded *via* homoconjugative addition to introduce the 5,7 deuteriums in an *endo,endo* configuration.[15] Analysis of the saturated product, 7-acetoxynorbornane (**8**), revealed that *ca.* 30–50% of the deuterium atoms had added *endo,cis*. Furthermore, of these *endo,cis* deuteriums, 70–80% were *syn* to the acetate group (**8a,c,d**) while the remainder were *anti* (**8d,e**). Conversely,

(7) The formation of 3-substituted nortricyclenes has also been observed during the reduction of 7-*t*-butoxynorbornadiene[4a] and 7-*t*-butylnorbornadiene; W. C. Baird, Jr., and J. H. Surridge, unpublished data.

(8) Nortricyclenes have been produced by a variety of heteropolar and homopolar additions to norbornadiene. (a) P. de Mayo, "Molecular Rearrangements," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1963, p 198; (b) S. Winstein and M. Shatavsky, *Chem. Ind.* (London), 56 (1956); (c) H. C. Kuivila and C. R. Warner, *J. Org. Chem.*, **29**, 2845 (1964), and references cited therein; (d) D. I. Davies and L. T. Parfitt, *J. Chem. Soc., C*, 2691 (1967); (e) M. Green, *ibid.*, 541 (1965); (f) H. Heaney and J. M. Jablonski, *Tetrahedron Lett.*, 2733 (1967); (g) T. V. van Auken and E. A. Rick *ibid.*, 2709 (1968).

(9) Transition metal catalyzed cleavage of the cyclopropane ring analogous to the valence isomerization of quadricyclene to norbornadiene was not detected. H. Hogeveen and H. C. Volger, *J. Amer. Chem. Soc.*, **89**, 2486 (1967).

(10) In reactions utilizing a prereduced catalyst, the catalyst was hydrogenated prior to the injection of the acetoxydiene into the catalyst–solvent suspension. All reagents were present prior to the admission of hydrogen in nonprereduced reactions. See also ref 4a

(11) H. C. Volger and H. Hogeveen, *Rec. Trav. Chim.*, **87**, 1356 (1968).

(12) Norbornane experienced only 4% deuterium–hydrogen exchange over palladium at 75°. R. L. Burwell, Jr., B. K. C. Shim, and H. C. Rowlinson, *J. Amer. Chem. Soc.*, **79**, 5142 (1957).

(13) For the chemical shifts of *endo* and *exo* protons in norbornyl and norbornenyl compounds, see (a) E. I. Snyder and B. Franzus, *ibid.*, **86**, 1166 (1964); (b) M. E. Brennan and M. A. Battiste, *J. Org. Chem.*, **33**, 324 (1968); (c) F. A. L. Anet, H. H. Lee, and J. L. Sudmeier, *J. Amer. Chem. Soc.*, **89**, 4431 (1957); (d) J. C. Davis, Jr., and T. V. van Auken, *ibid.*, **87**, 3900 (1965); (e) P. M. Subramanian, M. T. Emerson, and N. A. Lebel, *J. Org. Chem.*, **30**, 2624 (1965); (f) P. Laszlo and P. V. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964); (g) B. Franzus, W. C. Baird, Jr., N. F. Chamberlain, T. Hines, and E. I. Snyder, *ibid.*, **90**, 3721 (1968); (h) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968).

(14) For the stereochemistry and nmr spectra of deuterated norbornane, norbornene, and 7-acetoxynorbornenes and -norbornane, see ref 2, 3, and 6.

(15) Deuterium decoupling experiments by Dr. E. I. Snyder, University of Connecticut, have confirmed that the deuterium atoms occupy the 5,7 positions. The chemical shifts of the 5,7 protons are consistent with those anticipated for *exo* hydrogens.

SCHEME I

STERIC COURSE OF DEUTERIUM ADDITION TO 7-ACETOXYNORBORNADIENE AND 7-ACETOXYNORBORNENES

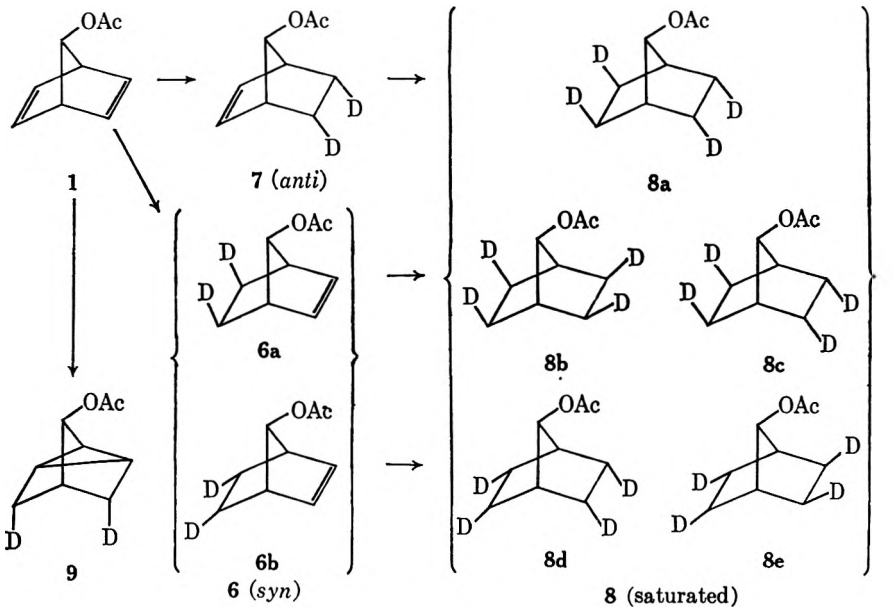


TABLE II

DIRECTION OF DEUTERIUM ADDITION TO 7-ACETOXYNORBORNADIENE

	% distribution of deuterium					
	syn 6		*anti* 7		Saturated 8	
Catalyst	*endo,cis* 6b	*exo,cis* 6a	*endo,cis*	*exo,cis*	*endo,cis* 8a,c–e	*exo,cis* 8a–c,e
Pd/C[a]	21	79	100	0	52	47
Pd/C[b]	15	85	100	0	33	67
HPd/C[b]	28	72	100	0	40	60

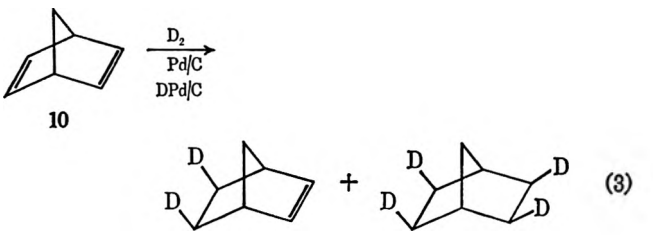
[a] 2 atm of D_2. [b] 1 atm of D_2.

60–70% of the *exo,cis* deuteriums were *anti* to the 7 substituent (**8a–c**).

The deuterium reduction of *syn*- and *anti*-7-acetoxynorbornenes revealed that the second stage of the hydrogenation reaction also involved *endo,cis* addition. That only the *syn*-acetate experienced *endo,cis* addition was shown by the reduction of 5,6-dideuterio-*syn*-7-acetoxynorbornene (**6a,b**) (Scheme I). While the initial olefin contained 21% *endo,cis* deuterium (**6b**) and 79% *exo,cis* (**6a**), reduction over a nonprereduced palladium catalyst yielded saturated ester containing 29% *endo,cis* and 71% *exo,cis* deuteriums. This change corresponded to 40% *endo,cis* deuterium addition; over a prereduced catalyst the degree of *endo,cis* reduction amounted to 30%.

Deuterium reduction of the dideuterated *anti*-acetate (**7**) gave exclusively *exo,cis* addition (Scheme I) independent of the state of reduction of the catalyst. Similarly, *syn*- and *anti*-7-hydroxynorbornenes were reduced with deuterium by exclusively *exo,cis* addition.

Unlike 7-acetoxynorbornadiene, the parent olefin, norbornadiene (**10**), undergoes reduction over either a nonprereduced[5a] or a prereduced palladium-on-charcoal catalyst[6] to yield only *exo,cis* deuterated products (eq 3). Neither reduction yielded any nortricyclene, a fact that indicates that the presence of a 7 substituent is a necessary condition for homoconjugative reduction.[7] Although these reductions exhibited the same stereochemistry, the selectivity to *exo,exo*-5,6-dideuterionorbornene (**11**) at *ca.* 50% reduction was definitely sensitive to catalyst prereduction (eq 3).



The different stereochemistry associated with the reduction of norbornadiene and 7-acetoxynorbornadiene over palladium catalysts generated a valuable experiment.[16] It was of interest to subject an equimolar mixture of the dienes to deuterium reduction, for it was conceivable that the coreduction of the diolefins over the same catalyst might change the direction of deuterium addition from that observed in the individual cases. Deuterium reduction of the diene mixture, however, did not exhibit any departures from previously observed stereochemistry; norbornadiene reduced exclusively *exo,cis* and the dienyl acetate experienced both *endo,cis*–*exo,cis* and homoconjugative addition. That the reductions occurred independent of one another was apparent.

An aspect of the coreduction of the diene mixture that was revealed after the fact was the impact that the

(16) This experiment was suggested by Professor H. C. Brown.

presence of an equimolar amount of norbornadiene, or norbornene, had on the product distribution. Determination of the relative rates of disappearance of the starting diolefins and of the appearance and disappearance of the various monoolefinic species established this reactivity order: norbornadiene $\gg$ 7-acetoxynorbornadiene $\geq$ norbornene $\gg$ *anti*-7-acetoxynorbornene $>$ *syn*-7-acetoxynorbornene.[6] This sequence indicated that the conversion of the *syn*- and *anti*-acetates to saturated product could be effectively suppressed by the presence of norbornene. Thus, if mixtures of dienyl acetate and norbornadiene, or norbornene, were reduced until no dienyl acetate remained, the product mixture was composed only of *syn*, *anti*, and nortricyclic esters. It should be emphasized that similar selectivity effects were not realized with platinum catalysts.

The addition of norbornene and norbornadiene to reductions of 7-acetoxynorbornadiene exerted one other influence on this reaction. In those reactions where norbornadiene was present, no differences in acetate product composition were noted when a prereduced or a nonprereduced catalyst was used. With the exception of the decreased formation of saturated product due to the inhibition of its formation by norbornene, the product mixtures derived from reductions containing norbornadiene bore a strong resemblance to those obtained over a nonprereduced catalyst. The loss of the effect of catalyst prereduction is attributed to the fact that the first olefin hydrogenated by the catalyst is norbornadiene. As a result, when the dienyl acetate is finally exposed to the palladium catalyst, the catalyst is not truly "prereduced." This situation does not apply to reductions performed in the presence of norbornene, for the first olefin to be hydrogenated by the catalyst is 7-acetoxynorbornadiene, and these reductions give product mixtures characteristic of a prereduced catalyst.

The final phase of this study of the hydrogenation of 7-acetoxynorbornadiene and *syn*- and *anti*-7-acetoxynorbornenes was the determination of the relative rates of reduction of the *syn* and *anti* double bonds in these compounds. For the isomeric *syn*- and *anti*-acetates, k_{syn} and k_{anti} were simply defined as the rates of conversion of these olefins to saturated ester. The relative rate, k_{anti}/k_{syn}, was determined by competitive hydrogenation of mixtures of the *syn* and *anti* compounds over various catalysts according to the general procedure described by Hussey, Baker, and Keulks;[17] these data are summarized in Table III. From the data of Table III, it is clear that only in the reduction of *syn*- and *anti*-7-hydroxynorbornenes is no preferential reactivity observed. Competitive reduction of *syn*- and *anti*-7-acetoxynorbornenes has shown a marked preference for *anti* double bond reduction independent of the catalyst, and there can be little doubt that the reduction of these isomeric monoolefins is controlled by steric factors. The sterically hindered *syn* double bond simply cannot compete as effectively for the catalyst sites. The diminished k_{anti}/k_{syn} value for the prereduced palladium catalyst relative to the nonprereduced would seem to reflect a more reactive, less discriminating nature for the former catalyst. The fact that the selectivity of the prereduced platinum catalyst tends toward that of the nonprereduced palladium catalyst is not understood.

(17) A. S. Hussey, R. H. Baker, and G. W. Keulks, *J. Catal.*, **10**, 258 (1968).

TABLE III

k_{anti}/k_{syn} FOR 7-SUBSTITUTED NORBORNENES

Substrate	Catalyst	k_{anti}/k_{syn}
syn-ol + *anti*-ol	Pd/C	0.94
syn-acetate + *anti*-acetate	Pd/C	16.8
syn-acetate + *anti*-acetate	HPd/C	5.4
syn-acetate + *anti*-acetate	PtO_2	3.7
syn-acetate + *anti*-acetate	Pt/C	3.4
syn-acetate + *anti*-acetate	HPt/C	10.1

In the reduction of 7-acetoxynorbornadiene, k_{anti} has been defined as the rate of reduction of the *anti* double bond to yield *syn* product, k_{syn} as the rate of reduction of *syn* double bond to form *anti* product. The relative rates of these reactions, k_{anti}/k_{syn}, have been determined from the ratio, *syn*-acetate produced/*anti*-acetate produced. For palladium catalysts, this value is readily obtained from reductions performed in the presence of norbornadiene, or norbornene, where the conversion of the monoolefins to saturated ester is suppressed. This technique cannot be used in the case of platinum catalysts, for the subsequent reduction of the *syn* and *anti* isomers cannot be prevented by norbornene. In the case of platinum catalysts, the assumption has been made that the saturated product formed arises predominately from the *anti* isomer. This view seems reasonable in the light of Table III. The values of k_{anti}/k_{syn} over platinum catalysts have therefore been determined by the ratio, *syn* acetate/*anti* acetate plus saturated acetate. While these relative rates are not so quantitative as those for palladium catalysts, they do constitute useful semiquantitative estimates. Table IV presents these k_{anti}/k_{syn} data for the reduction of 7-acetoxynorbornadiene.

TABLE IV

k_{anti}/k_{syn} FOR 7-ACETOXYNORBORNADIENE

Catalyst	k_{anti}/k_{syn}
Pd/C	3.42
HPd/C	0.58
PtO_2	1.2
Pt/C	1.1
HPt/C	1.8

Direct comparison of Tables III and IV shows that the reduction of 7-acetoxynorbornadiene is considerably less sensitive to purely steric control. Without exception, the reduction of the less sterically hindered *anti* double bond in the *anti*-acetate occurs with greater facility than reduction of the *anti* double bond in the diene. Table IV reveals a remarkable distinction between a prereduced and a nonprereduced palladium catalyst. While the latter shows a decided preference for *anti* double bond reduction of the diene, the former experiences an unanticipated reversal and preferentially hydrogenates the *syn* double bond. This dif-

ference in selectivity amounts to a factor of *ca.* 6 and certainly cannot be rationalized by steric arguments. Platinum catalysts as a group appear to demonstrate a very slight preference for *anti* double bond reduction, although these catalysts do not exhibit the pronounced tendencies observed with palladium. The results are consistent with the less selective behavior of platinum catalysts in these reductions.

Discussion

Analysis of the experimental observations described above has permitted certain conclusions to be drawn regarding the palladium-catalyzed hydrogenation of 7-acetoxynorbornadiene. The lack of comparably significant diagnostic data for the platinum-catalyzed reductions renders the interpretation of these reactions less meaningful; however, some general statements regarding these reductions can be made.

It has become apparent that the over-all reduction of the acetoxydiene over palladium is sensitive to two factors operating in concert, steric control and coordination control. The latter is a manifestation of the direction of olefin–catalyst complexation (exocyclic *vs.* endocyclic) and has been previously invoked to resolve other reactions of these ring systems involving group VIII metals.[8c] While the impact of these factors is detectable throughout the reduction, the degree of influence of either is determined largely by the structure of the unsaturated substrate experiencing hydrogenation.[18] The palladium-catalyzed hydrogenation of the isomeric *syn*- and *anti*-7-acetoxynorbornenes to saturated ester is controlled by steric factors, as evidenced by consistently high k_{anti}/k_{syn} ratios. The additional fact that the *anti* isomer is reduced exclusively by *exo,cis* addition is in accord with facile exocyclic coordination and reduction of the sterically unencumbered *anti* double bond. The olefinic bond of the *syn* isomer, shielded by the bulk of the acetate group, is impeded in its ability to compete for the catalyst sites. This steric effect is obviously dependent upon the 7 substituent exhibiting a reasonable steric requirement; in contrast to the corresponding acetate esters, *syn*- and *anti*-7-hydroxynorbornenes are both reduced totally *exo,cis* with a k_{anti}/k_{syn} value of *ca.* 1.

A secondary steric effect induced by a large 7 substituent is apparent in the reduction of the *syn*-acetate, where *ca.* 30–40% of the hydrogen is added *endo,cis*. The stereochemical distinctions between the reduction of the *syn*-7-ol (100% *exo,cis*) and the *syn*-7-acetate are reminiscent of those noted in the hydrogenation of 2-cyclopentylidene-1-hydroxy- and -alkoxycyclopentanes.[19] While the alkylidenecyclopentanol is reduced to the preferred *trans* isomer, introduction of the methoxyl group and higher homologs led to the formation of the *cis* isomer. As in the present case, the existence of a substituent of increased steric capacity diverted the olefin–catalyst coordination away from that side affected by this group.

If the palladium-catalyzed reduction of the dienyl acetate were controlled solely by steric effects comparable to those observed in the reactions of the monoolefins, then the diene reduction should also be characterized by equally high k_{anti}/k_{syn} values and predominant *exo,cis* addition. In fact, the values of k_{anti}/k_{syn} are diminished relative to those of the monoolefins over palladium; furthermore, the *syn* bond is preferentially reduced over prereduced palladium. The formation of the three primary reduction products, *syn*-, *anti*-, and nortricyclic acetates, has also involved substantial *endo,cis* addition. Consequently, it is concluded that the hydrogenation of the acetoxydiene is sensitive to coordination control and that a significant portion of the reaction proceeds through an endocyclic palladium–diene complex.[20] A favorable argument for coordination control is found in the formation of 3-acetoxynortricyclene, whose synthesis from a diene–catalyst *endo* complex which experiences homoconjugative *endo,cis* addition of hydrogen is envisioned.[21] The totally *endo,cis* reduction of the *syn* double bond of the diene to *anti*-acetate is only consistent with endocyclic coordination, as is *endo,cis* addition to the *anti* double bond to yield *syn* product. The preferential reduction of the *syn* double bond relative to the *anti* over prereduced palladium (Table IV) is not understood, although electronic activation of the *syn* double bond by the 7 substituent is a distinct possibility. Coordination control appears to play a more predominant role in reductions over a prereduced catalyst, as evidenced by the substantially increased formation of the nortricyclene and the *anti*-acetates and the greater degree of *endo,cis* deuteration.

The reduction of the dienyl acetate is not devoid of the influence of steric factors, for the hydrogenation of the *anti* bond occurs predominately (*ca.* 80%) *exo,cis*. It is interesting to note, however, that no *exo,cis* addition takes place with the *syn* double bond. The interplay between steric and coordination effects is also obvious in the reduction of the acetoxydiene, for the parent olefin, norbornadiene, experiences neither *endo,cis* nor homoconjugative hydrogenation.[7]

In general, the view is advanced that the reduction of 7-substituted norbornenes over palladium catalysts is considerably more sensitive to steric control than is that of the corresponding norbornadienes. Furthermore, the general principles governing the hydrogenation of the parent olefins cannot be applied indiscriminately to the reduction of their derivatives.

The lack of suitable data precludes a detailed analysis of the platinum-catalyzed reductions. Over-all, these reactions seem to be controlled by the same factors; reduction of the dienyl acetate is sensitive to both steric and coordination control; reduction of the *syn*- and *anti*-acetates is controlled solely by steric factors. The impact of these effects is greatly diminished over platinum catalysts, and as a group these catalysts exhibited less selectivity than the palladium catalysts, in accord with previous observations.[5b,11]

A major unresolved issue raised during this study is

(18) This interpretation accepts the *cis* addition of hydrogen by transfer of the hydrogen atoms to the plane of the olefin from that side facing the catalyst.[5b]

(19) (a) T. J. Howard and B. Morley, *Chem. Ind.* (London), 73 (1967); (b) T. J. Howard, *Rec. Trav. Chim.*, **83**, 992 (1964); (c) S. Mitsui, K. Hebiguchi, and H. Saito, *Chem. Ind.* (London), 1746 (1967).

(20) (a) Palladium metal is a surface on which such olefin π complexes are formed. G. C. Bond and P. B. Wells, *Advan. Catal.*, **15**, 125, 134, 136 (1964); (b) The palladium chloride–norbornadiene complex is endocyclic. N. C. Baenziger, J. R. Doyle, and C. L. Carpenter, *Acta Cryst.*, **14**, 303 (1961).

(21) The mechanism of this 2,6 addition is obscure; the participation of a π-homoallylic palladium–norbornadiene complex is suggested. D. R. Coulson, *J. Amer. Chem. Soc.*, **91**, 200 (1969).

the effect of prereduction of the palladium-on-carbon catalyst, for the principles controlling the chemistry of this system are obscure. The anomolous behavior of the prereduced catalyst is most apparent in two instances: (1) the marked effect of prereduction on the selectivities of the hydrogenation of both norbornadiene and 7-acetoxynorbornadiene; (2) the total influence of the prereduced catalyst on these reactions, for the olefin/catalyst ratios suggest that any special activity imparted to the catalyst by prereduction should be destroyed in the initial stages of the reaction. Inspection of the experimental data suggests that prereduction has sensitized the palladium catalyst toward preferential coordination with the diene system; as a result, hydrogenation of the diene predominates until the bulk of this substrate is removed from the reaction. This predilection for complexation of the diene is independent of the stereochemistry of the reduction, for the reduction of norbornadiene and 7-acetoxynorbornadiene exhibit different directions of deuterium addition. Consequently, this study has uncovered an unusual catalytic affect whose origins and significance are presently vague.

Experimental Section

Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Nmr spectra were measured on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Analytical vapor phase chromatography (vpc) was performed on a Varian Aerograph Model 202 chromatograph and a Perkin-Elmer Model 154D factometer. Preparative-scale gas chromatography was performed on a Varian Aerograph Model A-700.

Platinium oxide (Adam's catalyst), 5% platinum on carbon, and 10% palladium on carbon were obtained from Matheson Coleman and Bell. Matheson prepurified hydrogen and CP grade deuterium were employed for all reductions. 7-Acetoxynorbornadiene was purchased from Frinton Laboratories, Vineland, N. J. The following compounds were prepared by published procedures: *syn*-[22] and *anti*-7-norbornenol,[23] *syn*-[4a,13a] and *anti*-7-acetoxynorbornene,[13a] 7-acetoxynorbornane,[3] 3-acetoxynortricyclene,[24] *exo,exo*-5,6-dideuterio-*syn*-[6] and -*anti*-7-acetoxynorbornene,[2,3] *exo,exo,exo,exo*-2,3,5,6-tetradeuterio-7-acetoxynorbornane,[3] *exo,exo*-5,6-dideuterionorbornene,[3,6] and *exo,exo,exo,exo*-2,3,5,6-tetradeuterionorbornane.[3] Norbornadiene was distilled prior to use. All other reagents were obtained from commercial sources and were used as received.

Reductions utilizing a gas buret apparatus were carried out as previously described.[4a] Reductions requiring hydrogen or deuterium pressures of 20–40 psig were performed in a Parr low pressure hydrogenator.[25] Results derived from these hydrogenations are presented in Table I. In the majority of these reactions, hydrogen absorption was permitted to proceed until the amount theoretically required to reduce one double bond of the diene had been consumed. In other reactions, samples were periodically withdrawn in order to observe changes in composition as the reduction occurred. The reductions were not affected by a change in solvent from ethanol to methanol, nor were the product compositions altered over a range of acetoxydiene to catalyst ratios.

Reduction of 7-Acetoxynorbornadiene with Deuterium.—Into a Parr low pressure reactor were placed 10 g (67 mmol) of 7-acetoxynorbornadiene, 50 ml of absolute ethanol, and 0.5 g of 10% palladium on charcoal. The system was purged with nitrogen and deuterium and finally pressurized with deuterium to 31 psig. Reduction was permitted to proceed until 70 mmol of deuterium had been absorbed. The reaction mixture was filtered, and the filtrate was poured into 150–200 ml of water. The esters were extracted with pentane (three 50-ml portions), and the solution was washed with water and dried over magnesium sulfate. The solvent was removed on a rotary evaporator at 60° (14 mm) to give a crude yield of 12.6 g. The ester mixture was analyzed by vpc on a 11.5 ft × 0.25 in. 20% FFAP[26] column, 135°, helium flow 85 ml/min, detector and injector, 200°. The product had the following composition (retention time): 7-acetoxynorbornadiene (1, 32.0 min), 7%; 5,6-dideuterio-*syn*-7-acetoxynorbornene (6, 28.5 min), 43%; 5,6-dideuterio-*anti*-7-acetoxynorbornene (7, 21.9 min), 10%; 2,3,5,6-tetradeuterio-7-acetoxynorbornane (8, 24.1 min), 30%; 5,7-dideuterio-3-acetoxynortricyclene (9, 33.7 min), 11%.

The crude ester mixture was taken up in 100 ml of ether, and the ether solution was extracted with 5 *M* silver nitrate (four 30-ml portions).[4a] The ether layer was washed once with water and dried over magnesium sulfate. Removal of the solvent on a rotary evaporator gave 8 g of residue. Vpc analysis (see above) gave the following composition: 1, 0%; 6, 7%; 7, 17%; 8, 57%; 9, 19%. This material was separated by preparative vpc[27] into 5,7-dideuterio-3-nortricyclylacetate (9) (purity by vpc, 100%) and a mixture of 7 (24%) and 8 (76%). The mixture of 7 and 8 was taken up in 10 ml of pentane and was shaken for 4 hr with 30 ml of 5 *M* silver nitrate. The pentane solution was dried over magnesium sulfate, and the solvent was removed to give 1 g of 2,3,5,6-tetradeuterio-7-acetoxynorbornane (8), purity by vpc, 97%. The silver nitrate solution (from the separation of 7 and 8) was added to a chilled solution of 20 g of sodium cyanide in 50 ml of water. The aqueous solution was extracted with pentane (three 20-ml portions), and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave 0.2 g of crystalline 5,6-dideuterio-*anti*-7-norbornenol. Vpc analysis (5 ft × 0.25 in. 20% polypropylene glycol column, 150°, helium flow 65 ml/min, detector and injector, 200°) confirmed the structure of the alcohol[23] and showed it to be 93% pure.

The original 5 *M* silver nitrate solution was added to a solution of 100 g of potassium cyanide in 300 ml of water containing *ca.* 100 g of ice. The liberated esters were extracted with ether (three 50-ml portions), and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave 5.8 g of residue. Vpc analysis gave the following composition: 1, 15%; 6, 78%; 7, 7%. Preparative vpc[27] provided a sample of 5,6-dideuterio-*syn*-7-acetoxynorbornene (6, purity, 100%) and a sample of 5,6-dideuterio-*anti*-7-acetoxynorbornene (7, purity, 95%).

Deuterium analysis of the *syn*- (6) and the *anti*-7-acetoxynorbornenes (7) by chemical ionization mass spectrometry[28] indicated a deuterium content of *ca.* 90% d_2 and *ca.* 10% d_1. Analysis of tetradeuterio-7-acetoxynorbornane (8) showed 90% d_4, 5% d_3, 3% d_2, and 2% d_1.

The nmr spectra of the deuterated acetate esters (6, 7, 8, 9) were recorded on neat samples; dideuterio-*anti*-7-norbornenol was dissolved in $CDCl_3$. The relative areas of the *exo* protons (δ 1.50–1.83) and of the *endo* protons (δ 0.83–1.30)[13] served as a measure of *endo,cis* and *exo,cis* addition of deuterium. Analysis of the *endo*-proton areas indicated the relative amounts of *anti,endo* (δ *ca.* 1.18) and of *syn,endo* (δ *ca.* 1.27) protons. The nmr data for the esters (6, 7, 8, 9) and for the alcohol are summarized in Table V. Deuterium decoupling experiments[15] on 5,7-dideuterio-3-acetoxynortricyclene (9) showed a sharpening of the protons at δ 1.45 and 1.75. The chemical shifts of these protons are similar to that expected for *exo* hydrogens; consequently, the two deuterium atoms have been assigned an *endo,endo*-5,7 configuration.

3-Acetoxynortricyclene by Reduction of 7-Acetoxynorbornadiene.—Into a Parr low pressure reactor were placed 50 ml of ethanol, 0.5 g of 10% palladium on charcoal, and 4.5 g (30 mmol) of 7-acetoxynorbornadiene. The diolefin was hydrogenated at an initial hydrogen pressure of 20 psig until no further hydrogen consumption occurred (63 mmol absorbed). The reduction mixture was filtered, the filtrate was poured into 150 ml of saturated sodium chloride solution, and the product was extracted with pentane. From the pentane extract 4.6 g of crude ester was recovered. Vpc analysis (5 ft × 0.25 in. 20% polypropylene

(22) W. C. Baird, Jr., *J. Org. Chem.*, **31**, 2411 (1966).

(23) P. R. Story, *ibid.*, **26**, 287 (1961).

(24) L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Amer. Chem. Soc.*, **78**, 2819 (1956).

(25) Parr Instrument Co., Moline, Ill.

(26) Varian Aerograph, Walnut Creek, Calif.

(27) Preparative vpc conditions: 12 ft × 3/8 in. 30% FFAP column, 125°, helium flow 110 ml/min, detector and injector, 200°.

(28) M. S. B. Munson and F. H. Field, *J. Amer. Chem. Soc.*, **88**, 2621 (1966). The authors thank Dr. Field of these laboratories for obtaining and interpreting the mass spectral data.

TABLE V

NMR SPECTRA OF DEUTERATED REDUCTION PRODUCTS FROM 7-ACETOXYNORBORNADIENE

	Proton type, δ (relative area)							
Compd	CH=CH	H—C—OAc	>C—H	CH_3CO	*exo* $>C<^{H}_{H}$	*endo* $>C<^{H}_{H}$	% *endo* d_2 addition	% *exo* d_2 addition
6	5.95 (2)	4.43 (1)	2.84 (2)	1.85 (3)	1.75 (0.4)	0.90 (1.6)	21	79
7	6.00 (2)	4.30 (1)	2.72 (2)	1.98 (3)	1.72 (2)	...	100	0
8	...	4.65 (1)	2.10 (2)	1.96 (3)	1.75 (0.96)	1.17 (1.04)	52 (42 *syn*, 10 *anti*)	48 (13 *syn*, 35 *anti*)
anti-ol	5.95 (2)	3.53 (1)	2.52 (2)	3.30 (1) (OH)	1.78 (2)	...	100	0
9	...	4.56 (1)	1.93 (4)		1.45 (1) 1.75 (1)	1.23 (3) (*c*-Pr H)		

glycol, 150°, 80 ml/min) showed the composition of the product to be 87% 7-acetoxynorbornane (**4**, t_R 14.8 min) and 13% 3-acetoxynortricyclene (**5**, t_R 18.4 min). Pure 3-acetoxynortricyclene was separated by preparative vpc[27] and was shown to be identical to an authentic sample[24] by comparative nmr, vpc, and infrared techniques.

Deuterium Reduction of *syn*- and *anti*-7-Substituted Norbornenes.—Into a gas buret apparatus were placed 124.8 mg of 10% palladium on charcoal, 3 ml of methanol, and 464.7 mg (3.01 mmol) of 5,6-dideuterio-*syn*-7-acetoxynorbornene (**6**). The deuterium distribution in the *syn*-acetate was 21% *endo,cis* and 79% *exo,cis*. The olefin was reduced with deuterium until no further gas consumption occurred. The reduction mixture was filtered and added to 10 ml of ether. The ether solution was washed twice with water and then dried over calcium chloride. Removal of the ether by distillation gave 469.3 mg of acetate ester. Purification by preparative vpc[27] gave 280 mg of tetradeuterated 7-acetoxynorbornane. Nmr analysis of the saturated ester revealed the deuterium distribution to be 29% *endo,cis* and 71% *exo,cis*, which corresponded to 40% *endo,cis* deuterium addition. Further resolution of the *exo* proton area (29%) showed the proton distribution to be *ca.* 20% *exo,syn* and *ca.* 9% *exo,anti*. Similar analysis of the *endo* proton area (71%) revealed the composition to be *ca.* 32% *endo,syn* and *ca.* 39% *endo,anti*. The ratio of *endo,anti* protons to *exo,anti* protons was *ca.* 4.3:1, which corresponded reasonably well to the 3.8:1 ratio in the initial *syn*-acetate. The ratio of *endo,syn* protons to *endo,anti* protons of 1.6:1 agreed well with the ratio of 1.5:1 calculated on the basis of 40% *endo,cis* deuterium addition.

The deuterium reduction of *syn*-7-acetoxynorbornene was repeated using 58.9 mg of prereduced 10% palladium on charcoal and 256.2 mg (1.66 mmol) of acetate. Nmr analysis of the 2,3-dideuterio-7-acetoxynorbornane showed that the reduction had occurred with 30% *endo,cis* deuterium addition.

In a gas buret apparatus, 342.6 mg (2.22 mmol) of *exo,exo*-5,6-dideuterio-*anti*-7-acetoxynorbornene (**7**) was reduced with deuterium over 52.2 mg of 10% palladium on charcoal. Nmr analysis of the tetradeuterated 7-acetoxynorbornane revealed the presence of exclusively *endo,syn* and *endo,anti* protons, in accord with 100% *exo,cis* deuterium addition.

syn-7-Hydroxynorbornene (240.1 mg, 2.18 mmol) was reduced with deuterium over 41.6 mg of 10% palladium on charcoal. The saturated alcohol was purified by sulbimation to give 170 mg of pure 2,3-dideuterio-7-hydroxynorbornane. Nmr analysis ($CDCl_3$) revealed the existence of two *exo* protons and four *endo* protons, indicating 100% *exo,cis* deuterium addition.

A 198.5-mg sample of *exo*-5-deuterio-*anti*-7-hydroxynorbornene[2] was reduced with deuterium over 34.5 mg of 10% palladium on charcoal. Sublimation yielded 120 mg of pure 2,3,5-trideuterio-7-acetoxynorbornane. Nmr analysis ($CDCl_3$) showed the presence of one *exo* proton and four *endo* protons, in accord with 100% *exo,cis* addition of deuterium.

Competitive Reductions of *syn*- and *anti*-7-Hydroxy- and -Acetoxynorbornenes.—Competitive hydrogenation studies were performed according to the general procedure described by Hussey, Baker, and Keulks.[17] Into a gas buret apparatus were placed 3 ml of ethanol, 30 mg of 10% palladium on charcoal, 114.8 mg (1.04 mmol) of *syn*-7-hydroxynorbornene, 133.3 mg (1.21 mmol) of *anti*-7-hydroxynorbornene, and 78.6 mg of isoamyl alcohol as an internal standard. The mixture was analyzed by vpc, and the response factors for the *syn* and *anti* alcohols relative to isoamyl alcohol were calculated. Vpc analyses were performed on 2 m × 0.25 in. 20% polypropylene glycol and 1 m × 0.25 in. 5% polypropylene glycol columns in series at 135° and 120 ml/min: retention times—*syn*-ol, 17.6 min; *anti*-ol, 31.0 min; isoamyl alcohol, 6.2 min. The olefin mixture was reduced with hydrogen, and samples were withdrawn periodically through a septum and were analyzed by vpc. From the vpc data the changes in the *syn*- and *anti*-alcohol concentrations were determined. The relative rate of hydrogenation was calculated from the equation[17]

$$k_{anti}/k_{syn} = \frac{\log (anti)_0/(anti)}{\log (syn)_0/(syn)}$$

The value of k_{anti}/k_{syn} was also measured from the slope of the plot of log $(anti)_0/(anti)$ *vs.* log $(syn)_0/(syn)$. By these methods, the relative rate of hydrogenation of the *syn* and *anti* alcohols was determined to be 0.95 and 0.94, respectively.

The same general method was employed to determine k_{anti}/k_{syn} for the competitive hydrogenation of *syn* and *anti* 7-acetoxynorbornenes over various platinum and palladium catalysts. Vpc analyses were performed on a 11.5 ft × 0.25 in. 20% FFAP column at 135° and 85 ml/min. The data are presented in Table III; the accuracy and precision of these data are limited by the analytical method, by the small degree of *syn* double bond reduction that occurs in the early stages of the reduction, and by the absence of *anti*-acetate in the final stages.

Control reductions were performed with pure *syn*- and *anti*-acetate to ensure that no isomerization reactions were occurring during the hydrogenation. Periodic analysis of reductions of these isomeric olefins over various catalysts showed the reaction mixture to contain only 7-acetoxynorbornane and the starting olefin. No *syn–anti* or *anti–syn* isomerizations were detected.

Competitive Reduction of Norbornadiene and 7-Acetoxynorbornadiene.—The general procedure for the competitive reduction of norbornadiene and 7-acetoxynorbornadiene has been described.[6] In a preparative experiment, a mixture of 890 mg (5.93 mmol) of 7-acetoxynorbornadiene, 640.1 mg (6.95 mmol) of norbornadiene, and 293.1 mg of ethylbenzene (internal standard) was reduced with deuterium in 10 ml of methanol over 302 mg of 10% palladium on charcoal. The reduction was permitted to proceed until 454 ml of deuterium (73% of theory) was absorbed. Vpc analysis of the reduction mixture[6] showed that the norbornadiene had been converted to norbornane and that the acetoxydiene had been reduced to *syn*-7-acetoxynorbornene (38%), 7-acetoxynorbornane (55%), and 3-acetoxynortricyclene (7%). The norbornane and methanol were removed by distillation, and the distillate was added to 20 ml of water. The norbornane was extracted with pentane (two 10-ml portions), and the extract was dried over magnesium sulfate. The pentane solution was reduced by distillation to *ca.* 1 ml, and the residue was subjected to preparative vpc (12 ft × 3/8 in. 20% FFAP column, 100°, 120 ml/min) to isolate 150 mg of norbornane. The nmr spectrum ($CDCl_3$) of the hydrocarbon was identical with that of an authentic sample of *exo,exo,exo,exo*-2,3,5,6-tetradeuterionorbornane; the reduction of norbornadiene had proceeded *via* 100% *exo,cis* deuterium addition.

The residue from the methanol distillation was separated by preparative vpc (12 ft × 3/8 in. 20% FFAP column, 135°, 120 ml/min) into 7-acetoxynorbornane (171 mg) and *syn*-7-acetoxynorbornene (121 mg). Nmr analysis ($CDCl_3$) of the *syn*-acetate showed it to be composed of 85% *exo,cis*-5,6-dideuterio isomer and 15% *endo,cis*-5,6-dideuterio isomer. Nmr analysis ($CDCl_3$) of 7-acetoxynorbornane revealed a deuterium distribution of 66% *exo,cis* and 34% *endo,cis*.

A sample that had been withdrawn from this reduction after the absorption of 372 ml of deuterium (60% of theory) was

analyzed for acetate ester content by vpc. The composition of the acetate fraction was shown to be 74% *syn*-7-acetoxynorbornene, 16% *anti*-7-acetoxynorbornene, 3% 7-acetoxynorbornane, and 7% 3-acetoxynortricyclene. Based on the direction of deuterium addition in forming these isomeric acetates during reduction of dienyl acetate, the mixture of norbornenyl acetates corresponded to 20% *endo,endo*-5,6-dideuterio-*anti*-7-acetoxynorbornene, 68% *exo,exo*-5,6-dideuterio-*syn*-7-acetoxynorbornene, and 12% *endo,endo*-5,6-dideuterio-*syn*-7-acetoxynorbornene. Since it had been shown (*vide supra*) that the *anti* isomer experienced 100% *exo,cis* deuterium addition and that the *syn* isomer (over a nonprereduced catalyst) underwent 40% *endo,cis* and 60% *exo,cis* deuterium addition, the deuterium distribution of tetradeuterated 7-acetoxynorbornane was predicted to be 33.6% *endo,cis* and 66.4% *exo,cis*. The values agreed with the observed distribution of 34% and 66%, respectively.

Competitive Reduction of Norbornene and 7-Acetoxynorbornadiene.—In a gas buret apparatus 268.5 mg of 10% palladium on charcoal in 5 ml of methanol was reduced with deuterium. Into the catalyst slurry a solution of 764 mg (4.8 mmol) of 7-acetoxynorbornadiene and 990 mg (10.5 mmol) of norbornene in 5 ml of methanol was injected. The reduction reaction was sampled periodically and analyzed by vpc.[6] The composition of the acetate mixture was determined and is summarized in Table VI below.

TABLE VI

Reduction, %	Composition, %					
	Norbornene	Dienyl acetate	*syn*-	*anti*-	Satd	Nortricyclic
24	81	49	11	20	0	20
48	56	11	23	37	0	30
64	34	0	25	40	4	30
80	6	0	26	38	7	30
96	0	0	16	0	54	30
100	0	0	0	0	70	30

Determination of k_{anti}/k_{syn} for Reduction of 7-Acetoxynorbornadiene to *syn*- and *anti*-7-Acetoxynorbornenes.—In the reduction of 7-acetoxynorbornadiene, k_{anti} is derived from the rate of reduction of the *anti* double bond to yield *syn*-7-acetoxynorbornene. Conversely, k_{syn} is a measure of the rate of reduction of the *syn* double bond to produce *anti*-7-acetate. The relative rate, k_{anti}/k_{syn}, has been determined by the ratio, % *syn*-acetate produced/% *anti*-acetate produced. For palladium-on-charcoal catalysts, this ratio is readily calculated from reductions performed in the presence of excess norbornene or norbornadiene, where the subsequent conversion of *syn*- and *anti*-acetates to saturated product is effectively suppressed. In the case of a prereduced palladium-on-charcoal catalyst (norbornene present), k_{anti}/k_{syn} = 0.56–0.61 (average 0.58). In the case of a nonprereduced palladium catalyst (norbornadiene present), k_{anti}/k_{syn} = 3.22–3.52 (average 3.41).

Reductions utilizing platinum catalysts are complicated by the fact that conversion of initially formed *syn*- and *anti*-acetates to saturated ester cannot be suppressed. In these cases the assumption has been made that the saturated product formed while dienyl acetate is present arises predominately from reduction of the *anti* isomer. This rationale is predicated on the observed preference for *anti* double bond reduction in the competitive reduction of *syn*- and *anti*-acetates over platinum catalysts (see Table III). Consequently, k_{anti}/k_{syn} for dienyl acetate reductions over platinum catalysts has been estimated from the ratio, % *syn* produced/% *anti* + % saturated produced. For the platinum oxide catalyst, values of k_{anti}/k_{syn} were calculated to be 1.01–1.36 (average 1.19). A platinum-on-carbon catalyst gave an average value for k_{anti}/k_{syn} of 1.11; a prereduced platinum catalyst gave an average value of 1.81.

Registry No.—**1**, 13426-49-8; **2**, 13426-52-3; **3**, 13426-55-6; **6a**, 15649-38-4; **6b**, 20843-70-3; **7**, 20843-71-4; **8a**, 20843-72-5; **8b**, 20843-73-6; **8d**, 20843-74-7; **8e**, 20843-75-8.

The Oxymercuration–Demercuration of Cycloalkadienes

SUNG MOON, JOHN M. TAKAKIS, AND BURTON H. WAXMAN

Department of Chemistry, Adelphi University, Garden City, New York 11530

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The oxymercuration–demercuration of isomeric cyclooctadienes was studied. The major product from 1,3-cyclooctadiene is 9-oxabicyclo[4.2.1]non-7-ene (2). 1,4-Cyclooctadiene yields mostly 3-cycloocten-1-ol and 1,4-epoxycyclooctane. Treatment of 3-cycloocten-1-ol with mercuric acetate, followed by reduction with sodium borohydride, is a convenient preparatory method for isomerically pure 1,4-epoxycyclooctane.

Oxymercuration–demercuration of olefins has been shown to be an excellent method for obtaining alcohols.[1] Previous studies[1,2] have shown that the direction of the addition is according to Markovnikov's rule and that the addition is controlled by steric factors. Relatively little work, however, has been done on the reactions of dienes. Bordwell[3] recently reported that the oxymercuration of 1,5-cyclooctadiene yielded a cyclization product instead of a simple addition product. We wish to report our studies on the reaction of some cyclic dienes, and related olefinic alcohols. The dienes that were chosen for our studies were 1,3-,1,4,- and 1,5-cyclooctadienes and 1,3- and 1,4-cyclohexadienes.

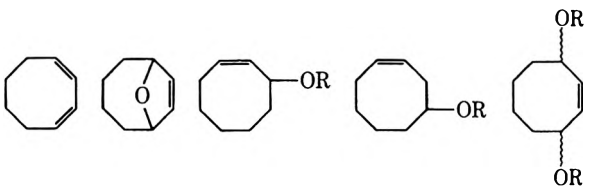
(1) For excellent review articles, see (a) J. Chatt, *Chem. Rev.*, **48**, 7 (1951); (b) N. S. Zefirove, *Russ. Chem. Rev.*, **34**, 527 (1965); (c) W. Kitchins, *Organometal. Chem. Rev.*, **3**, 61 (1968).

(2) H. C. Brown and P. Geogegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

(3) F. G. Bordwell and M. S. Douglass, *ibid.*, **88**, 993 (1966).

Results and Discussion

Treatment of 1,3-cyclooctadiene (1) with mercuric acetate in tetrahydrofuran (THF) and water, followed, by alkaline demercuration with sodium borohydride gave 9-oxabicyclo[4.2.1]non-7-ene (2) in 37% yield, in



1 2 3 4 5

a, R = H
b, R = Ac

addition to **3a**, **4a**, and **5a**. When the diene was treated with mercuric nitrate instead of mercuric acetate, 2 was obtained in a lower yield.

The structure of **2** was assigned on the basis of elemental analysis and spectroscopic properties and by its facile conversion into 1,4-epoxycyclooctane (**9**) by hydrogenation. The nmr spectrum showed signals at τ 4.2 (s, 2) for the olefinic hydrogens, at 5.1 (d, 2) for the tertiary hydrogens, and at 8.3 (m, 8) for the methylene protons. Of the structures **2**, **2a**, and **2b**, only **2** is consistent with the nmr spectrum.

2a

2b

When the reaction product of the oxymercuration–demercuration of **1** was not washed with water, but was concentrated and treated with acetic anhydride and pyridine, four additional products were observed on gas chromatography.

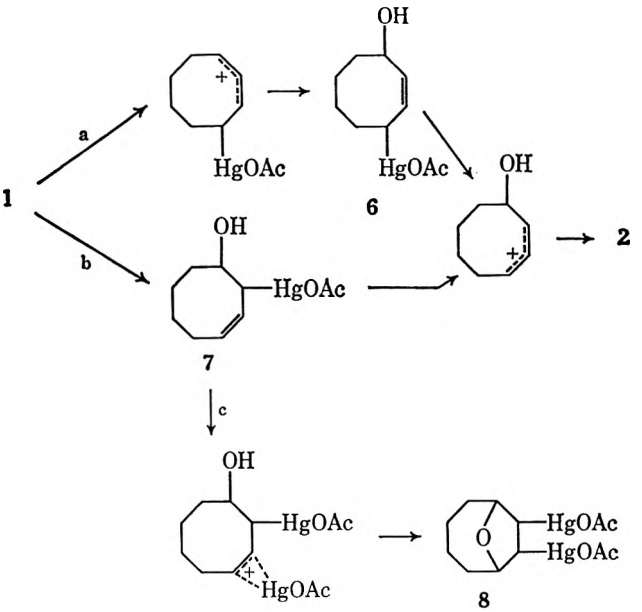
The infrared spectrum of each of the two major products, isolated by gas chromatography, indicated ester bands and olefinic hydrogens. The nmr spectrum of the mixture of the two major products showed two olefinic hydrogens, two different methyl peaks (acetates) of about equal strength, and two allyl hydrogens alpha to the acetate group. The mixture of these two compounds was hydrogenated, but the products were not separable on gas chromatography. The infrared spectrum of the hydrogenated product had all of the bands characteristic of *cis*-1,4-cyclooctanediol diacetate, plus several more. That the product was not *trans*-1,3-cyclooctanediol diacetate was indicated by comparison of its spectrum and retention time on gas chromatography with those of an authentic sample. On the basis of ir, nmr, gas chromatographic, and hydrogenation data, we believe the major products to be *cis*- and *trans*-2-cyclooctene-1,4-diol diacetates (**5b**). The configuration of **5a** and **5b** was not determined. Two minor products were identified as 3-cycloocten-1-yl acetate (**4b**, 3%) and 2-cycloocten-1-yl acetate (**2b**, 1.5%).

An attractive rationale[4] for the formation of **2** from **1** would involve the addition of mercuric acetate to **1**, yielding, by path a or b, respectively, either **6** or **7**, which may solvolyze to give **2** (Scheme I), as allylic mercurials would be expected to solvolyze rapidly. Formation of **6** implies a 1,4 addition of mercuric acetate to **1**. We know of no reported case of the 1,4 addition of mercuric acetate to dienes. The addition of mercuric acetate to 1,3-butadiene gave only 1,2-addition product.[5] The product obtained from norbornadiene appeared to involve 1,4 addition, but it was later found that the initial intermediate resulted from 1,2 addition.[6]

Alternatively, the dimercurial acetate **8** can be envisioned as a possible intermediate (path c). The reduction of **8** to **2** with sodium borohydride could be rationalized along the path similar to one suggested by Bordwell[3] for the demercuration of 2-acetoxymercuri-2-oxabicyclo[4.2.1]nonane to 4-cycloocten-1-ol in acidic media. Definite choice between these mechanisms must await further work.

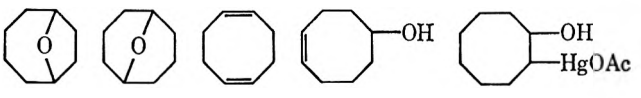
Since the acetoxymercurial **7** was thought to be one of the possible intermediates in the formation of **2** from

SCHEME I



1, we investigated the reaction of 3-cycloocten-1-ol (**4**). Treatment of **4** with mercuric acetate in THF–water mixture gave 1,4-epoxycyclooctane (**9**) in 64% yield based on distilled product. Since **9** obtained in this manner was not contaminated by 1,5-epoxycyclooctane (**10**) and no by-product was detected, this procedure constitutes a convenient synthesis of **9**.

Bordwell[3] reported that the oxymercuration of 1,5-cyclooctadiene (**11**) with mercuric nitrate followed by demercuration with sodium borohydride yielded **10** uncontaminated by the 1,4 isomer **9**. We reinvestigated this reaction and our results confirmed those of Bordwell (see Table I). We also treated **11** with mercuric acetate and obtained, after demercuration with sodium borohydride, a mixture of **9** and **10** in a ratio of 55:45. Variation of conditions (see Table I) did not have any appreciable effect on the ratio of **9** and **10**. The results were surprising, as we expected the oxymercuration–demercuration of **11** to closely parallel the oxymercuration–demercuration of 4-cycloocten-1-ol (**12**), since the oxymercuration–demercuration of **11** probably proceeds through the hydroxyacetoxymercurial **13**.



9 **10** **11** **12** **13**

In as much as Bordwell[3] reported that the oxymercuration and demercuration of **12** in acidic media resulted in the 1,5-epoxide, and, in basic media, the 1,4-epoxide, we had hoped to prepare the 1,4-epoxide isomerically pure by the oxymercuration of much more readily available **11** with mercuric acetate. As our results indicate, the reaction is not selective. Owing to the contradiction in predicted and realized results we reinvestigated the oxymercuration of **12**. In our hands, the epoxycyclooctane **9**, obtained from the alcohol **12** under the same reaction conditions, was contaminated by 15% **10**. The discrepancy could possibly be due to the method of analysis. Gas chromatography[7] and infrared spectroscopy[3] were used for analysis of the relative amounts of **9** and **10**. We found

(4) This is a modification of a mechanism proposed by one of the referees.

(5) K. H. McNeely and G. F. Wright, *J. Amer. Chem. Soc.*, **77**, 2553 (1955).

(6) K. C. Paude and S. Winstein, *Tetrahedron Lett.*, 3393 (1964).

(7) A. C. Cope, M. Gordon, S. Moon and C. H. Park, *J. Amer. Chem. Soc.*, **87**, 3119 (1965).

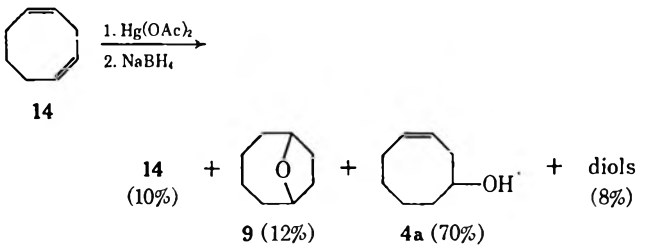
TABLE I
COMPOSITION OF CYCLIC ETHERS OBTAINED FROM CYCLOOCTENOLS AND CYCLOOCTADIENES

Starting material	Solvent	Mercuric salt	Products,[a] % 9	10
12	H_2O	$Hg(OAc)_2$[b]	86	14
12	H_2O–THF	$Hg(OAc)_2$[b]	85	15
11	H_2O–THF	$Hg(OAc)_2$	54	46
11	H_2O–THF	$Hg(OAc)_2$[b]	56	44
11	H_2O–THF	$Hg(NO_3)_2$	0	100
4a	H_2O–THF	$Hg(OAc)_2$	100	0

[a] Ratio of ether isomers as determined by nmr analysis. [b] Sodium acetate added to water before mercuric acetate.

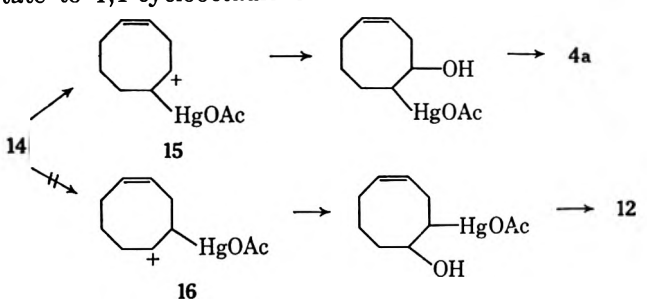
that nmr spectroscopy was superior to either of these methods. In nmr analysis, advantage was taken of the fact that **9** has a signal at τ 5.7 for the tertiary hydrogens, whereas **10** has a signal at 6.2. The infrared spectrum of **9**, contaminated with 15% **10**, as shown by nmr analysis, was practically the same as that of pure **9**. Thus we conclude that infrared sepctroscopy cannot detect less than 10% **10** which might be present in **9**.

The major product from 1,4-cyclooctadiene[8] on oxymercuration–demercuration was 3-cycloocten-1-ol. The addition of mercuric acetate is specific, for the isomeric 4-cycloocten-1-ol was not detected. There was only a small amount of cyclization product, namely, 1,4-epoxycyclooctane **9**, which was not contaminated by the 1,5 isomer.



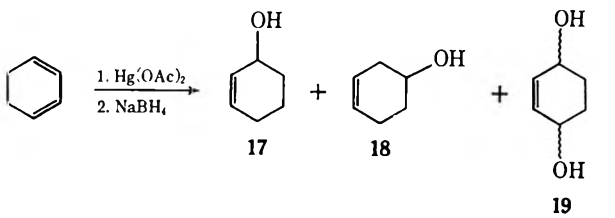
Since the diacetates were more readily detected on gas chromatography, the above reaction mixture was treated with acetic anhydride to determine the amount of diols formed. The diacetates formed were less than 8% of the total mixture, and no further attempts were made to identify them.

Specific addition of mercuric acetate to 1,4-cyclooctadiene may be rationalized on the basis of the stability of the mercuric acetate addition intermediate in terms of carbonium-ion character. It has been shown[9] that no rearrangement occurs during the addition of mercuric acetate to olefins, indicating that the intermediate does not involve a free carbonium ion. However, the intermediate might have enough ionic character to cause the selective addition of mercuric acetate to 1,4-cyclooctadiene. The intermediate **15** is a

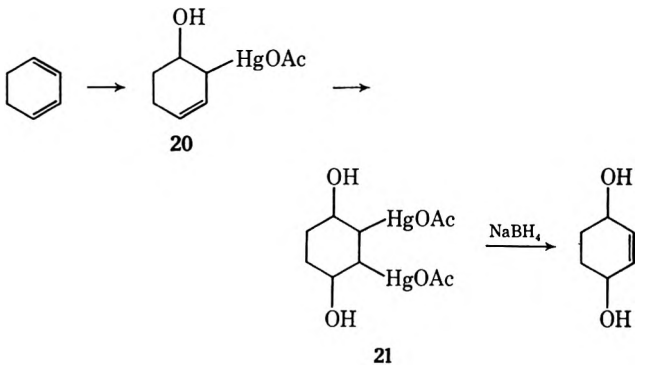


homoallylic carbonium ion, which is expected to be more stable than the intermediate **16**. An alternative explanation for the selective addition may be based on coordination between the mercuric acetate and one of the double bonds, thus directing the addition of the mercuric acetate to the second double bond. We have previously shown[10] that a hydroxyl group in a position allylic to a double bond directs the addition of mercuric acetate. Thus, cyclohexen-1-ol gave mainly *trans*-1,3-cyclohexanediol. There may be an analogous coordination between mercury and a double bond. However, a study of a molecular model of 1,4-cyclooctadiene does not show clearly why the mercury coordinated with a double bond in the 1,2 position should add to the 4 position exclusively.

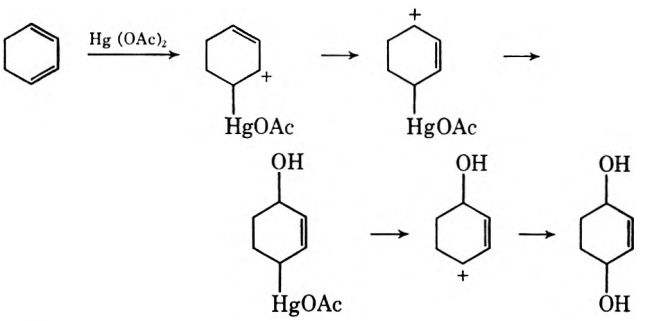
Similar treatment of 1,3-cyclohexadiene did not yield any cyclization product, but gave the alcohols **17**, **18**, and **19**. To better estimate the relative amounts, the alcohol mixture was converted into the corresponding acetates. The relative ratio of the acetates of **17**, **18**, and **19** was 13:13:74.



The formation of **19** may be rationalized as the addition of 2 mol of mercuric acetate, followed by reduction of the dimercurial to form the double bond, as shown below.



Alternatively, the formation of **19** may be envisioned as a product of 1,4 addition of mercuric acetate, followed by solvolysis of the allyl mercurial. We favor



this mechanism over the first one for the following reasons. First, only a 1:1 molar ratio of mercuric acetate to diene was used. It is therefore unlikely that a

(8) We are grateful to Mr. Charles Ganz for a sample of 1,4-cyclooctadiene
(9) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Amer. Chem. Soc.*, **89**, 1525 (1967).
(10) S. Moon and B. H. Waxman, *Chem. Commun.*, 1283 (1967).

two-step mechanism should provide a predominance of diol. Halpern[11] indicates that the addition of a hydroxy group to the 4 position of 1-butene slows the addition of mercuric acetate to the carbon–carbon double bond by a factor of ten. We therefore suggest that the first mechanism should yield little or no diol. Second, while Henbest[12] demonstrated that 3-cyclohexen-1-ol, which is similar to **20**, adds mercuric acetate selectively yielding only the 1,4-diol, he also demonstrated that the reaction gives only the *trans* product. Our results indicate that both the *cis*- and *trans*-diols are present. Third, it is known that mercuric chloride adds across norbornadiene, yielding the tricyclic derivative.[13] The reaction shows no rearrangement products characteristic of a free carbonium intermediate and suggests a molecular rather than an ionic addition. 1,3-Cyclohexadiene should be prone to a similar attack. Finally it was suggested above that allylic mercurials solvolyze rapidly. Upon the addition of sodium hydroxide, prior to sodium borohydride reduction, a black suspension formed, indicative of free mercury. Such evidence is suggestive of solvolysis of the mercurial acetate group.

1,4-Cyclohexadiene also did not give any cyclization product, but gave 4-cyclohexen-1-ol and a diol. The alcohols were converted into the corresponding acetates. The diacetate peaks on gas chromatography were separated into three small peaks. Attempts to separate these peaks were unsuccessful and no further work was done to identify them individually.

Experimental Section[14]

3,4-Epoxycyclooctene.—The monoepoxide was prepared by the method of Crandall.[15] Treatment of 73.5 g of 1,3-cyclooctadiene with 126 g of 40% peracetic acid in 750 ml of dichloromethane and 290 g of powdered anhydrous sodium carbonate gave 61.3 g (73%) of 3,4-epoxycyclooctene: bp 69–71° (13 mm) [lit.[16] bp 81–87° (22 mm)]. It was noted that, when the crude epoxycyclooctene was injected on a gas chromatograph (silicone oil), it partially rearranged to 3-cycloocten-1-one, probably owing to the high temperature at the injection port (over 200°).

3-Cycloocten-1-ol.—Treatment of 44.6 g of 3,4-epoxycyclooctene with 7.65 g of lithium aluminum hydride in ether according to the method of Cope and Peterson[16] gave 36 g (71%) of the alcohol **4a**: bp 82–84° (13 mm) [lit.[16] 74.5–76.0° (3.1 mm)].

5,6-Epoxycyclooctene.—1,5-Cyclooctadiene (54 g) was treated with 40% peracetic acid by the method of Cope[16] and yielded 28.0 g (46%) of 5,6-epoxycyclooctene: bp 98° (11 mm).

4-Cycloocten-1-ol.—Treatment of 26 g of 5,6-epoxycyclooctene with 2.2 g of lithium aluminum hydride in THF gave[14] 16 g (61%) of 4-cycloocten-1-ol: bp 110° (10 mm).

Oxymercuration–Demercuration of 1,3-Cyclooctadiene with Mercuric Acetate.—To a yellow suspension of 288 g (0.9 mol) of mercuric acetate, 500 ml of THF, and 500 ml of water, 33 g (0.3 mol) of 1,3-cyclooctadiene was added and the mixture was stirred for 4 days at room temperature. To this white-yellow mixture, 390 ml of 3 *M* sodium hydroxide was added and the mixture acquired a brown-green color; the mixture, on stirring for 10 min, became black. The black mixture was then treated with 24 g of sodium borohydride in 390 ml of 3 *M* sodium hydroxide solution; the reaction was exothermic. Metallic mercury was formed at the bottom. The mixture was saturated with sodium chloride and extracted with ether. The organic layer was washed twice with water and dried ($MgSO_4$). The solution was concentrated by distillation and the crude product was distilled through a Vigreux column giving 12.5 g (37%) of 9-oxabicyclo[4.2.1]non-7-ene (**2**): bp 74° (10 mm); ir (CS_2) 3050, 1115, 1090, 1020, 975, 950, 880, 825, 805, 765, and 695 cm^{-1}; nmr (CCl_4) τ 4.2 (s, 2), 5.1 (d, 2), and 8.3 (m, 8).

Anal. Calcd for $C_8H_{12}O_1$: C, 77.28; H, 9.85. Found: C, 77.22; H, 9.65.

When 1,3-cyclooctadiene was treated with mercuric nitrate, it gave **2** only in 15% yield.

The reaction of 1,3-cyclooctadiene with mercuric acetate was repeated in the same way as above, except that the ether–THF layer was not washed with water to avoid the loss of the diols which are water soluble. Thus, from 2.2 g of 1,3-cyclooctadiene was obtained 2.1 g of a crude product. This was treated with acetic anhydride in pyridine. Gas chromatographic analysis (silicone oil) indicated four peaks. The first peak was 1,3-cyclooctadiene (4%), the second peak the unsaturated ether **2** (49%), and the third peak a mixture of 3- and 4-cycloocten-1-yl acetates (6%). The infrared spectrum of the third peak indicated that the two isomeric acetates were present in about equal amount. The fourth peak (41%) was further separated into two peaks, which are believed to be a mixture of *cis*- and *trans*-2-cyclooctene-1,4-diol diacetates.

Oxymercuration–Demercuration of 3-Cycloocten-1-ol.—To a yellow suspension of 63.7 g (0.2 mol) of mercuric acetate, 150 ml of THF, and 150 ml of water, 12.6 g (0.1 mol) of 3-cycloocten-1-ol was added and the mixture was stirred overnight at room temperature. The yellow color persisted owing to the excess mercuric acetate. The mixture was then treated with 150 ml of 3 *M* sodium hydroxide solution and the yellow color intensified to darker yellow. The mixture was then treated with 5 g of sodium borohydride in 150 ml of 3 *M* sodium hydroxide solution (the reaction was exothermic) and after it stirred for 30 min metallic mercury, a gray suspension, and a THF layer at the bottom were observed. The resulting mixture was saturated with sodium chloride and extracted with 300 ml of ether. The combined ether extracts were washed with water, dried ($MgSO_4$), concentrated, and distilled through a Vigreux column giving 8.0 g (63%) of 1,4-epoxycyclooctane (**9**), a camphorlike waxy solid: mp 31.5–32.5° (lit.[17] mp 30.8–32.2°); nmr (CCl_4) τ 5.7 (s, 2) and 8.3 (m, 12).

Oxymercuration–Demercuration of 1,5-Cyclooctadiene.—1,5-Cyclooctadiene (11 g, 0.1 mol) was treated with mercuric acetate (70 g, 0.22 mol) in 100 ml of water and 100 ml of THF. The reaction was fast, as indicated by the change of color from yellow to colorless in 40 sec. The product was isolated as described above, and 8.0 g (63%) of a mixture of 1,4- and 1,5-epoxycyclooctanes was obtained. Nmr analysis indicated that the mixture contained **9** and **10** in a ratio of 55:45.

Oxymercuration–Demercuration of 1,4-Cyclooctadiene.—1,4-Cyclooctadiene (3.0 g, 0.028 mol) was treated with mercuric acetate (8.9 g, 0.028 mol) in 20 ml of water and 30 ml of THF. The yellow color disappeared after 3 min. The mixture was stirred for 0.5 hr. A test with 3 *M* sodium hydroxide for mercuric ion was negative. The mixture was treated with 20 ml of 3 *M* sodium hydroxide, followed by addition of 2 g of sodium borohydride in 20 ml of 3 *M* sodium hydroxide. The mixture was stirred for 20 min and then saturated with sodium chloride. The solution was extracted with ether and the ethereal extract was dried ($MgSO_4$) and concentrated. The products were identified as **14** (13%), **9** (12%), **4a** (70%), and unidentified diols (8%). The reaction mixture was treated with acetic anhydride in pyridine. Gas chromatography and ir analysis showed that, in addition to **9** and **4b** (70%), unidentified acetates (8%) were also present.

Oxymercuration–Demercuration of 1,3-Cyclohexadiene.—A yellow mixture of mercuric acetate (11.5 g, 0.036 mol), 25 ml of water, and 30 ml of THF was treated with cold 1,3-cyclohexadiene (3.0 g, 0.036 mol). The reaction was fast, since the yellow color disappeared in 10 sec, giving a white color to the solution; slight precipitation was also observed. The mixture was stirred until a negative mercuric ion test was obtained on addition of 3 *M* sodium hydroxide. Sodium hydroxide (3 *M*, 20 ml) was added to the mixture, producing a black suspension

(11) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).

(12) H. B. Henbest and B. Nichols, *J. Chem. Soc.*, 227 (1959).

(13) S. Winstein and M. Shatavaky, *Chem. Ind.* (London), 56 (1956).

(14) For gas chromatographic analysis, an F & M Model 720 gas chromatograph was used. Infrared spectra were recorded with a Perkin-Elmer Infracord Model 337, and a Varian A-60 nmr spectrometer was used to record the nmr spectra. The chemical shifts are shown in τ units with tetramethylsilane as an internal standard.

(15) J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, **33**, 423 (1968).

(16) A. C. Cope and P. E. Peterson, *J. Amer. Chem. Soc.*, **81**, 1643 (1959).

(17) A. C. Cope and B. C. Anderson, *ibid.*, **79**, 3892 (1957).

which was treated with 2.0 g of sodium borohydride in 25 ml of 3 *M* sodium hydroxide. Mercury metal was observed after the reduction. The suspension was then saturated with sodium chloride and the product was extracted with 100 ml of ether. The ethereal extract was dried ($MgSO_4$) and the solvent was removed by distillation through a Vigreux column. The mixture contained 2-cyclohexen-1-ol (13%), 3-cyclohexen-1-ol (13%), and a fraction which is believed to be *cis*- and *trans*-2-cyclohexene-1,4-diols (74%).

About 1 g of the reaction mixture was treated with acetic anhydride in pyridine. The resulting acetate mixture was shown to be 2-cyclohexen-1-yl acetate (13%), 3-cyclohexen-1-yl acetate (13%), and a diacetate fraction (74%). The infrared spectrum of the diacetate indicated unsaturation, and its nmr had absorptions at τ 4.25 (d, 2 olefinic hydrogen), 5.0 (m, 2, tertiary hydrogen), 8.03 (m, 6 acetoxymethyl hydrogen), and 8.3 (m, 4 H).

About 0.5 g of the above mixture was hydrogenated in acetic acid under atmospheric pressure using platinum oxide as a catalyst. The mixture contained cyclohexyl acetate (26%) and diacetates. Comparison of the infrared spectrum and nmr spectrum of the diacetate with those of authentic samples of *cis*- and *trans*-1,4-cyclohexanediol diacetates indicated that the diacetate was a mixture of the latter two compounds, perhaps with a different isomeric ratio.

Oxymercuration–Demercuration of 1,4-Cyclohexadiene.—1,4-Cyclohexadiene (2 g, 0.025 mol) was treated with mercuric acetate (8 g, 0.025 mol) in 15 ml of water and 25 ml of THF. The reaction color changed from yellow to clear in 50 sec. The product was isolated as described for oxymercuration–demercuration of 1,3-cyclohexadiene and was shown to be 3-cyclohexen-1-ol (67%) and unidentified diol (33%). The mixture was converted into the corresponding acetates by treatment with acetic anhydride in pyridine.

Registry No.—1, 1700-10-3; 2, 20642-83-5; 11, 111-78-4; 12, 4277-34-3; 14, 1073-07-0; 5,6-epoxycyclooctene, 637-90-1; 1,3-cyclohexadiene, 592-57-4; 1,4-cyclohexadiene, 628-41-1.

The Base-Catalyzed Reaction of Hydrogen Sulfide with α-Chloromethyl Acrylate and α-Chloroacrylonitrile

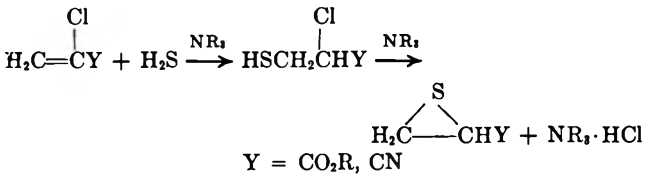
W. H. Mueller

Central Basic Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey

Received November 8, 1968

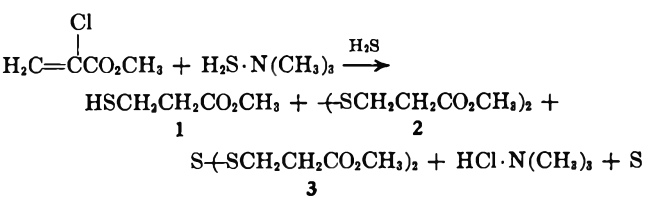
The amine-catalyzed reaction of hydrogen sulfide with α-chloromethyl acrylate produced β-mercaptomethyl propionate, di(β-carbomethoxyethyl) disulfide, di(β-carbomethoxyethyl) trisulfide, trimethylamine hydrochloride, and sulfur. Analogous products were obtained from α-chloroacrylonitrile. These unexpected products are explained by thiirane intermediates which spontaneously expel sulfur.

Base-catalyzed Michael addition of hydrogen sulfide to α-chloroacrylates, followed by the well-established internal displacement of the chloride,[1] was considered to be a convenient one-step synthetic route to apparently unknown thiiranes.[2]



The occurrence of unexpected products and their mode of formation is the topic of the present paper.

α-Chloromethyl Acrylate.—Reaction of equimolar amounts of α-chloromethyl acrylate and trimethylamine–hydrogen sulfide complex dissolved in an excess of liquid hydrogen sulfide at − 78° resulted in five identified products.



The solid products, trimethylamine hydrochloride and sulfur, were isolated in 91 and 22% yield, respectively. These yields are based on molar equivalents of amine or α-chloromethyl acrylate used in the reaction.

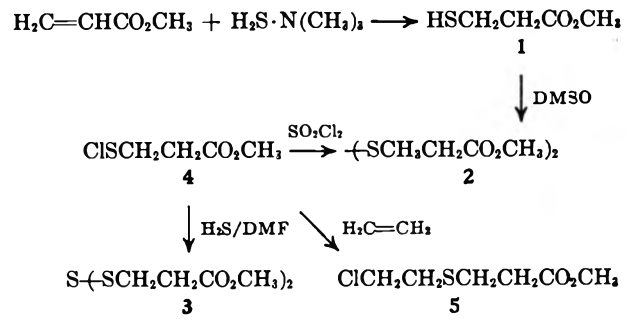
Glpc analysis of the liquid product showed three major components, β-mercaptomethyl propionate, **1** (15%), di(β-carbomethoxyethyl) disulfide, **2** (61%), and di(β-carbomethoxyethyl) trisulfide, **3** (19%). In addition, several minor unidentified impurities (5%) were present. A mixture of disulfide **2** and trisulfide **3** was obtained on removal of the volatile impurities and the mercaptan **1** at high vacuum and elevated temperature. Attempts to separate **2** from **3** by fractional distillation failed, owing to substantial sulfur extrusion which converted trisulfide **3** into disulfide **2**. A similar situation was experienced with independently synthesized **3**. It was also observed that invariably 10–20% disulfide **2** was formed upon glpc analysis of **3**. This finding made it necessary to deduce a 7:3 ratio as a more realistic product ratio for compounds **2** and **3** from elemental analysis data and molecular weight determination of the mixture. The presence of minor amounts of polysulfides containing more than three sulfurs, however, cannot be excluded in view of the observed disproportionation of trisulfide **3** during glpc analysis.

The structure elucidation of products **1**, **2**, and **3** is based on comparison of spectral data and glpc retention times with those of independently synthesized compounds (Scheme I). Amine-catalyzed addition of H_2S to methyl acrylate afforded the β-mercaptomethyl propionate, **1**, which was oxidized with dimethyl sulfoxide to the corresponding disulfide **2**. Chlorination of this disulfide with sulfuryl chloride resulted in the β-carbomethoxyethanesulfenyl chloride, **4**. The compound's nmr spectrum is consistent with its structure; however, positive identification of this thermally labile sulfenyl chloride was achieved through its stable ethylene adduct **5**. Reaction of sulfenyl chloride **4** with

(1) W. Coltof, U. S. Patent 2,183,860 (1939); British Patent 508,932 (1939); Dutch Patent 47,835 (1940).

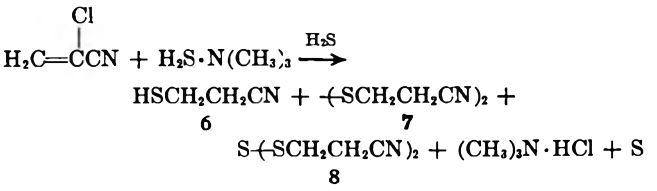
(2) M. Sanders, *Chem. Rev.*, **66**, 297 (1966).

SCHEME I



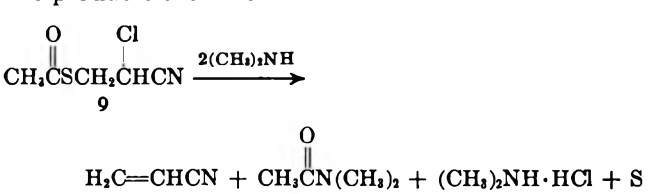
hydrogen sulfide in the presence of dimethylformamide as acid acceptor finally led to the trisulfide **3**.

α-Chloroacrylonitrile.—When α-chloroacrylonitrile was allowed to react with an equimolar amount of trimethylamine in excess liquid hydrogen sulfide, products similar to those observed from α-chloromethylacrylate were obtained.



The solid products, trimethylamine hydrochloride and sulfur, amounted to 91 and 50% yield if based on the molar equivalents of α-chloroacrylonitrile and trimethylamine used in the reaction. Glpc and nmr analysis of the crude, liquid product indicated *ca.* 65% β-mercaptopropionitrile, **6**, accompanied by some higher boiling products. Fractional distillation afforded pure **6** in 46% yield. In analogy to the results from α-chloromethyl acrylate, disulfide **7** and trisulfide **8** are most likely the predominant constituents of the higher-boiling product mixture. The nmr spectrum of the mixture and the relative glpc retention times of its components are consistent with this assumption. However, as with α-chloromethyl acrylate, the concomitant formation of small amounts of higher polysulfides cannot be excluded.

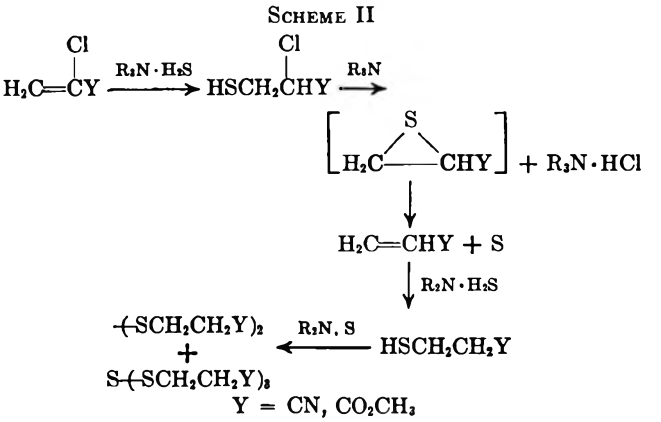
α-Chloro-β-Acetylthiopropionitrile.—The above-described complications experienced during the attempted synthesis of thiiranes from α-chloromethylacrylate or α-chloroacrylonitrile, and the possible unique role of the hydrogen sulfide–amine system, led to an investigation of the aminolysis of α-chloro-β-acetylthiopropionitrile, **9**. Pyridine-catalyzed addition of thiolacetic acid to α-chloroacrylonitrile provided compound **9**. Its reaction with 2 equiv of dimethylamine at −30° resulted in the products shown below.



Acrylonitrile and dimethylacetamide were isolated in 70 and 75% yield, respectively. The solid products, dimethylamine hydrochloride and sulfur, amounted to 89% yield each. No cyanoethylenethiirane was found, although some effort was made to detect it as a transient product by nmr analysis of the reaction mixture at temperatures below 0°.

All of the unexpected products obtained during this work are best explained by the intermediacy of the desired thiiranes. Spontaneous expulsion of sulfur from these thiiranes then prompts the formation of methyl acrylate or acrylonitrile, which in turn are transformed under the prevailing reaction conditions into the corresponding thiol, disulfide, and trisulfide (Scheme II).

SCHEME II



The possibility of sulfur expulsion in its atomic form has been considered. However, attempts to trap it as episulfide by having an olefin present during the reaction failed.

Facile loss of sulfur by some electronegatively substituted thiiranes with the formation of olefins has been previously reported.[3-6] Examples which show some resemblance to our cases are a tetrasubstituted thiirane bearing two geminal cyano groups[5] and a trisubstituted thiirane with an ethyl carboxylate group.[6] The unusual structural complexity of these thiiranes, however, did not allow an *a priori* assessment of the influence of cyano or carboxylate substituents on their stability. This is particularly true, since in at least one instance a stable thiirane with a carboxylate substituent is known.[2]

The formation of disulfide **2**, trisulfide **3**, and possibly small amounts of higher polysulfides from methyl acrylate is a consequence of base-catalyzed addition of hydrogen sulfide to form mercaptan **1** and subsequent oxidation of equimolar amounts of either methyl acrylate or β-mercaptomethyl propionate and sulfur in liquid hydrogen sulfide–trimethylamine. In both cases, product distributions of **1**, **2**, and **3** were found to be identical with that obtained from β-chloromethyl acrylate. Base-catalyzed oxidation of mercaptans by sulfur to polysulfides is well established[7,8] and has been recently investigated in detail.[9]

Experimental Section

Materials.—The α-chloroacrylonitrile from Columbia Organic Chemicals Company and α-chloromethyl acrylate and methyl acrylate from Borden Chemical Company were purified by fractional distillation prior to their use. All other reagents were used in the highest purity grade commercially available.

(3) D. S. Tarbell and D. P. Harnisch, *Chem. Rev.*, **49**, 21 (1951).
(4) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Org. Chem.*, **30**, 1378 (1965).
(5) W. J. Middleton, *ibid.*, **31**, 3731 (1966).
(6) A. Schönberg and E. Frese, *Chem. Ber.*, **96**, 2420 (1963).
(7) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., New York, N. Y., 1960, p 387.
(8) W. A. Pryor, "Mechanism of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 9.
(9) B. D. Vineyard, *J. Org. Chem.*, **32**, 3833 (1967).

Methods of Analysis.—Nmr spectra were recorded on a Varian Model A-60 resonance spectrometer using tetramethylsilane as an internal standard.

Gas–liquid partition chromatography was done on an Aerograph 1520 programmed temperature gas chromatograph with a 5 ft × 0.125 in. o.d. column. The packing consisted of 3% Dowfax 9N40 (an ethylene oxide–*p*-nonylphenol polyether of a 40:1 molar ratio) on 60–80 mesh Gas Chrom W. Operating conditions were as follows: detector, 270°; injector, 190°; flow rate, 50 ml/min.; column heating rate, 4°/min.; starting temperature, 50°; final temperature, 200°.

Reaction of Hydrogen Sulfide with α-Chloromethyl Acrylate in the Presence of Trimethylamine.—Trimethylamine (12 g, 0.204 mol) in 68 g (2 mol) of hydrogen sulfide were condensed at −78° into a heavy-wall Pyrex tube equipped with a Teflon valve. The tube was sealed and allowed to warm to ambient temperature, which caused the solid amine–hydrogen sulfide complex to dissolve in the excess hydrogen sulfide. After cooling this solution again to −78°, the α-chloromethyl acrylate (24.1 g, 0.2 mol) was slowly added. Mixing of the contents was accomplished by inverting the tube several times. The sealed tube was subsequently allowed to stand at ambient temperature for 30 min. The unreacted gases were then slowly released and the semisolid residue was suspended in ether. Filtration afforded 19 g of solid. Treatment of this solid with water followed by filtration yielded 1.4 g of elemental sulfur. Removal of the water from the filtrate resulted in 17.4 g (0.182 mol) of trimethylamine hydrochloride, mp 269–274° dec.

The ether-soluble portion of the products, a pale yellow oil (18.6 g), showed the following product distribution on glpc analysis: 15% β-mercaptomethyl propionate (**7**), 61% di(β-carbomethoxyethyl)disulfide (**2**), and 19% di(β-carbomethoxyethyl)-trisulfide (**3**). A 5% total of several minor impurities remained unidentified. Product identification is based on comparison of glc retention times with authentic samples. Heating of this product to 100° (0.1 mm) for 1 hr removed essentially all of the β-mercaptomethyl propionate and the impurities; glpc analysis now indicated products **2** and **3** in a 4:1 ratio. Elemental analysis data, however, are more consistent with a 7:3 ratio. This is explained by the apparent sulfur extrusion, *i.e.*, formation of **2**, observed during glpc analysis of independently synthesized **3**.

Anal. Calcd for a mixture of 70% $C_8H_{14}O_4S_2$ and 30% $C_8H_{14}O_4S_3$: C, 39.48; H, 5.71; S, 29.51; mol wt, 248. Found: C, 39.61; H, 5.82; S, 29.74; mol wt, 255.

Di(β-carbomethoxyethyl) Disulfide (2).—Hydrogen sulfide (102 g, 3 mol) and trimethylamine (10 g, 0.17 mol) were condensed into a Pyrex tube and mixed as described above. Methyl acrylate (43 g, 0.5 mol) was then slowly added at −78°. After completion of the addition, the contents of the sealed tube were allowed to gradually reach room temperature. The excess hydrogen sulfide and the trimethylamine were then slowly released. Fractional distillation of the residual product afforded 49.55 g (82% yield) of β-mercaptomethyl propionate (**1**), bp 73° (24 mm).

A solution of 24 g (0.2 mol) of **1** in *ca.* 20 ml of dimethyl sulfoxide (DMSO) was heated for 10 hr at 100°. The excess DMSO was then extracted with water. Distillation of the dried ($MgSO_4$) residue afforded 18.8 g (80% yield) of di(β-carbomethoxyethyl) disulfide (**2**): bp 118–120° (10^{-4} mm); nmr ($CDCl_3$) δ 2.55–31

(m, 4, SCH_2CH_2C) and 3.69 (s, 3, OCH_3).

Anal. Calcd for $C_8H_{14}O_4S_2$: C, 40.32; H, 5.92; S, 26.91. Found: C, 40.16; H, 5.82; S, 26.68.

β-Carbomethoxyethanesulfenyl Chloride (4).—To a solution of 11.9 g (0.05 mol) of disulfide **2** in 50 ml of methylene chloride, 6.75 g (0.05 mol) of sulfuryl chloride was slowly added at −50°. Removal of the solvent and SO_2 at 0° (10 mm) afforded 15.2 g (98% yield) of a tan oil whose nmr spectrum is consistent with that of **4**: nmr ($CDCl_3$) δ 2.65–3.00 (m, 2, $CH_2C{=}O$), 3.27–3.55 (m, 2, SCH_2), and 3.70 (s, 3, OCH_3).

The sulfenyl chloride decomposed on attempted distillation, and was, therefore, further identified through its stable ethylene adduct **5**. Ethylene was blown through a solution of **4** in methylene chloride at −30°. Removal of the solvent and distillation resulted in adduct **5**: bp 76–78° (0.1 mm); nmr ($CDCl_3$) δ 2.42–3.03 (m, 6, $CH_2SCH_2CH_2C{=}O$), 3.50–3.82 (m, 2, CH_2Cl), and 3.68 (s, 3, OCH_3).

Anal. Calcd for $C_6H_{11}O_2SCl$: C, 39.45; H, 6.07; S, 17.55. Found: C, 39.75; H, 6.04; S, 17.19.

Di(β-carbomethoxyethyl) Trisulfide (3).—Hydrogen sulfide was slowly introduced into a solution of 6.18 g (0.04 mol) of sulfenyl chloride **4** and 8 g of dimethylformamide in 50 ml of methylacetate at −20°. The completion of the reaction was indicated by the disappearance of the typical orange color of sulfenyl chloride **4**. The solvent was then removed, ether was added, and the ethereal solution was washed with 5% aqueous sodium bicarbonate followed by water. Drying over magnesium sulfate and removal of the ether afforded 9.4 g (87% yield) of essentially pure trisulfide **3**: nmr ($CDCl_3$) δ 2.60–3.30 (m, 4, $SCH_2CH_2C{=}O$) and 3.69 (s, 3, OCH_3).

Anal. Calcd for $C_8H_{14}O_4S_3$: C, 35.54; H, 5.22; S, 35.58. Found: C, 35.29; H, 5.12; S, 35.87.

During an attempt to distil trisulfide **3** at 114–134° (10^{-4} mm), sulfur extrusion was observed which resulted in a distillate containing *ca.* 40% of disulfide **2**. A similar, although less extensive, degradation of **3** apparently occurs during glpc analysis. Undistilled trisulfide **3**, whose elemental analysis is in good agreement with its structure, showed invariably 10–20% of disulfide **2** with our glc conditions.

Reaction of Hydrogen Sulfide with α-Chloroacrylonitrile in the Presence of Trimethylamine.—The α-chloroacrylonitrile (17.5 g, 0.2 mol) was allowed to react with 60 g (1.76 mol) of hydrogen sulfide and 11.8 g (0.2 mol) of trimethylamine. Reaction conditions and work-up were identical with those described above for the analogous reaction with α-chloromethyl acrylate. Trimethylamine hydrochloride (17.4 g, 1.82 mol), 3.2 g of sulfur, and 15.8 g of a yellow oil were isolated. Glpc and nmr analysis of this crude product indicated *ca.* 65% β-mercaptopropionitrile, **6**, accompanied by some higher boiling products, most likely the corresponding di- and trisulfides **7** and **8**.

Distillation afforded 8 g (46% yield) of pure β-mercaptopropionitrile, bp 55–56° (6 mm), which was identified by comparison of glpc retention time and spectral data with those of an authentic sample.

α-Chloro-β-acetylthiopropionitrile (9).—The α-chloroacrylonitrile (35.00 g, 0.4 mol) was slowly added to 33.44 g (0.44 mol) of thiolacetic acid containing 3.16 g (0.04 mol) of pyridine. The reaction temperature was kept between −5 and 0° during the addition. The reaction mixture was then allowed to warm to ambient temperature. After 30 min at ambient temperature, 500 ml of ether was added and the ethereal solution was washed with 5% aqueous sodium bicarbonate solution followed by water. Drying and removal of the ether afforded 59.2 g (91% yield) of α-chloro-β-acetylthiopropionitrile (**9**): nmr ($CDCl_3$) δ 2.41 (s, 3, CH_3O), 3.53 (ABX spin system, pair of overlapping quartets, 2, CH_2S), 4.80 (dd, 1 CH(Cl)CN).

Anal. Calcd for C_6H_5ClNOS: C, 36.70; H, 3.70; S, 19.60. Found: C, 36.91; H, 3.57; S, 20.21.

Reaction of Dimethylamine with α-Chloro-β-acetylthiopropionitrile (9).—Dimethylamine (4.5 g, 0.1 mol) was slowly introduced into a solution of 8.2 g (0.05 mol) of α-chloro-β-acetylthiopropionitrile in 10 ml of methylene chloride at −30°. After completion of the addition, the reaction mixture was allowed to warm to 0°. The solvent and volatile products were then condensed *in vacuo* into a Dry Ice cooled trap. Nmr analysis of this condensate showed acrylonitrile and very small amounts of dimethylamine and dimethylacetamide to be present in the solvent. Fractional distillation yielded 1.86 g (70% yield) of pure acrylonitrile.

The residue from the initial low-temperature transfer was taken up in ether and the insoluble material was filtered off. Removal of the ether from the filtrate afforded 3.26 g (75% of dimethylacetamide. Treatment of the ether-insoluble material with water and subsequent filtration yielded 1.43 g (89%) of elemental sulfur. Removal of the water from the filtrate and recrystallization of the solid residue from methanol resulted in 3.6 g (89%) of dimethylamine hydrochloride, mp 168–170°.

Registry No.—Hydrogen sulfide, 7783-06-4; α-chloromethyl acrylate, 80-63-7; α-chloroacrylonitrile, 920-37-6; **2**, 15441-06-2; **3**, 20707-94-2; **5**, 20707-95-3; **9**, 20707-96-4.

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Hydration Study of Acetaldehyde and Propionaldehyde

G. SOCRATES

Brunel University, London, England

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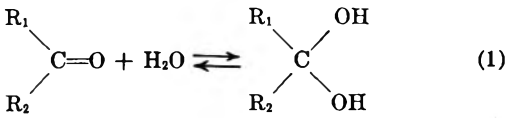
The presence of the hemihydrate of acetaldehyde, which has previously been suggested to be responsible for the unusual hydration kinetics observed, was detected by nmr spectroscopy for dilute, as well as rich, aqueous solutions of acetaldehyde. The sharp nuclear magnetic resonances observed for solutions of acetaldehyde with high acid concentration were explained by the presence of paraldehyde. In addition, the proton exchange of protonated 1,1-dihydroxyethane with water was detected. The hydration of propionaldehyde was also studied in order to determine whether its behavior was similar to that of acetaldehyde. The equilibrium constant K_h = [EtCHCO]/[EtCH(OH)$_2$] was determined. The catalytic constants for the hydrogen ion in the acid-catalyzed hydration and dehydration were found to be 460 and 650 l. mol^{-1} sec^{-1}, respectively.

The formation of *gem*-diols by the reversible hydration of the carbonyl group of ketones and aldehydes is well known and has been the subject of a large number of publications. A recent and comprehensive review of various aspects of the hydration of carbonyl groups has been published by Bell.[1]



(1)

In dilute aqueous solution, the equilibrium constant of hydration has been correlated by Bell with Taft

$$K_h = \frac{[R_1R_2CO]}{[R_1R_2C(OH)_2]}$$

polar and steric substituent constants, σ^* and E_s, respectively,[2-4] for a number of carbonyl-containing compounds. Even though the range of the equilibrium constant K_h extends over eight orders of magnitude, a reasonable correlation is obtained.

The hydration of carbonyl groups has been found to be catalyzed by acids and bases. It has been suggested that the mechanism of the hydration involves several water molecules.[5-8]

The hydration of acetaldehyde to form the hydrate, 1,1-dihydroxyethane, has been found to be anomalous. In dilute aqueous solution, in the presence of acid catalyst, the acetaldehyde and 1,1-dihydroxyethane proton magnetic resonance signals are broad owing to the fast reversible hydration of the carbonyl group. However, in acetaldehyde-rich mixtures, the hydrate signals observed are sharp, even though the acetaldehyde signals are broad. In order to explain this, Ahrens and Strehlow suggested that the hemihydrate $CH_3CH(OH)OCH(OH)CH_3$ is formed in acetaldehyde-rich aqueous solutions.

$$CH_3CHO + CH_3CH(OH)OH_2^+ \rightleftharpoons CH_3CH(OH)OCH(OH_2)^+CH_3 \rightleftharpoons CH_3CH(OH)OCH(OH)CH_3 + H^+ \quad (2)$$

The purpose of the present study was to investigate this and other apparently unusual occurrences in the acid-catalyzed hydration of acetaldehyde. An investigation was also made to determine whether propionaldehyde behaved in a similar fashion, the equilibrium constant of the hydration of propionaldehyde being determined. The hydrogen ion dependent rate constants of both the hydration and dehydration processes at 34.5° were computed.

Experimental Section

The Perkin-Elmer R10 high resolution nuclear magnetic resonance spectrometer was employed, using a 60-MHz probe. The magnetic assembly was thermally insulated at 34.5°.

The aldehydes were purified by distillation under reduced pressure. Bromothymol blue indicated that aqueous solutions of the purified aldehyde were neutral, thus showing the absence of acids which could be produced by oxidation. The samples prepared were allowed to attain the temperature of the magnet assembly. Owing to signal-to-noise considerations, all the solutions employed in the kinetic study were 1.5 mol l.$^{-1}$ propionaldehyde. The acid catalyst employed was prepared from hydrochloric acid (analytical reagent) and the solutions were standardized with sodium tetraborate (analytical reagent), using methyl red as indicator.

Results and Discussion

Acetaldehyde.—From the nmr spectra of aqueous acetaldehyde, the chemical shifts of the methyl doublet and aldehyde quartet were found to be τ 7.73 and 0.22 and those for the corresponding protons in the hydrate to be τ 8.66 and 4.69, employing the sodium salt of 3-trimethylsilylpropanesulfonic acid as internal standard. Aqueous solutions of acetaldehyde in the presence of hydrochloric acid at various concentrations of both aldehyde and acid were studied, and the solutions were prepared and examined immediately. In some cases, the spectra were observed to alter with time, and the changes in the spectra were complete within minutes of the preparation of the mixture. Typical examples are the spectra of 2.5 *M* acetaldehyde with 0.04 *M* hydrochloric acid and 5.3 *M* acetaldehyde with 0.06 *M* hydrochloric acid. Originally, both methyl doublets were broad. However, under conditions of good resolution, two doublets were observed to appear in the region of the originally broad hydrate methyl doublet. The chemical shifts of the two doublets are τ 8.63 and 8.66, and the coupling constants are 5.4 and 5.2 Hz, respectively.

The spectra may be explained as follows. Both methyl resonances of acetaldehyde and 1,1-dihydroxyethane are broad owing to fast reversible hydration. The doublet which appears at τ 8.63 may be attributed to a new compound that is formed with time and is probably the hemihydrate. The latter may be ex-

(1) R. P. Bell, *Advan. Phys. Org. Chem.*, **4** (1966).
(2) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **74**, 2729 (1952).
(3) R. W. Taft, Jr., *ibid.*, **75**, 4538, (1953).
(4) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956.
(5) R. P. Bell and B. de B. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950).
(6) R. Gibert, *J. Chim. Phys.*, **51**, 372 (1954).
(7) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5224 (1963).
(8) M. Eigen, *Discussions Faraday Soc.*, **39**, 7 (1965).

pected to have a doublet in the region of the hydrate methyl resonances. The other doublet at τ 8.66 is due to the hydrate methyl resonance. There is evidence to support the formation of a hemihydrate, since formaldehyde,[9-11] dichloroethanal,[11] and fluoral[12] form similar hemihydrates. If the acetaldehyde–acid solutions are neutralized, a typical spectrum of an aqueous solution of acetaldehyde is obtained, thus showing that the reactions occurring are reasonably fast and reversible, as would be expected of the reaction forming the hemihydrate. By reasonably fast, it is meant that the rate constant is of the order of minutes. This is in agreement with the observed appearance of the doublet at τ 8.63.

The spectra of aqueous acetaldehyde-rich solutions in which the acid catalyst concentration is less than 0.1 *M* also change with time. The acetaldehyde proton resonances remain broad, but only one sharp doublet at τ 8.63 is observed. Neutralization of these solutions results in the nmr spectrum being typical of an aqueous solution of acetaldehyde at the concentration studied. Acetaldehyde-rich solutions in which the acid concentration is greater than 0.1 *M*, when neutralized, exhibit, in addition to the typical aqueous acetaldehyde solution spectrum, a doublet at τ 8.63 and a quartet at τ 4.69. The latter two signals may be attributed to paraldehyde.

The nmr spectra of 5.3 *M* acetaldehyde with hydrochloric acid at various concentrations exhibit a number of interesting features. In the concentration range 0–0.020 *M* hydrochloric acid, the broadening is consistent with the reversible hydration of acetaldehyde (Figure 1), and also with the computed theoretical spectra.[13] By comparing the experimental and theoretical spectra of the acetaldehyde and 1,1-dihydroxyethane resonances, the mean lifetimes of both the acetaldehyde and the hydrate are obtained. Hence, the hydrogen ion dependent rate constants for the hydration, 520 l. mol^{-1} sec^{-1}, and the dehydration, 540 l. mol^{-1} sec^{-1}, were computed.[14,15]

With further increase in the hydrochloric acid concentration, from 0.020 to 0.20 *M* (Figure 1), the widths of both methyl doublets increase. The doublet in the region of τ 8.6, however, remains relatively sharp, which is not in agreement with reversible hydration. The observed sharpness of this doublet may be attributed to the formation of a hemihydrate. When using 1 *M* acetaldehyde solutions for a similar study, both the acetaldehyde and the hydrate methyl doublets were observed to collapse, the hydrate doublet collapsing at a concentration of about 0.06 *M* hydrochloric acid. The theoretically computed and the experimental spectra were consistent over a much wider range of acid concentration than those for higher acetaldehyde concentrations. This fact is added proof of compound hemihydrate formation, since in acetaldehyde–dilute aqueous solutions the concentration of hemihydrate is expected to be low.

(9) S. Bezzi, N. Dallaporta, G. Giacometti, and A. Ilicato, *Gazz. Chim. Ital.*, **81**, 915 (1951).
(10) P. Skell and H. Suhr, *Chem. Ber.*, **94**, 3317 (1961).
(11) K. Moedritzer and J. R. Van Wazer, *J. Phys. Chem.*, **70**, 2025 (1966).
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(13) H. M. McConnell, *J. Phys. Chem.*, **28**, 430 (1958).
(14) G. Socrates, M.S. Thesis, 1962, and Ph.D. Thesis, 1965 (University of London).
(15) M. L. Ahrens and H. Strehlow, *Discussions Faraday Soc.*, **39**, 112 (1965).

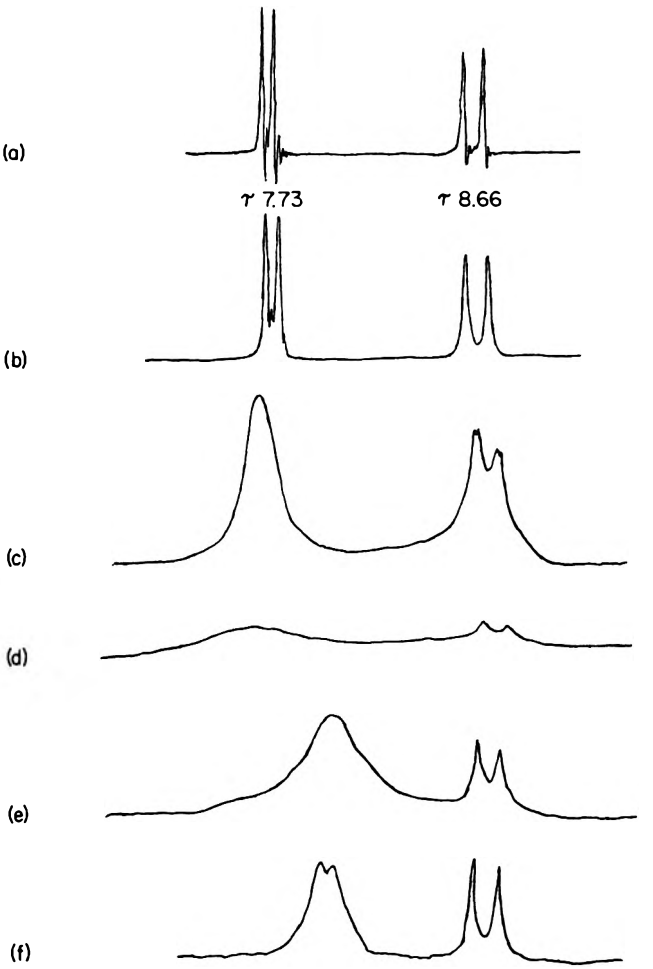

Figure 1.—5.3 *M* acetaldehyde with (a) no acid present; (b) 0.0195 *M* hydrochloric acid; (c) 0.0380 *M* hydrochloric acid; (d) 0.110 *M* hydrochloric acid; (e) 0.700 *M* hydrochloric acid; (f) 2.21 *M* hydrochloric acid.

With still further increase in the concentration of the hydrochloric acid (0.20–2.0 *M*) in the 5.3 *M* acetaldehyde solutions, the methyl signals do not appear to coalesce. Instead, the signal widths are observed to decrease. Finally, with 3.5 *M* hydrochloric acid, two doublets at τ 8.63 and 8.03 (with coupling constants 5.2 and 4 Hz respectively), a broad signal at τ 1.66, and a quartet at τ 4.96 (buried under the water resonance) are observed. Proton double resonance shows that when irradiating at τ 1.66 the doublet at τ 8.03 collapses, thus indicating that the protons producing these resonances are coupled.

The explanation of the observations made is as follows. The signals of acetaldehyde and 1,1-dihydroxyethane have coalesced, the doublets coalescing to the signal at τ 8.03 and the quartets coalescing to the signal at τ 1.66. The signals at τ 8.63 and 4.96 are due to paraldehyde, which is formed at these acid concentrations. Increase in the acid concentration makes the signal at τ 4.96 observable.

In 4 *M* hydrochloric acid, the two doublets and the quartet are sharp. The signal at τ 1.66 remains broad even at very high acid concentrations (10 *M*). This may be attributed to reactions 3–5. Unfortunately,

$$CH_3CH(OH)OH_2^+ + H_2O \rightleftharpoons CH_3CH(OH)_2 + H_3O^+ \quad (3)$$

$$CH_3CH(OH)OH_2^+ + CH_3CH(OH)_2 \rightleftharpoons CH_3CH(OH)_2 + CH_3CH(OH)OH_2^+ \quad (4)$$

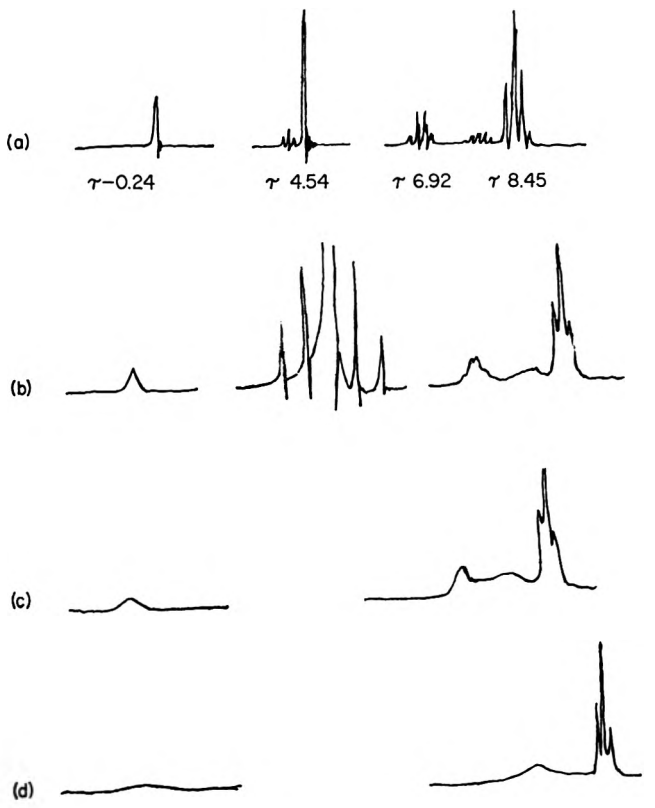

Figure 2.—The nmr spectra of aqueous propionaldehyde at various hydrochloric acid concentrations: (a) 0.005 *M* hydrochloric acid (propionaldehyde in heavy water); (b) 0.003 *M* hydrochloric acid; (c) 0.080 *M* hydrochloric acid; (d) 0.160 *M* hydrochloric acid.

$$CH_3CH(OH)OH_2^+ + \overset{H}{\underset{|}{O}}\!-\!H + (HO)_2CHCH_3 \rightleftharpoons CH_3CH(OH)_2 + H\!-\!\overset{H}{\underset{|}{O}} + H_2{}^+O(HO)CHCH_3 \quad (5)$$

since the slow exchange state is not observed, the kinetics cannot, without undue difficulty, be studied by nmr.

The ratio of the concentration of paraldehyde to the concentration of acetaldehyde, as determined from the ratio of the intensities of the methyl doublets for 5.3 *M* acetaldehyde with 4 *M* hydrochloric acid, is 0.16.

A number of important points have thus been deduced.

(i) A hemihydrate is formed not only in aqueous acetaldehyde-rich solutions but even in dilute solutions.

(ii) Paraldehyde is formed with increase in acetaldehyde and acid concentrations, but this is not responsible for the sharpness of the doublet at τ 8.6 at low concentrations of aldehyde and acid.

(iii) The unusual narrowing of the doublet resonances has now been explained.

(iv) Proton exchange of protonated 1,1-dihydroxyethane with water must be responsible for the broad signal at τ 1.66 which is observed for solutions containing high acid concentrations.

Propionaldehyde.—The nmr spectrum of propionaldehyde consists of a triplet at τ 8.45, a quartet of triplets at τ 6.92, and a triplet at τ −0.24, employing the sodium salt of 3-trimethylsilylpropanesulfonic acid as reference. From consideration of intensities, chemical shifts, and coupling constants, these resonances may be

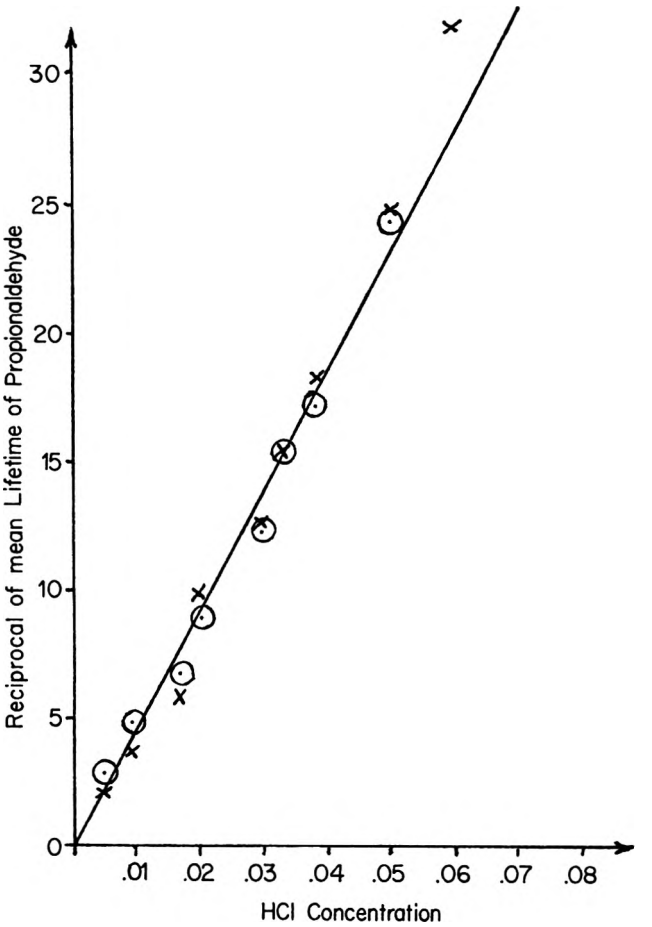

Figure 3.—The graph of the reciprocal of the mean lifetime of propionaldehyde against hydrochloric acid concentration. Points denoted by × were determined from the aldehydic proton resonance, points denoted by ⊙ from the methylene quartet of propionaldehyde.

assigned to the methyl, methylene, and aldehydic proton resonances, respectively.

The spin–spin coupling constant between the methylene and methyl protons was found to be 7.5 Hz, and that between the aldehydic and methylene protons, 1.3 Hz.

The spectrum of propionaldehyde in heavy water (Figure 2a) had additional signals: a triplet at τ 8.59, a complicated multiplet at τ 7.92, and a triplet at τ 4.54. These signals may be assigned to the methyl, methylene, and methylyne, $CH(OH)_2$, protons of the hydrate of propionaldehyde, 1,1-dihydroxypropane. This is consistent with the assignments given to the nmr spectra of aqueous solutions of other aldehydes.[15–20]

Employing the proton double resonance technique, the coupling constant between the methyl and methylene protons of the hydrate was found to be 7.0 Hz. Proton decoupling of the resonance at τ 7.92 was observed by irradiating and saturating the methylyne triplet. The coupling constant between the methylene and methylyne protons was found to be 5.5 Hz. On addition of acid catalyst, the methylene resonance of propionaldehyde in Figures 2a and 2b no longer appears to be a quartet with each component split into a triplet.

(16) E. Lombardi and P. G. Sogo, *J. Phys. Chem.*, **32**, 635 (1960).
(17) Y. Fujiwara and S. Fujiwara, *Bull. Chem. Soc. Jap.*, **36**, 574 (1963).
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(19) G. Socrates and V. Griffith, *Trans. Faraday Soc.*, **63**, 673 (1967).
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Instead, a quartet with the usual second-order splitting is observed. It would therefore seem that the small splitting of the methylene protons by the aldehydic protons, together with the second-order splitting of the quartet, have produced these four triplets. Also, the triplet of the aldehydic proton resonance of propionaldehyde in Figure 2a has collapsed to give a sharp signal. The changes in the resonances of the methylene and aldehydic protons may be explained by the fact there are two possible magnetic environments for the protons: (i) in propionaldehyde; (ii) in 1,1-dihydroxypropane. Owing to the reversible hydration, protons experience a rapid interchange of these environments. From the collapse of the aldehydic proton triplet, the mean lifetime of propionaldehyde was calculated to be 450 msec.

The equilibrium constant K_h was determined to be 1.4 from the ratio of the intensities of (i) the aldehydic and methylyne proton resonances and (ii) the methylene proton resonances of propionaldehyde and its hydrate. This value is in good agreement with that obtained by the ultraviolet photometric technique.[21] The equilibrium constant did not vary with concentration. The lowest concentration observed was determined by the detection limits of the instrument and the highest concentration, about 6 mol $l.^{-1}$ of propionaldehyde, by solubility.

Various changes were observed in the spectra obtained on addition of hydrochloric acid to the aqueous solution of propionaldehyde. The methylene quartets, the methyl triplets and the aldehydic resonances all broadened (see Figures 2a–d), owing to the hydration–dehydration exchange which became more rapid.

The reciprocal of the mean lifetime of propionaldehyde was obtained by observing the aldehydic and methylene resonances of propionaldehyde and comparing these with theoretical spectra which had been computed for various lifetimes. The theoretical triplets and quartets were computed from the imaginary part of the total complex magnetization as determined by McConnell's method.[13]

The reciprocal of the mean lifetime of propionaldehyde is plotted against the hydrochloric acid concentration in Figure 3. The straight-line graph obtained indicates a rate law of the type

$$\text{specific rate} = k_0 + k_{H^+}[H^+]$$

where k_0 is the spontaneous rate constant and k_{H^+} is the hydrogen ion dependent rate constant. This is consistent with the general acid–base catalysis observed for the hydration of carbonyl-containing compounds.

For the hydration, the hydrogen ion dependent rate constant was 460 l. mol^{-1} sec^{-1}, as determined from the slope of the straight line obtained in Figure 3.

It is reasonable to assume that the spontaneous rate constants for the hydration and dehydration are small compared to the hydrogen ion dependent rate constants. Therefore, the equilibrium constant K_h was employed to estimate the hydrogen ion dependent rate constant, which was found to be 650 l. mol^{-1} sec^{-1}. These results are in good agreement with those of Gruen and McTigue,[7] who employed a thermal method.

No anomalous behaviour similar to that of acetaldehyde was observed for the hydration of propionaldehyde.

Registry No.—Acetaldehyde, 75-07-0; propionaldehyde, 123-38-6.

Acknowledgment.—The author wishes to acknowledge helpful discussion with Professor V. Gold of King's College, London.

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Mechanism of Ozonation Reactions. IV. Carbon–Nitrogen Double Bonds

RONALD E. ERICKSON,[1] PETER J. ANDRULIS, JR.,[2]
JAMES C. COLLINS, MELVIN L. LUNGLE, AND GARY D. MERCER

The Department of Chemistry, University of Montana, Missoula, Montana 59801, and the Chemistry Department, Canisius College, Buffalo, New York

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A study of the mechanism of the ozonation of carbon–nitrogen double bonds has been carried out using product analysis data and competitive rate studies on dimethylhydrazones, oximes, and Schiff bases. It was found that variation of Y in I ($XC_6H_4CR{=}NY$) had a much larger effect on relative rates than variation of X. A generalized mechanism involving initial electrophilic attack of ozone on the carbon atom of the carbon–nitrogen double bond is proposed, and some specific suggestions are made as to pathways in the breakup of initial adducts. In all cases the complete reaction pathways are quite complex. Carbon–nitrogen double bonds, if properly substituted, are as reactive toward ozone as are carbon–carbon double bonds.

Previous work in this series has included one paper involving nitrones, a system which formally contains a carbon–nitrogen double bond.[3] At that time we showed that relative rate studies could be useful in distinguishing between nucleophilic and electrophilic ozone attack in such systems.

The literature contains ozonation studies on several other classes of compounds containing carbon–nitrogen double bonds in both acyclic and heterocyclic compounds. Acyclic systems include Schiff bases,[4] ni-

(1) To whom requests for reprints should be sent: Department of Chemistry, University of Montana, Missoula, Mont. 59801.

(2) Abstracted in part from the M.S. thesis of P. Andrulis, Jr., Canisius College, 1964.

(3) R. E. Erickson and T. M. Myszkiewicz, *J. Org. Chem.*, **30**, 4326 (1965); for paper number III in this series, see R. E. Erickson, R. T. Hanson, and J. Harkins, *J. Amer. Chem. Soc.*, **90**, 6777 (1968).

(4) (a) A. H. Riebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *ibid.*, **82**, 1801 (1960); (b) J. S. Belew and J. T. Person, *Chem. Ind.* (London), 1246 (1958); (c) R. E. Miller, *J. Org. Chem.*, **26**, 2327 (1961).

TABLE I
PRODUCT DATA

Substrate	Ozonation conditions	Products analyzed (yields, %)
Acetophenone dimethylhydrazone	CH_2Cl_2, −78°, 2–2.2 mol of O_3	Acetophenone (97), N-nitrosodimethylamine (65), chloride ion (1.7)
p-Bromoacetophenone dimethylhydrazone	CH_2Cl_2, −78°, 2–2.2 mol of O_3	*p*-Bromoacetophenone (98–100), N-nitrosodimethylamine (57–65)
Acetone dimethylhydrazone	CH_2Cl_2, −78°, 2–2.2 mol of O_3	Acetone (96), N-nitrosodimethylamine (51), chloride ion (1.1)
Cyclopentanone dimethylhydrazone	CH_2Cl_2, −78°, 2–2.2 mol of O_3	Cyclopentanone (62–65)
Cyclohexanone dimethylhydrazone	CH_2Cl_2, −78°, 2–2.2 mol of O_3	Cyclohexanone (90–91)
p-Nitroacetophenone O-methyl oxime	CH_2Cl_2, 0°, 2.1 mol of O_3	*p*-Nitroacetophenone (72)
Acetophenone O-methyl oxime	CH_2Cl_2, −78°, 2.1 mol of O_3	Acetophenone (83–86)
Acetone oxime	CH_2Cl_2, −78°, 1.3 mol of O_3	Acetone (77–83), chloride ion (1.3–1.5), nitric oxide, 2-nitroso-2-nitropropane (trace)
Acetone oxime	CH_2Cl_2, −78°, 1.3 mol of O_3, CF_3COOH added at end of reaction at −78°	Acetone (50–70), chloride ion (1.3), 2-nitroso-2-nitropropane (16–28)
Acetone oxime	CH_2Cl_2, −78°, CF_3COOH (equimolar with oxime)	No reaction
Acetone oxime	CH_2Cl_2–pyridine (1:1), −78°, 2.2 mol of O_3	Acetone (70–84), chloride ion (9–16), *no* 2-nitroso-2-nitropropane, pyridine salt (HNO_3) (33–35)
Acetone oxime	CH_3OH, −78°, 2.0 mol of O_3	Acetone (100), *no* 2-nitroso-2-nitropropane
Acetone oxime	CH_2Cl_2, −78°, 1.47 mol of O_3, pyridine added at −60° after ozonation	Acetone oxime (34), acetone (47), pyridine salt (HNO_3) (27)

trones,[4a] azines,[5] 2,4-dinitrophenylhydrazones,[6] N-methylphenylhydrazones,[5] and diazo compounds.[5,7] Wibaut and coworkers have ozonized several heterocyclic systems in which some products indicate that carbon–nitrogen double-bond cleavage occurs[5,8] while Moriconi and Spano[9] have carried out a definitive study of the ozonation of several azaaromatics and their N-oxides. Quite recently Bachman and Strawn reported products and yields for the ozonation of selected oximes and Schiff bases.[10]

In this paper we report on the ozonation of Schiff bases, oximes, and dimethylhydrazones. Using product analysis, and, of greater pertinence, relative rate studies, a generalized mechanism for the ozonation of carbon–nitrogen double bonds is suggested.

Experimental Section

Materials.—Solvents were the best commercial grades available and were not purified further. Dimethylhydrazones,[11] Schiff bases,[12] and oximes[13] were prepared by standard methods and had physical constants and spectra identical with or consistent with literature values.

Product Analyses.—Some products were analyzed by gas chromatography as related in previous communications.[3] Several of the analyses in Table I were determined by nmr spectroscopy (Varian HA-60), using an internal standard for the determination of absolute yields.

Chloride ion analyses listed in Table I were determined using a standard titration method, after water extraction of the methylene chloride solutions. Blanks were determined by ozonizing pure methylene chloride for the equivalent period of time and were never more than 20% of the total amount of chloride ion found.

Active oxygen was determined iodometrically in the usual fashion. All of the solutions ozonized except the benzaldehyde Schiff bases contained only slight (1–4%) amounts of peroxidic materials. Product (and rate) studies gave essntially identical results whether ozone–oxygen or ozone–nitrogen streams were used.

Ozone stoichiometry was readily determined for oximes and dimethylhydrazones which absorbed ozone almost quantitatively. When the ozonized solution became blue or the potassium iodide trap darkened, the ozonation was stopped, the time of ozonation was noted, and excess ozone in the ozonized solution was flushed into the trap. Comparison of the trap titration with that of the known ozone output (concentration/minute) yielded the number of moles absorbed in a particular ozonation.

Identification of Colored Product from Acetone Oxime Ozonations.—Ozonation of acetone oxime in methylene chloride at −78° produced a colorless solution which became colored (blue-green) upon warming and gave off nitric oxide at about 0°. The color of the solution changed slowly to blue and remained blue for several days. An nmr spectrum of the solution showed a weak peak at 1.50 ppm (δ) in addition to a relatively strong signal for acetone but isolation of the material was not successful. However, addition of 1 ml of trifluoroacetic acid to a freshly ozonized solution of acetone oxime in methylene chloride produced a considerably more intense blue coloration. Quantitative analysis was carried out by nmr (Table I) while evaporation *in vacuo* of solvent and acetone gave a crystalline material which, after crystallization, was shown (mixture melting point and identical ir and nmr spectra) to be 2-nitroso-2-nitropropane.

Identification of Methyl Nitrite from Acetone O-Methyl Oxime Ozonation.—One of the expected products of O-methyl oxime ozonations, methyl nitrite, is quite volatile (bp −12°) and might well be lost during ozonations. Gas chromatographic analysis of acetone O-methyl oxime ozonations indicated the presence of a volatile substance (retention time slightly longer than air) and showed that methanol was not a product. Infrared spectra, both of an extremely small amount of condensate in a Dry Ice trap placed after the ozonation flask and of the ozonation mixture itself (which also showed acetone and the solvent, methylene chloride, absorptions) indicated methyl nitrite to be a product. Specifically bands at 1640 and 1610 (*trans*- and *cis*-N=O) and 800 and 815 cm^{-1} (N—O stretch) are known nitrite

(5) J. P. Wibaut and J. W. P. Boon, *Helv. Chem. Acta*, **44**, 1171 (1961).
(6) R. E. Erickson, A. H. Riebel, A. M. Reader, and P. S. Bailey, *Ann.*, **653**, 129 (1962).
(7) A. M. Reader, P. S. Bailey, and H. M. White, *J. Org. Chem.*, **30**, 784 (1965); P. S. Bailey, A. M. Reader, P. Kolsaker, H. M. White, and J. C. Barborak, *ibid.*, **30**, 3042 (1965).
(8) Bailey [P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958)] reviewed much of Wibaut's earlier work along with other ozonations of heterocyclic systems.
(9) E. J. Moriconi and J. A. Spano, *J. Amer. Chem. Soc.*, **86**, 38 (1964).
(10) G. B. Bachman and K. G. Strawn, *J. Org. Chem.*, **33**, 313 (1968).
(11) G. R. Newkome and D. L. Fishel, *ibid.*, **31**, 677 (1966); R. Wiley and G. Irick, *ibid.*, **24**, 1925 (1959).
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(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1966, p 289.

absorptions[14a] while methyl nitrite is also reported[14b] to have bands around 1000 and 1150 cm^{-1} (found 1012 and 1155 cm^{-1}).

Low Temperature Nmr Studies.—Several ozonations were carried out on the acetone oxime and acetophenone oxime solutions (methylene chloride solvent) directly in an nmr probe at temperatures between −60 and −70°. An ozone–nitrogen stream (ozone adsorbed on silica gel at −78°) was used for these studies. The course of the reaction was followed by removing the capillary bubbler from the nmr tube and recording the nmr spectra at regular intervals during the ozonation. The methyl group of the ketonic product appeared as soon as ozonation had begun but the methyl peak for the oxime shifted continuously to lower field as is shown for one specific case in Table II. All signals were singlets and percentages in the table were calculated *via* integration and comparison with the area on an internal standard (*t*-butyl benzoate).

TABLE II

NMR OZONATION OF ACETOPHENONE OXIME[a] AT −70°

	—Acetophenone—		—Acetophenone oxime—	
Sample no.	Chemical shift[b]	% yield	Chemical shift[b]	% reacted
1	64	0	43.5	0
2	64	7.4	44	9.0
3	63	9.1	44	14.6
4	64	13.5	44	17.3
5	64	16.7	45	25.9
6	64	23.5	47	29.4
7	64	26.4	48	35.9
8	64	30.0	50	44.0
9	63	33.3	51	49.0
10	63	42.0	56	63.0
10[c]	63	58.8		>95

[a] Solution (0.5 ml) from 0.500 g of acetophenone oxime and 0.225 g of *t*-butyl benzoate in 7.5 ml of methylene chloride. [b] Cycles per second downfield from internal standard (*t*-butyl group in *t*-butyl benzoate). [c] Sample 10 warmed to 30° and then cooled to −70° before the spectrum was taken.

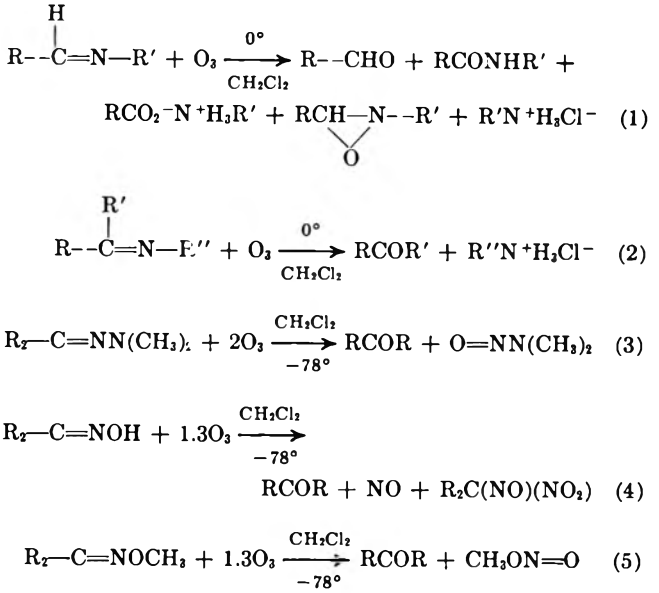
Relative Rate Methods.—Competitive ozonations were carried out using gas chromatography with an internal standard as has been described in previous publications.[3,15] The columns (40% Dow Corning high vacuum silicone grease on 60–80 mesh Chromosorb W, 5% SE-30 on Chromosorb G, 5% FFAP on 60–80 mesh DMCS-treated Chromosorb G, and 5% Carbowax 20M on 60–80 mesh Chromosorb G), gas chromatographic conditions, and internal standards (aromatic esters, aromatic nitro compounds, etc.) were varied widely to obtain good analytical data. Finding proper conditions for each analysis often involved an extensive series of gas chromatography experiments.

Relative rate constants were determined from a computer program for the least-squares analysis of the slope of a log concentration *vs.* log concentration plot.

Reaction of Schiff Bases with Ozonized Oximes.—A methylene chloride solution of 1.50 g of cyclohexanone oxime and 1.31 g of methyl benzoate (internal standard) was ozonized at −78° until 27.8% of the oxime had reacted. At that point a solution (gas chromatographically analyzed) of 1.31 g of N-isobutylcyclohexanone imine and 1.04 g of *n*-propyl benzoate (internal standard) was cooled to −78° and added to the cold ozonized solution. Analysis within 1 min of the addition showed that 48.8% of the Schiff base had reacted with oxime ozonation products.

Results

Tables I, III, and IV list the major quantitative results of this investigation. Equations 1–5 indicate the general stoichiometry and show the major products of the ozonations.



$$\mathrm{R{-}\overset{H}{\underset{|}{C}}{=}N{-}R' + O_3 \xrightarrow[CH_2Cl_2]{0^\circ} R{-}CHO + RCONHR' + RCO_2^-N^+H_2R' + RCH(O)N{-}R' + R'N^+H_2Cl^-} \quad (1)$$

$$\mathrm{R{-}\overset{R'}{\underset{|}{C}}{=}N{-}R'' + O_3 \xrightarrow[CH_2Cl_2]{0^\circ} RCOR' + R''N^+H_2Cl^-} \quad (2)$$

$$\mathrm{R_2{-}C{=}NN(CH_3)_2 + 2O_3 \xrightarrow[-78^\circ]{CH_2Cl_2} RCOR + O{=}NN(CH_3)_2} \quad (3)$$

$$\mathrm{R_2{-}C{=}NOH + 1.3O_3 \xrightarrow[-78^\circ]{CH_2Cl_2} RCOR + NO + R_2C(NO)(NO_2)} \quad (4)$$

$$\mathrm{R_2{-}C{=}NOCH_3 + 1.3O_3 \xrightarrow[-78^\circ]{CH_2Cl_2} RCOR + CH_3ON{=}O} \quad (5)$$

The products indicated in eq 1 were those found for the N-*t*-butyl benzaldimine system studied in earlier work.[4a] As titrations showed a maximum of 3% active oxygen in the ozonation of Schiff bases from cyclic ketones and acetophenones in this study, very little oxaziridine is formed. Ketone yields were generally high in the reactions described by 2–5, while yields of products containing nitrogen were generally lower.

The behavior of acetone oxime upon ozonation was very striking and seemed to indicate the possibility that some precursor to the products was formed. Ozonation at −78° in methylene chloride showed complete absorption of about 1.3–1.4 mol of ozone/mol of acetone oxime. The solution remained colorless until the end of the ozonation, whereupon it became blue (ozone color). The solution again became colorless when the excess ozone was swept out by nitrogen. On warming, the solution changed color again (blue-green) and at about 0° gave off large quantities of nitric oxide (shown by its typical reaction with oxygen in the air to form nitrogen dioxide). Gas chromatography and nmr showed that no starting material was present. The color of the solution was shown to be due to 2-nitroso-2-nitropropane and several experiments were carried out (see Table I) to determine the conditions necessary for its formation. Low temperature nmr studies (Table II) and product analysis (Table I) partially resolved this unusual ozonation behavior (see Discussion).

Competitive ozonations listed in Tables III and IV were carried out with no particular difficulty. However, attempts to determine the relative rates of ozonation of either oximes or O-methyl oximes and Schiff bases by the competitive method gave widely variable results, with the Schiff base normally reacting faster than the oxime. It was shown (see Experimental Section) that the disappearance of Schiff base in these competitive ozonations was in fact due to reaction with ozonation products of the oxime. Experiments involving competitive ozonations of oxime pairs gave erratic results (*e.g.*, relative rates varied from 1.5 to 5.5 for the system cyclohexanone oxime–cyclopentanone oxime) unless pyridine was used as a cosolvent. The trapping of the reaction product (nitric oxide) by the pyridine before it could react with the oximes is the obvious explanation for this solvent effect.

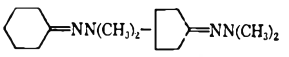
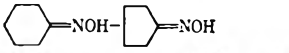
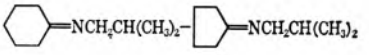
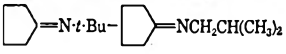
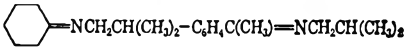
(14) (a) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1967, p 99. (b) P. Tarte, *Bull. Soc. Chim. Belges*, **60**, 227 (1951); *Chem. Abstr.*, **46**, 826d (1952).

(15) R. E. Erickson, D. Bakalik, C. Richards, M. Scanlon, and G. Huddleston, *J. Org. Chem.*, **31**, 461 (1966).

TABLE III
COMPETITIVE OZONATIONS. SUBSTITUENT EFFECTS

	Temp (°C), solvent	Relative rate	r
Schiff Bases			
$C_6H_5CH{=}N\text{-}t\text{-}Bu\text{-}3NO_2C_6H_4CH{=}N\text{-}t\text{-}Bu$	0, CH_2Cl_2	2.3 ± 0.2	0.976
$C_6H_5CH{=}N\text{-}t\text{-}Bu\text{-}4NO_2C_6H_4CH{=}N\text{-}t\text{-}Bu$	0, CH_2Cl_2	2.5 ± 0.2	0.945
$C_6H_5CCH_3{=}NCH_2CH(CH_3)_2\text{-}4BrC_6H_4CH{=}NCH_2CH(CH_3)_2$	0, CH_2Cl_2	1.7 ± 0.1	0.999
$C_6H_5CCH_3{=}NCH_2CH(CH_3)_2\text{-}4NO_2C_6H_4CH{=}NCH_2CH(CH_3)_2$	0, CH_2Cl_2	2.9 ± 0.1	0.992
N,N-Dimethylhydrazones			
$C_6H_5CCH_3{=}NN(CH_3)_2\text{-}4BrC_6H_4CCH_3{=}NN(CH_3)_2$	−78, CH_2Cl_2	1.06 ± 0.1	0.990
$4BrC_6H_4CCH_3{=}NN(CH_3)_2\text{-}3NO_2C_6H_4CCH_3{=}NN(CH_3)_2$	−78, CH_2Cl_2	1.06 ± 0.1	0.987
O-Methyl Oximes			
$C_6H_5CCH_3{=}NOCH_3\text{-}4BrC_6H_4CCH_3{=}NOCH_3$	−78, CH_2Cl_2–CH_3OH (2:1)	1.4 ± 0.1	0.999
$C_6H_5CCH_3{=}NOCH_3\text{-}4NO_2C_6H_4CCH_3{=}NOCH_3$	0, CH_2Cl_2–CH_3OH (2:1)	4.6 ± 0.5	0.930
Substitution on Nitrogen			
$C_6H_5CCH_3{=}NN(CH_3)_2\text{-}C_6H_5CCH_3{=}NCH_2CH(CH_3)_2$	−78, CH_2Cl_2	20.4 ± 0.4	0.902
$C_6H_5CCH_3{=}NN(CH_3)_2\text{-}c\text{-}C_6H_{10}{=}NOH$	−78, CH_2Cl_2	9.8 ± 0.6	0.800
$(CH_3)_2C{=}NN(CH_3)_2\text{-}(CH_3)_2C{=}NOCH_3$	−78, $CH_3COOCH(CH_3)_2$	14.2 ± 0.2	0.940

TABLE IV
COMPETITIVE OZONATIONS. STRAIN EFFECTS

	Temp (°C), solvent	Relative Rate	r
	−78, CH_2Cl_2	0.49 ± 0.08	0.990
	−78, CH_2Cl_2,	2.17 ± 0.07	0.996
	pyridine	2.06 ± 0.12	0.990
	−78, CH_2Cl_2	1.63 ± 0.18	0.978
	−78, CH_2Cl_2	9.3 ± 0.3	0.981
	−78, CH_2Cl_2	10.8 ± 0.3	0.985

Discussion

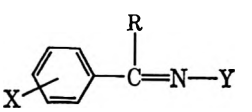
Several mechanisms for the ozonation of the carbon–nitrogen double bond have been considered in the literature. Riebel, *et al.*,[4a] suggested four principal ways in which initial ozone attack could occur: (1) an addition to the double bond as with carbon–carbon double bonds to give a four- or five-membered ring, (2) an electrophilic attack on the nitrogen atom of the double bond followed by loss of oxygen, (3) an electrophilic attack on the entire double bond followed by loss of oxygen, and (4) a nucleophilic attack on the carbon atom of the double bond followed by loss of oxygen. Wibaut and Boon[5] have proposed initial attack on nitrogen by the central atom of ozone followed by formation of a four-membered ring and breaking of the nitrogen–oxygen single bond. Present understanding of ozonation mechanisms rules out attack by the central oxygen atom and the existence of four-membered rings.

Another possibility, electrophilic attack on carbon for nitrones, was suggested by Riebel, *et al.*,[4a] and confirmed by us in an earlier study.[3]

The product analysis data from both Riebel, *et al.*,[4a] and from Moriconi and Spano's investigation of aza-aromatics and their N-oxides[9] were interpreted in favor of the fourth possibility listed above, nucleophilic attack of ozone on carbon.

At the beginning of this research we hoped to discover if all carbon–nitrogen double bonds react with ozone by a similar mechanism. Although the hypothesis of a single mechanism for the initial attack of ozone on the variety of systems investigated is an appealing one, we recognized that the possibility of secondary reactions, either of ozone with products or of highly unstable products with starting material, may complicate the over-all mechanism of any carbon–nitrogen double-bond ozonation. For example, earlier work has shown that nitrosobenzene, one of the major products of nitrone ozonation itself, reacts with ozone and that chlorinated solvents are attacked by an ozonation product of Schiff bases (a nitrene was suggested as the reactive ozonation product).[4a] In this work it has been shown that N,N-dimethylhydrazone ozonations are complex in that 2 mol of ozone are absorbed/mol of hydrazone. Attack on the solvent (methylene chloride) is evident for both oximes and dimethylhydrazones and oxime ozonations reveal particularly unusual secondary reactions.

Substituent effects were studied with several classes of compounds represented by formula I.



I

The choice of substituents X, R, and Y was based on the following factors. Since the electrophilic attack of ozone on the aromatic ring was a possible competing reaction,[16] the X substituent used was generally an electron-withdrawing group such as the nitro group or a bromine atom. The known reactivity of aldehydic hydrogen to ozone-catalyzed autoxidation[15,17] led to the use of acetophenone derivatives (R = CH_3) rather than benzaldehyde derivatives for most of the systems

(16) T. W. Nakagawa, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, **82**, 269 (1960).

(17) H. M. White and P. S. Bailey, *J. Org. Chem.*, **30**, 3037 (1965).

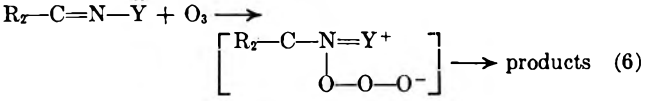
investigated. The Y group was varied from carbon to oxygen to nitrogen to test electron donation to the nitrogen as a factor on the rate of ozonation. Acetophenone oximes had unfavorable gas chromatographic behavior and the O-methyl oximes were used instead. As previous studies on the ozonation of 2,4-dinitrophenylhydrazones[6] indicated possible involvement of the nitrogen–hydrogen bond in the ozonation, the simplest dialkylhydrazones, the acetophenone dimethylhydrazones, were used.

Table III shows that changing the substituent (X) on the aromatic ring to a more electron-withdrawing group has a rate-retarding effect for Schiff bases and O-methyl oximes and essentially no effect on dimethylhydrazones. Rate differences for all compounds are relatively small as has been found previously for aldehyde, nitrone, and ether ozonations.[3,15] No relative rate sequence studied thus far has given any evidence for nucleophilic ozone attack (which has been suggested for some ozonation mechanisms on the basis of product studies).[18]

The data in Table III indicate that changing the substituent on the nitrogen end of the double bond can have a large effect on the relative rate of ozonation. The order found (dimethylhydrazones > O-methyl oximes ≫ Schiff bases) indicates electron donation from an atom α to the nitrogen to be significant.

This pattern (small rate effect on variation of X, large rate effect on variation of Y) is the same as that found by Hegarty and Scott in the bromination of substituted benzaldehyde arylhydrazones.[19] Specifically they found ρ −0.62 for substituents on the phenyl group on the benzylidene carbon *vs.* ρ −2.17 for substituents on the phenyl group on the hydrazone. In a similar study on the reaction of aryl diazonium ions on substituted benzaldehyde hydrazones the same authors found ρ −1.3 for substitution on the hydrazone ring and ρ −0.38 for substitution on the benzylidene ring.[19]

Our data indicate that initial attack of ozone on carbon–nitrogen double bonds is electrophilic and may be strongly assisted by an electron-donating group on nitrogen as is shown in eq 6.

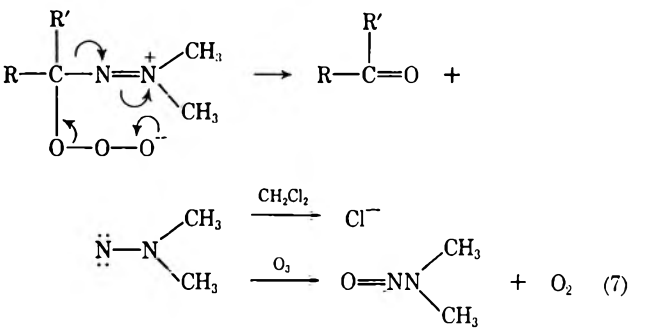


For Schiff bases where Y cannot donate a lone pair of electrons, the initial adduct might be a five-membered ring, similar to the initial ozonide formed in the ozonation of alkenes[20] in which attack is also electrophilic.

The use of cyclic systems as models in structure reactivity relationships has been widespread.[21] One generalization has been that a change in hybridization in a cyclic compound from sp^2 to sp^3 during a reaction will lead to a relative rate sequence of cyclic C_6 > cyclic C_5 rings. For example cyclohexanone reacts considerably faster than cyclopentanone with all addition reagents, supposedly because of the increased number of nonbonded interactions in the five-membered ring containing all sp^3-hybridized atoms. The only example of which we are aware that does not follow this pattern is the finding of Garbisch, *et al.*, that methylenecyclopentane reacts slightly faster than methylenecyclohexane with diimide.[21]

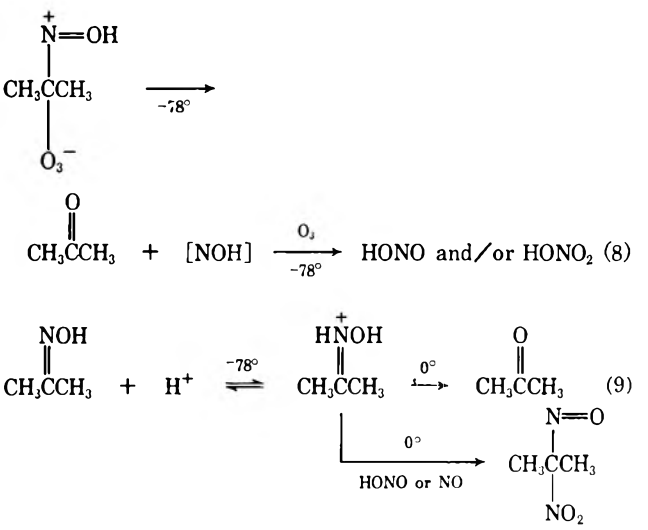
Table IV shows that for Schiff bases and oximes the six-membered rings are more reactive than the five-membered rings as expected. However, cyclopentanone dimethylhydrazone definitely reacts faster with ozone than does the cyclohexanone analog.

Although several explanations might be suggested to explain this finding and speculative correlations with the product data in Table I are possible, we prefer to hypothesize our current views on dimethylhydrazone ozonations with the aid of a single equation, eq 7,



Equation 7 is similar in some regard to earlier hypothesis for the ozonation of Schiff bases[4a] and accounts qualitatively for all of the data in the paper.

The complete mechanistic pathway for the ozonation of oximes is also of interest. After initial electrophilic attack on carbon (with assistance by electron donation from oxygen), the exact pathway is still speculative. However, careful inspection of the quantitative data on the acetone oxime ozonations of Table I and the nmr data in Table II leads to a minimal assumption of eq 8 and 9 to describe the reaction.



(18) Dr. Bryant W. Rossiter (Eastman Kodak Co., Rochester, N. Y.) has informed us (private communication) that substituted pyrazolone–azomethine dyes also undergo electrophilic attack by ozone at the carbon–nitrogen double bond of the azomethine linkage.

(19) A. F. Hegarty and F. L. Scott, *J. Chem. Soc., B*, 672 (1966); *J. Org. Chem.*, **32**, 1957 (1967).

(20) P. S. Bailey, J. A. Thompson, and B. A. Shoulders, *J. Amer. Chem. Soc.*, **88**, 4098 (1966); L. J. Durham and F. L. Greenwood, *J. Org. Chem.*, **33**, 1629 (1968).

(21) H. C. Brown, J. H. Brewster, and H. Shechter, [*J. Amer. Chem. Soc.*, **76**, 467 (1954)] originally discussed the usefulness of relative rate studies with ring systems for structure reactivity correlation. Semiquantitative calculations involving angle strain, torsional strain, and polar effects for the relative rates of diimide additions to cyclic and acyclic alkenes [E. V. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson, and C. M. Sprecher, *ibid.*, **87**, 2932 (1965)] are perhaps the most sophisticated made for this type of study.

The mechanism of the Schiff base ozonation remains as the most perplexing of all of the carbon–nitrogen double-bond systems. The original product analysis data could be rationalized reasonably well by any of six different types of initial attack as noted above.[4a,5] The major problem with both product analysis and competitive ozonation studies lies in the reactivity of Schiff bases. They react very slowly with ozone but may react quite rapidly with ozonation products. Thus, although amides and oxaziridines are very likely primary products, they account for only 39% of products even in favorable cases, and major cleavage products may well be derived from secondary processes. Relative rate studies are also inconclusive. Originally we attempted to carry out competitive rate studies on benzaldehyde Schiff bases at −78° in methylene chloride. Ozonation was extremely slow; less than half of either Schiff base reacted in a 12-hr period. Dimethylhydrazones and oximes, on the other hand, react quantitatively with ozone at −78°. Thus, although the results in Table III are "real" in that they show Schiff bases to react considerably more slowly with ozone than do dimethylhydrazones, we believe the true relative rate spread may be considerably larger.[22] In other words, the decreasing concentration of Schiff base measured in our experiments may be caused by reaction with products of either the competing system or of the Schiff base itself.[23]

It has been believed generally that carbon–nitrogen double bonds are considerably less reactive than carbon–carbon double bonds. The data from these experiments appear to suggest, however, that carbon–nitrogen double-bond reactivity is dependent on the group attached to nitrogen. In fact *trans*-stilbene and acetophenone dimethylhydrazone have essentially equivalent rates of ozonation (competitive rate 1.01 ± 0.05).

Registry No.—Methyl nitrite, 624-91-9; acetophenone oxime, 613-91-2.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(22) True rate comparisons could be made if experiments with stop-flow systems such as used by Williamson and Cvetanovic [D. G. Williamson and R. J. Cvetanovic, *ibid.*, **90**, 3668 (1968)] for alkene ozonations were carried out with dimethylhydrazones and oximes. The Schiff base ozonations are slow enough to be treated by conventional kinetic methods.

(23) A referee has suggested that nucleophilic attack on carbon to yield cleavage products may be competing with electrophilic bond attack on Schiff bases. The notion that ozone can act as a nucleophilic reagent is, of course, tantamount to calling it a reducing agent. Although such a situation is conceivable, we believe that rigorous proof would be necessary before postulating such a mechanism. As the proceeding paragraphs have indicated, such experimental justification is lacking.

New Carbonyl Compounds from Dehydrogenation of *p*-Cresol

C.-L. CHEN, W. J. CONNORS, AND W. M. SHINKER[1a]

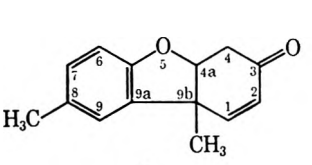
Forest Products Laboratory,[1b] Forest Service, U. S. Department of Agriculture

Received January 24, 1969

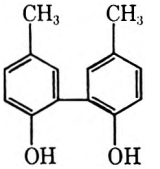
Chemical one-electron-type oxidation of *p*-cresol with ferric chloride yielded a previously unreported diphenyl ether **4** and three new ketonic trimers **5**, **6**, and **7**, the structures of which are related to Pummerer's ketone **1**, which was also formed in the reaction mixture as were the known compounds **2** and **3**. When *p*-cresol was oxidized enzymatically by peroxidase and peroxide, **5** was the only new unknown compound which could be isolated.

It is well established that the oxidation of *p*-cresol by one-electron-type chemical oxidants yields 4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (Pummerer's ketone) (**1**), 2,2′-dihydroxy-5,5′-dimethyldiphenyl (**2**), and 2,2′,2″-trihydroxy-5,5′,5″-trimethylterphenyl (**3**).[2–5] These products have also been isolated from the peroxidase-catalyzed oxidation of *p*-cresol with hydrogen peroxide.[6] A general review of the oxidative coupling of phenols, including *p*-cresol, and the significance of this type of reaction in biosynthesis have been published.[7]

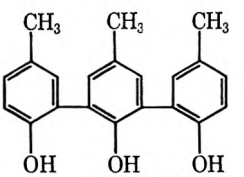
Hayes reported that in the oxidation of phenols by one-electron-type oxidants, more than 1 equiv of the oxidizing agent is consumed and that this must be the result of further oxidation of the low molecular weight products initially formed.[5] Mixtures of higher molecular weight substances were isolated in that work, but the constituents of the mixture were not identified. We have now oxidized *p*-cresol with 1.4 equiv of ferric chloride in aqueous solution, and have found that at least 10 compounds are present.



1



2



3

The reaction mixture was separated into alkali- and ether-soluble fractions, and further separation was

(1) (a) 1967 Summer Student Trainee, Forest Products Laboratory. (b) Maintained at Madison, Wis., in cooperation with the University of Wisconsin.

(2) R. Pummerer and F. Frankfurter, *Ber.*, **47**, 1472 (1913).

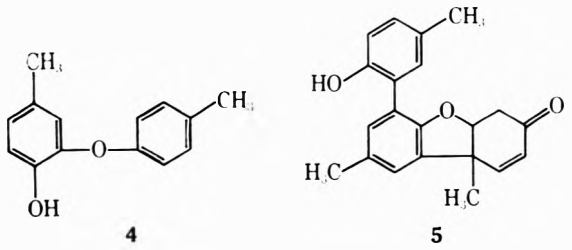
(3) R. Pummerer, H. Puttfarcken, and P. Schopflocher, *ibid.*, **58B**, 1808 (1925).

(4) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *Chem. Ind.* (London), 1039 (1955).

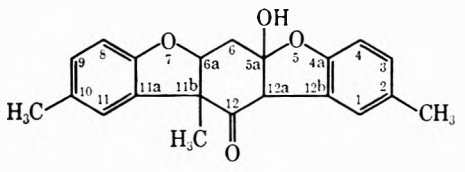
(5) C. G. Haynes, A. H. Turner, and W. A. Waters, *J. Chem. Soc.*, 2823 (1956).

(6) W. W. Westerfield and C. Lowe, *J. Biol. Chem.*, **145**, 463 (1942).

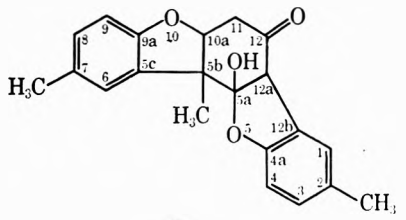
(7) A. I. Scott, *Quart. Rev.* (London), XIX, 1 (1965).



4 5



6

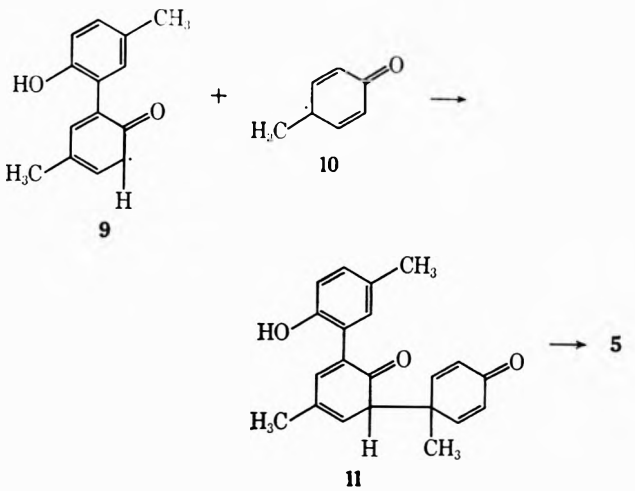


7

carried out by column chromatography on silicic acid and preparative tlc.

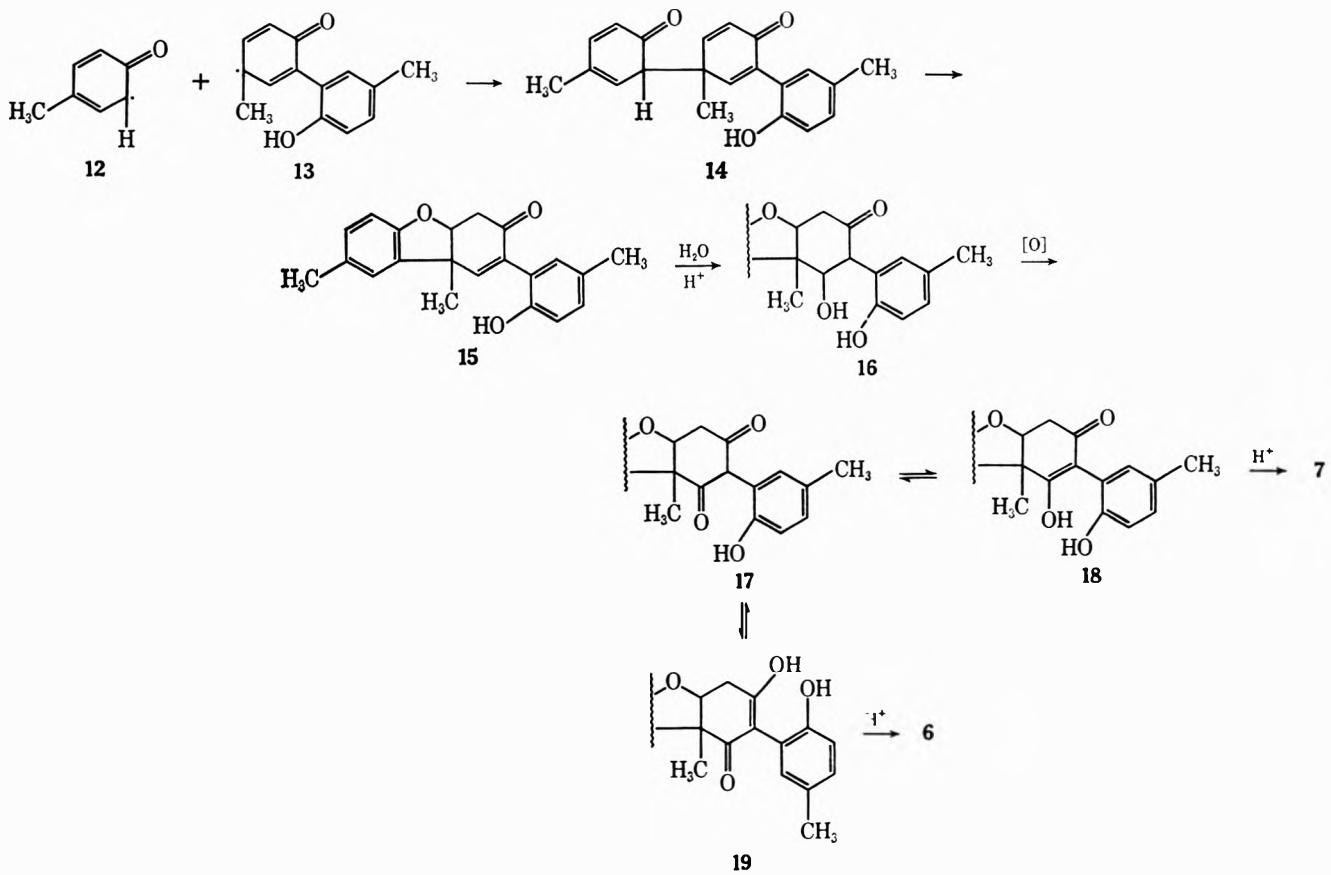
The alkali-soluble fraction contained **3** as the major product, a lesser amount of **2**, and a trace of 2-hydroxy-4′,5-dimethyl diphenyl ether (**4**), an *o-diphenyl* ether not previously isolated. The ether-soluble fraction contained **1**, **4**, and trimeric ketones, 6-(2′-hydroxy-5′-methylphenyl)-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (**5**), 5a-hydroxy-5a,6a,11b,12a-tetrahydro-2,10,11b-trimethyl-12(6H)-benzo[1,2-*b*:5,4-*b*′]bisbenzofuranone (**6**), and 5a-hydroxy-5a,5b,10a,12a-tetrahydro-2,5b,7-trimethyl-12-(11H)-benzo[1,2-*b*:3,4-*b*′]bisbenzofuranone (**7**). A tetrameric ketone, **8**, $C_{28}H_{26}O_5$, was also isolated from the ether fraction, but the exact structure of this compound could not be determined. It is interesting that in the enzymatic dehydrogenation of *p*-cresol with peroxidase and peroxide catalyst, compounds **1**, **2**, **3**, **4**, and **5** were shown to be present, but **6**, **7**, and **8** could not be detected.

The formation of **5** could take place through the coupling of an *ortho* radical, **9**, from the dehydrogenation of **2** with a *para* radical from *p*-cresol (**10**) to give the intermediate **11**, which could then cyclize to **5**.



9 10 11

The formation of **6** and **7** in the ferric chloride oxidation could take place through the coupling of an *ortho* radical, **12**, formed from the oxidation of *p*-cresol with a *para* radical, **13**, formed from the oxidation of **2** to give



12 13 14 15 16 17 18 19

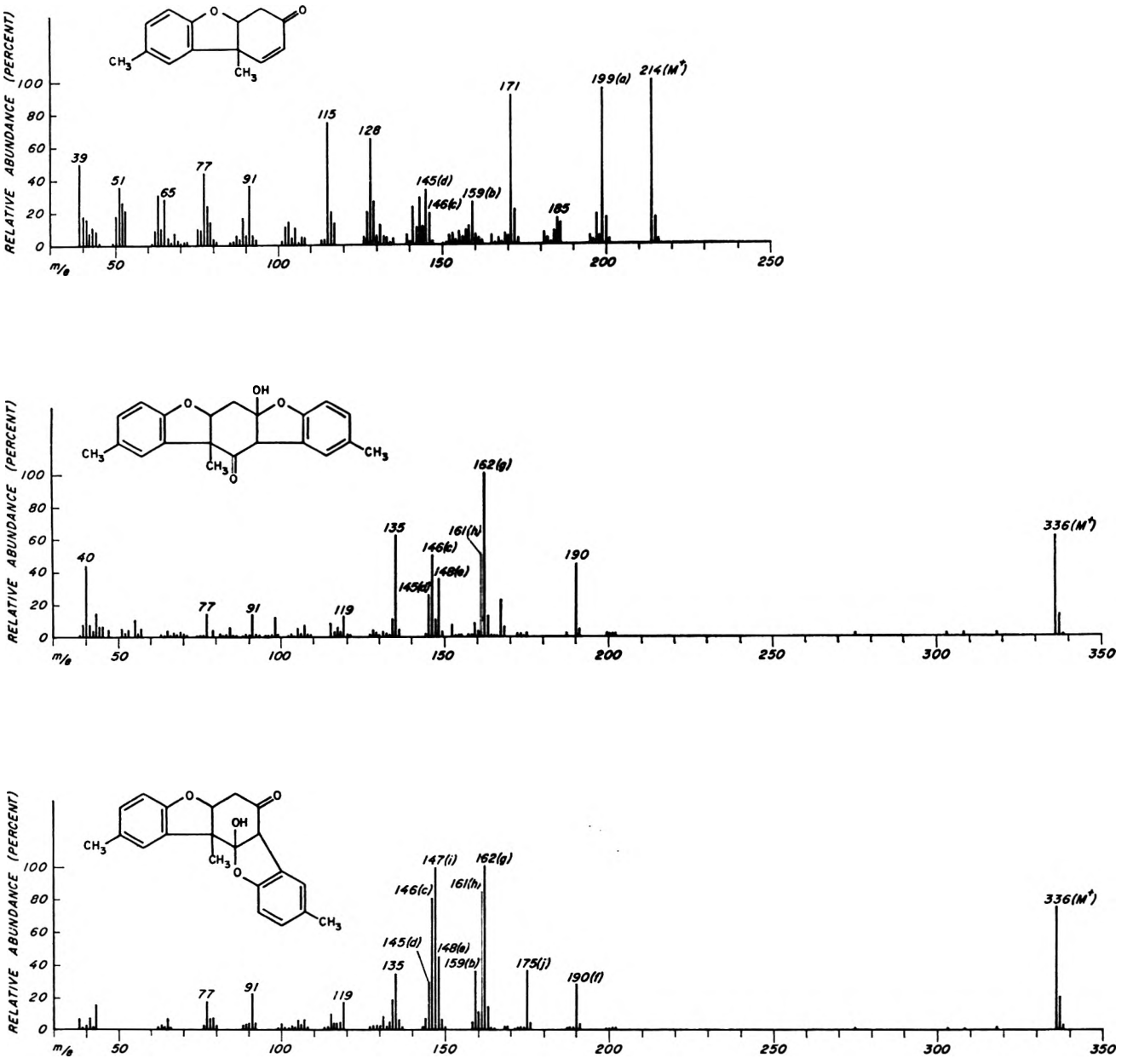


Figure 1.—Mass spectra of compounds **1**, **6**, and **7**.

the intermediate trimer **14**, which could then cyclize to **15**. From **15** to **6** and **7**, the sequences would then be the addition of water and oxidation of the resulting β-hydroxyketo compound **16** to the β-diketo compound **17** which has enol tautomers **18** and **19**. These, under the influence of acid, could cyclize to form hemiacetals **6** and **7**.

The mass spectrum of **1** (Figure 1, Scheme I) showed prominent peaks corresponding to the molecular ion M $-$ CH_3 and M $-$ (CH_3 + CO) ions. Loss of a methyl radical from the molecular ion caused by α fission of the substituted coumaran at C-9b afforded the stable ion at *m/e* 199 (a) which gave the ion at *m/e* 171 through further loss of carbon monoxide. Breakdown of the molecular ion at ring junctures C-4a and C-9b gave the ion at *m/e* 146 (c) which loses a hydrogen atom to produce the stable ion at *m/e* 145 (d).[8] Alternative breakdown of the molecular ion at C-4 and C-9b with hydrogen transfer and elimination of C_3H_3O could produce the ion at *m/e* 159 (b). This required α fission of the substituted coumaran at C-9b and a subsequent McLafferty rearrangement involving the C-4a hydrogen. The vinylic cleavage was presumably induced by the allylic stabilization of the coumaran ring; this may not be intrinsically unfavorable. 4-Alkyl- or aryl-Δ^2-cyclohexanone derivatives exhibit a characteristic M $-$ 42 ion peak on electron impact.[9] Absence of this ion peak in the mass spectrum of Pummerer's ketone, and the presence of the ions b and c, should be regarded as caused by the effect of the coumaran moiety fused to the cyclohexanone.

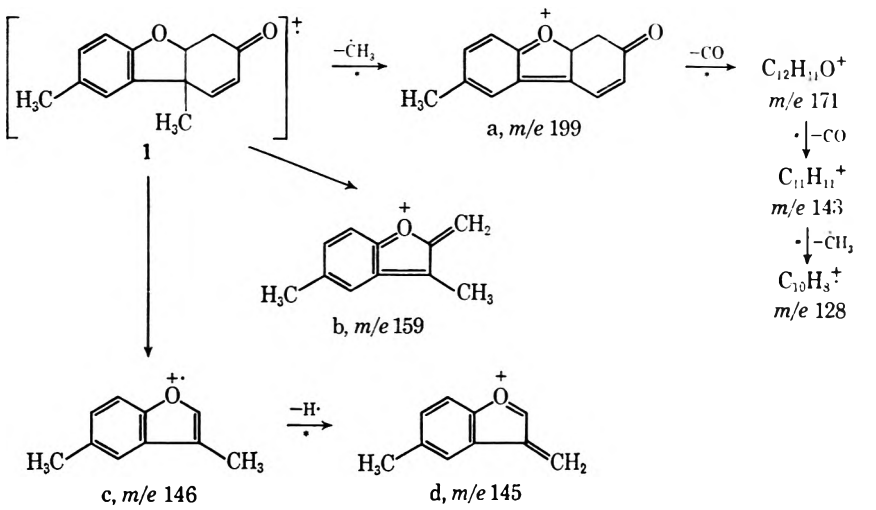
The nuclear magnetic resonance spectrum of **5** was similar to **1**,[10] and consistent with the structure presented for this compound. The C-4 geminal protons and the C-4a proton constitute an ABX spin pattern with coupling constants J_{AB} = 18.0 Hz, J_{AX} = 3.0 Hz, and J_{BX} = 4.0 Hz. The X component is further

(8) B. Willhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron*, **20**, 1185 (1964).

(9) A. L. Burlingame, C. Fenselau, W. J. Richter, W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Amer. Chem. Soc.*, **89**, 3346 (1967).

(10) J. Shoji, *Chem. Pharm. Bull.* (Tokyo), **10**, 483 (1962).

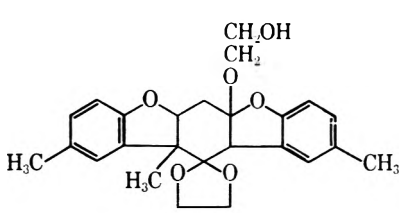
SCHEME I[a]



[a] Transitions substantiated by an appropriate metastable peak are indicated by an asterisk.

split by the C-1 olefinic proton (J = 1.8 Hz) because of long-range four-bond σ–π spin–spin interactions which had been reported earlier for **1**.[11] The mass spectrum of **5** showed a strong molecular ion peak and less abundant ion peaks corresponding to M − CH_3 and M − (CH_3 + CO), as in **1**.

Trimeric ketone **6** had a molecular formula $C_{21}H_{20}O_4$ which contained one oxygen atom more than the expected trimeric dehydrogenative condensation product of *p*-cresol. The infrared spectrum of the compound showed the presence of a hydroxyl group (3470 cm^{-1}) and a six-membered cyclic ketone (1721 cm^{-1}). In the nmr spectrum in deuteriochloroform, the alicyclic protons were not well resolved. However, in pyridine, **6** did give a first-order spectrum compatible with the structure presented. A two-proton doublet (J = 3.2 Hz) at δ 3.25 (C-6) and a one-proton triplet (J = 3.2 Hz) at δ 4.78 (C-6a) constituted a characteristic A_2X system.[10] The one-proton singlet at δ 4.98 (C-12a) was caused by the β-proton of a coumaran adjacent to a carbonyl group.[12] In deuteriochloroform the signals for C-6a and C-12a protons merged at δ 4.65, whereas signals for C-6 geminal protons appeared as a multiplet at δ 3.25, although no distinct geminal coupling could be observed. This could be attributed to absence of π-bond contribution and to the electronegative groups substituted on the carbon atom adjacent to the C-6 methylene group.[13] When **6** was refluxed with ethylene glycol under the catalytic influence of *p*-toluenesulfonic acid, it reacted with 2 mol of ethylene glycol to afford β-hydroxyethyl ether ethylene ketal **20**. This furnished a proof of the hemiacetal structure of **6**.



20

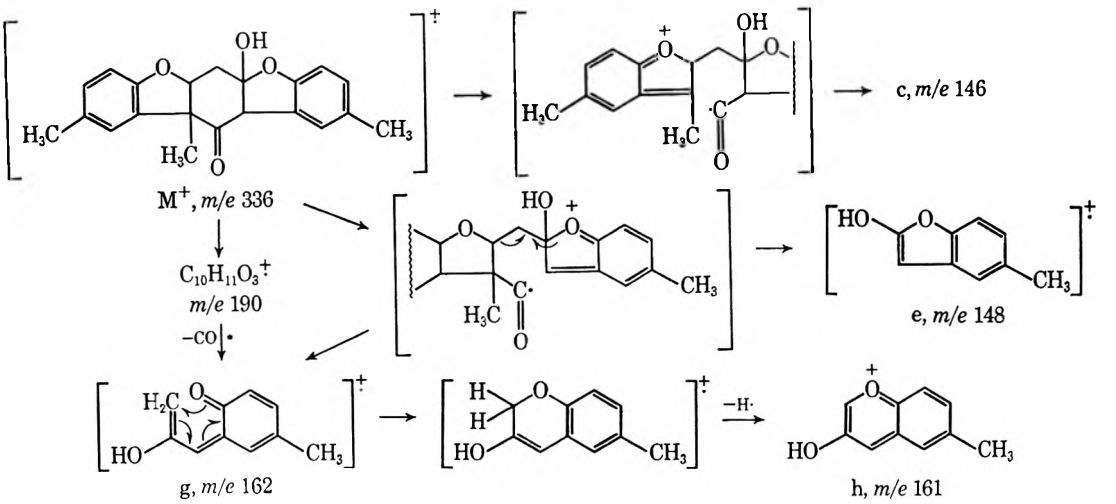
A further support of the structure of **6** was obtained by the mass spectrum (Figure 1, Scheme II). Breakdown of the molecular ion at ring juncture either at C-11b or C-12a caused by α fission of coumaran and subsequent allylic cleavage produced the ions at m/e 146 (c) and 148 (e), which retained the skeletons of both coumaran moieties. Alternative breakdown of the molecular ion at C-12a and C-6a with ether cleavage afforded the ion at m/e 162 (g) which cyclized and aromatized by loss of a hydrogen atom to give the ion at m/e 161 (h). The latter reaction bears close analogy to the cyclization reaction in 2-(β-butenyl)benzoquinone derivatives[14] and the cyclization of benzalacetone derivatives.[15] Expulsion of a neutral fragment corresponding to c from the molecular ion gave the ion at m/e 190. Loss of carbon monoxide from this ion at m/e 190 also produced the ion g, indicated by the metastable peak at m/e 138.2.

Trimeric ketone **7** also had molecular formula $C_{21}H_{20}O_4$, and gave a uv spectrum which resembled that of **6**. This, with an infrared spectrum which showed a hydroxyl band at 3440 cm^{-1} and a six-membered cyclic ketone band at 1735 cm^{-1}, revealed that the compound was an isomer of **6**. The higher carbonyl frequency was indicative of ring strain caused by fusion of additional rings to cyclohexanone.[16] In the nmr spectrum, the alicyclic protons showed a different splitting pattern from that of **6**. Two one-proton quartets (C-11 geminal protons) with resonance centers at δ 2.50 (J = 19.4 and 3.8 Hz) and at δ 2.95 (J = 19.4 and 2.6 Hz) and a one-proton multiplet (J = 3.8 and 2.6 Hz) at δ 4.46 (C-10a) constituted a characteristic ABX system. A one-proton singlet at δ 4.72 was caused by a C-12a proton. The large geminal coupling constant indicated a large π-bond contribution from the carbonyl group adjacent to the methylene group. This also indicated a ring strain of the cyclohexanone ring caused by two adjacent coumaran rings.

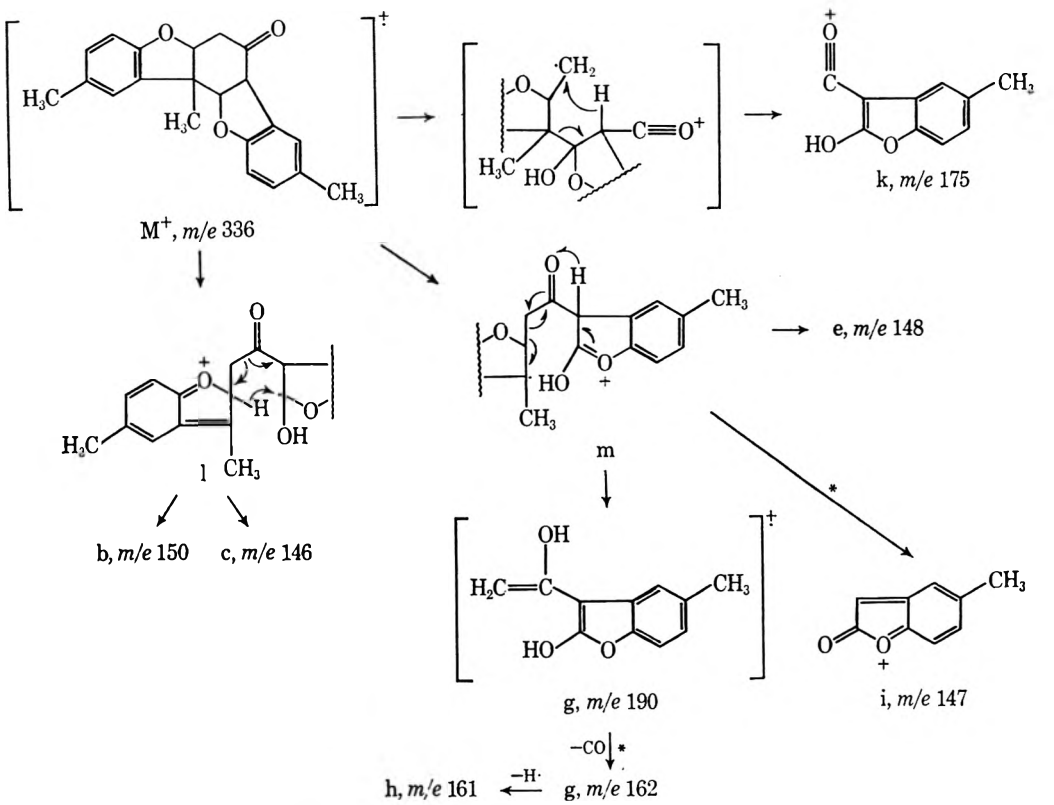
When the compound was refluxed with ethylene glycol under the catalytic influence of *p*-toluenesulfonic acid, it reacted with 1 mol of ethylene glycol with elim-

(11) G. W. Kirby and H. P. Tiwari, *J. Chem. Soc.*, 4655 (1964).
(12) A. Stoessl, *Can. J. Chem.*, **45**, 1745 (1967).
(13) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963).
(14) S. J. Di Mari, J. H. Supple, and H. Rapoport, *ibid.*, **88**, 1226 (1966).
(15) J. Ronayne, D. H. Williams, and J. H. Borwie, *ibid.*, **88**, 4980 (1966).
(16) C. F. H. Allen, T. Davis, D. W. Stewart, and J. A. VanAllan, *J. Org. Chem.*, **20**, 306 (1955).

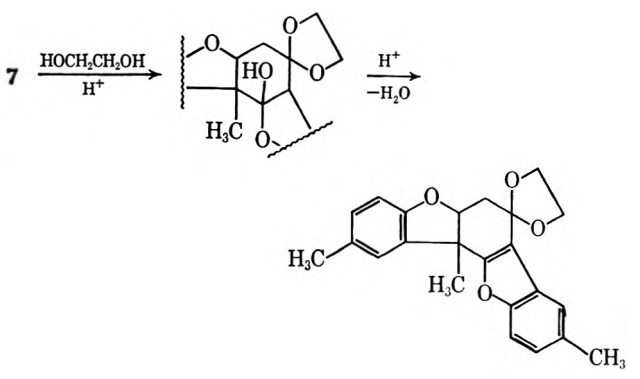
SCHEME II



SCHEME III



ination of 2 mol of water to afford the compound **21**. Elimination of water could result from the formation of the ethylene ketal followed by dehydration involving the hemiacetal hydroxy as such, or by loss of ethylene glycol from the β-hydroxyethyl ether of the ethylene ketal of **7**, which could form in this reaction medium.



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The mass spectrum of **7** (Figure 1, Scheme III) was considerably different from that of **6**. In addition to the important ion peaks which appeared in **6**, **7** contained a very strong peak at *m/e* 147 and two moderate ion peaks at *m/e* 175 and 159. A breakdown of the molecular ion at ring juncture C-5a caused by α fission of the coumaran ring could produce two intermediates, l and m. Elimination of a neutral fragment corresponding to c from m gave the ion at *m/e* 190, which might have structure f. Loss of carbon monoxide from the f ion produced the ion at *m/e* 162 (g).[17] An alternative allylic cleavage afforded the ion at *m/e* 148 (e). The ion at *m/e* 147 (i) could arise

(17) R. Grigg, H. J. Jakobsen, S.-O. Lawesson, M. V. Sargent, G. Schroll, and D. H. Williams, *J. Chem. Soc., B*, 331 (1966).

from the ion e by the loss of a hydrogen atom. However the metastable peak at *m/e* 64.4 indicated that the ion at *m/e* 147 was produced from the molecular ion. Hydrogen transfer caused by allylic stabilization probably took place during the allylic cleavage. An allylic cleavage of the intermediate l produced the ion at *m/e* 146 (c), whereas a McLafferty rearrangement involving C-10a gave the ion at *m/e* 159 (b). The formation of the ion at *m/e* 175 (k) was caused by α cleavage of carbonyl and subsequent McLafferty rearrangement.

Experimental Section

Nmr spectra were determined on a Varian HA-100 instrument. Chemical shifts are reported in δ values relative to tetramethylsilane standard. The mass spectrum of 1 was determined on an AEI MS 12 mass spectrometer, others on an Atlas CH-4.

Dehydrogenation of *p*-Cresol with Ferric Chloride.—*p*-Cresol (10.5 g) and ferric chloride hexahydrate (32.5 g) were stirred together in water (1.5 l.) for 72 hr at room temperature; the solution changed color from orange to green. The reaction mixture was made alkaline and extracted with ether. The ether solution was then examined by tlc and showed 10 substances present, with 4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (1) the major product. A total of 1.16 g of alkaline-insoluble material was obtained.

Dehydrogenation of *p*-Cresol with Peroxidase Peroxide.—A mixture of 10.8 g (0.1 equiv) of *p*-cresol and 50 mg of horseradish peroxidase was dissolved in 100 ml of 50% aqueous ethanol. While the mixture was stirred for 30 min, 17 ml of 1% H_2O_2 (0.1 equiv) was added, and then the mixture was stirred for an additional 60 min. The mixture was allowed to stand overnight and separated into neutral and alkaline-soluble fractions as in the dehydrogenation of *p*-cresol with ferric chloride.

5a-Hydroxy-5a,6a,11b,12a-tetrahydro-2,10,11b-trimethyl-12-(6H)-benzo[1,2-*b*:5,4-*b'*]bisbenzofuranone (6).—The reaction mixture (5.8 g) from the ferric chloride dehydrogenation was dissolved in 30 ml of cold acetone. The insoluble residue was collected, washed with cold acetone (three 5-ml portions), and recrystallized from $CHCl_3$; white plates (121 mg) were obtained, mp 252–253°; uv λ_{max} (95% EtOH) 288 (ϵ 5.34 × 10^3) and 294 mμ (ϵ 5.11 × 10^3); λ_{max} (95% EtOH + 1 drop/ml of 1 *N* EtONa) 300 mμ (ϵ 7.11 × 10^3); ir (KBr) 3470 (OH), 3025 (ArH), 2960, 2920, 2860 (CH_3), 1720 (C=O), 1612, 1490 (ArH) cm^{-1}; nmr ($CDCl_3$) δ 1.44 (s, 3, Anu-CH_3), 2.21 (s, 3, ArCH_3), 2.28 (s, 3, ArCH_3), 3.25 (m, 2, OCHCH_2COO), 4.42 (s, 1, OH, eliminated by exchange with D_2O), 4.64 (m, 1, OCHCH_2), 4.65 (s, 1, OCCHAr), 6.44 (d, 1, *J* = 8.0 Hz, ArH), 6.54 (d, 1, *J* = 8.2 Hz, ArH), 6.86 (m, 2, *J* = 2.2, 8.2 Hz, ArH), 6.97 (s, 1, ArH), 7.39 (d, 1, *J* = 2.2 Hz, ArH); nmr (pyridine) δ 1.35 (s, 3, Anu-CH_3), 1.98 (s, 3, ArCH_3), 2.10 (s, 3, ArCH_3), 3.25 (d, 2, *J* = 3.2 Hz, OCHCH_2COO), 4.62 (s, 1, OH, eliminated by exchange with D_2O), 4.78 (t, 1, *J* = 3.2 Hz, OCHCH_2), 4.98 (s, 1, OCCHAr), no aromatic protons could be analyzed owing to pyridine.

Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 74.93; H, 6.12.

5a-(β-Hydroxyethoxy)-5a,6a,11b,12a-tetrahydro-2,10,11b-trimethyl-12(6H)-benzo[1,2-*b*:5,4-*b'*]bisbenzofuranone Ethylene Ketal (20).—A mixture of 5a-hydroxy-5a,6a,11b,12a-tetrahydro-2,10,11b-trimethyl-12(6H)-benzo[1,2-*b*:5,4-*b'*]bisbenzofuranone (6) (40 mg), *p*-toluenesulfonic acid (20 mg), toluene (15 ml), and ethylene glycol (4 ml) was heated at reflux temperature with continuous slow removal of the solvent for 6 hr. After cooling, a few drops of pyridine were added to the reaction mixture to neutralize the acid. The organic phase was extracted with ether, washed with distilled water, dried, and evaporated *in vacuo*. The residue (recrystallized from methanol–acetone) was white rhombic crystals (18 mg), mp 208–210°; uv λ_{max} (95% EtOH) 282 and 289 mμ; ir (KBr) 3520 (OH), 2942 and 2892 (CH_3 and $-CH_2-$), 1620, 1500 (ArH); nmr ($CDCl_3$) δ 1.54 (s, 3, Anu-CH_3), 2.25 (s, 3, ArCH_3), and 2.30 (s, 3, ArCH_3).

Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.78; H, 6.60; M^+ *m/e* 424.18859. Found: C, 70.59; H, 6.49; M^+ *m/e* 424 (low resolution).

4a,9b-Dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (Pummerer's Ketone) (1).—After 5a-hydroxy-5a,6a,11b,12a-tetrahydro-2,10,11b-trimethyl-12(6H)-benzo[1,2-*b*:5,4-*b'*]bisbenzofuranone (6) was crystallized from the neutral fraction, Pummerer's ketone (1) was isolated by column chromatography on silicic acid with chloroform–cyclohexane (4:1) as solvent and purified by preparative tlc on silica gel: mp 124–125° (lit.[2] mp 124°).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.53; H, 6.58. Found: C, 78.48; H, 6.59.

2-Hydroxy-4',5-dimethyl Diphenyl Ether (4).—This compound was isolated as an oil in the same manner as Pummerer's ketone (1). It had uv λ_{max} (95% EtOH) 278 and 283.5 mμ; λ_{max} (95% EtOH + 1 drop/ml of 1 *N* EtONa) 287.5 and 302 mμ; ir (film) 3525, 3450 (OH), 3035 (ArH), 2920, 2860 (CH_3), 1600, 1510 (ArH), 1278 (ArO), 1225 cm^{-1} (phenolic CO); nmr ($CDCl_3$) δ 2.14 (s, 3, ArCH_3), 2.26 (s, 3, ArCH_3), 5.50 (s, 1, OH, eliminated by D_2O), 6.6–7.3 (seven aromatic protons); mass spectrum (70 eV) *m/e* (re. intensity) 215 (12.7), 214 (100), 198 (23), 197 (5), 183 (6), 123 (5), 107 (12.5), 94 (15), 92 (24), 91 (23), 78 (12), 77 (12), 66 (8), 65 (13), 52 (5), 51 (9), 41 (5), 39 (12).

6-(2'-Hydroxy-5'-methylphenyl)-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (5).—The compound was isolated and purified in the same manner as Pummerer's ketone (1); it formed white needles (34 mg), mp 135–136°; uv λ_{max} (95% EtOH) 299 mμ (ϵ 6.49 × 10^3); λ_{max} (95% EtOH + 1 drop/ml of 1 *N* EtONa) 321 mμ (ϵ 7.86 × 10^3); ir (KBr) 3395 (OH), 3015 (ArH), 2970, 2925, 2860 (CH_3), 1675 (C=C—C=O), 1620, 1500 (ArH), 1260 (OH), 802 (*cis*-CH=CH—) cm^{-1}; nmr ($CDCl_3$) δ 1.60 (s, 3, Anu-CH_3), 2.30 (s, 3, ArCH_3), 2.37 (s, 3, ArCH_3), 2.76 (m, 1, *J* = 4.0, 18.0 Hz, $CHCH_AH_BCO$), 3.08 (m, 1, *J* = 3.0, 18.0 Hz, $CHCH_AH_BCO$), 4.82 (m, 1, *J* = 1.8, 3.0, 4.0 Hz, $ArOCHCH_AH_B$), 5.95 (d, 1, *J* = 10.4 Hz, CH=CHCO), 6.04 (s, 1, OH, eliminated by exchange with D_2O), 6.50 (m, 1, *J* = 1.8, 10.4 Hz, CH=CHCO), 6.90 (d, 1, *J* = 8.8 Hz, ArH), 7.07 (m, 4, ArH); mass spectrum *m/e* (rel intensity) 321 (25.5), 320 (100), 305 (17), 303 (5), 302 (5.5), 287 (8.5), 277 (10.5), 212 (5.5), 211 (6.5), 166 (5), 115 (5), 77 (5), 43 (6).

Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.75; H, 6.25. Found: C, 78.70; H, 6.30.

5a-Hydroxy-5a,5b,10a,12a-tetrahydro-2,5b,7-trimethyl-12-(11H)-benzo[1,2-*b*:3,4-*b'*]bisbenzofuranone (7).—This compound was isolated and purified in the same manner as Pummerer's ketone (1). The compound was recrystallized from methanol, yielding white needles (106 mg), mp 208–209°; uv λ_{max} (95% EtOH) 287.4 (ϵ 5.98 × 10^3) and 293.4 mμ (ϵ 5.58 × 10^3); λ_{max} (95% EtOH + 1 drop/ml of 1 *N* EtONa) 242 (ϵ 1.42 × 10^4) and 304 mμ (ϵ 6.87 × 10^3); ir (KBr) 3440 (OH), 3025 (ArH), 2970, 2925, 2865 (CH_3), 1735 (C=O), 1615, 1494 (ArH) cm^{-1}; nmr ($CDCl_3$) δ 1.49 (s, 3, Anu-CH_3), 2.36 (s, 6, ArCH_3), 2.50 (m, 1, *J* = 3.8, 19.4 Hz, $OCHCH_AH_BCO$), 2.95 (m, 1, *J* = 2.6, 19.4 Hz, $OCHCH_AH_BCO$), 4.28 (s, 1, OH, eliminated by exchange with D_2O), 4.45 (m, 1, *J* = 2.6, 3.8 Hz, OCHCH_2), 4.72 (s, 1, OCCHAr), 6.71 (d, 1, *J* = 7.8 Hz, ArH), 6.82 (d, 1, *J* = 8.0 Hz, ArH), 6.92 (m, 1, ArH), 6.99 (m, 1, ArH), 7.08 (m, 1, *J* = 2.2, 8.0 Hz, ArH), 7.62 (d, 1, *J* = 2.2 Hz).

Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99. Found: C, 75.19; H, 5.95.

5b,10a-Dihydro-2,5b,7-trimethyl-12(11H)-benzo[1,2-*b*:3,4-*b'*]-bisbenzofuranone Ethylene Ketal (21).—5a-Hydroxy-5a,5b,10a,-12a-tetrahydro-2,5b,7-trimethyl-12(11H)-benzo[1,2-*b*:3,4-*b'*]bisbenzofuranone (7) (40 mg) was treated according to the procedure for the preparation of 5a-(β-hydroxyethoxy)-5a,6a,11b,12a-tetrahydro-2,10,11b-trimethyl-12(6H)-benzo[1,2-*b*:5,4-*b'*]bisbenzofuranone ethylene ketal (20). This yielded white needles (16 mg), mp 178–180°; uv λ_{max} (95% EtOH) 287 and 294 mμ; ir (KBr) 3010 (ArH), 2970, 2925, 2880 (CH_2 and CH_3), 1617, 1495 cm^{-1} (ArH); nmr ($CDCl_3$) δ 1.16 (s, 3, Anu-CH_3) and 2.28 (s, 6, ArCH_3).

Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.24; H, 6.08; M^+ *m/e* 362.15181. Found: C, 76.19; H, 6.15; M^+ *m/e* 362 (low resolution).

Registry No.—*p*-Cresol, 106-44-5; **1**, 546-24-7; **4**, 10568-14-6; **5**, 21272-73-1; **6**, 21272-74-2; **7**, 21272-75-3; **20**, 21272-76-4; **21**, 21272-77-5.

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The Reaction of Nitriles with Phosgene. II.[1] The Preparation of 6-Chloro-2,5-Disubstituted 4(3H)-Pyrimidones

SHOZO YANAGIDA, MASATAKA OHOKA, MITSUO OKAHARA, AND SABURO KOMORI

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita City, Osaka, Japan

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The reaction of aliphatic nitriles (1) with phosgene in the presence of hydrogen chloride at 60–65° in a sealed glass tube gives good yields of 6-chloro-2,5-disubstituted 4(3H)-pyrimidone hydrochlorides (2) and small amounts of 4,6-dichloro-2,5-disubstituted pyrimidines (4). These pyrimidone hydrochlorides (2) are easily converted into free bases (3) by treatment with water or by standing under reduced pressure, and are regenerated with dry hydrogen chloride. However, attempts to obtain the corresponding pyrimidones from 3-substituted propionitriles and most substituted acetonitriles were unsuccessful. The mechanism of this reaction is discussed.

Since the first aminopyrimidines were prepared from nitriles and alkali, such as sodium methoxide,[2] numerous methods for elaborating the pyrimidine nucleus have been extensively investigated.[3] The most important and practical synthetic route is ring closure between amidines and 1,3-difunctional compounds, such as β-diketones, β-keto esters, and malonates.

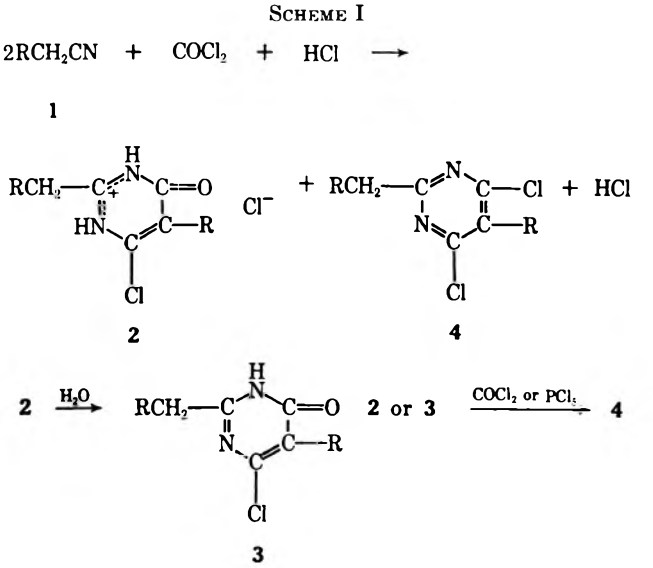
Some nitriles are reported to react with hydrogen halides to give 1,3,5-triazine,[4] substituted 3H-azepines,[5,6] pyridine derivatives,[7] and pyrroline derivatives,[8] but nitriles have been considered to be unreactive with phosgene.[9] In our preceding paper,[1] however, we reported that acetonitrile or propionitrile reacts with phosgene in the presence of hydrogen chloride to give 6-chloro-2-methyl-4(3H)-pyrimidone and 6-chloro-2-ethyl-5-methyl-4(3H)-pyrimidone, respectively.

In this paper, we report more detailed studies on this reaction.

We have studied the effect of varying the ratios of HCl to phosgene from 0.07 to 1.8 on the yield of 6-chloro-2-methyl-4(3H)-pyrimidone hydrochloride (**2a**) (Scheme I). Optimum yields were obtained with a ratio of 1:1 or greater ratio.

To determine the scope of this reaction, several other aliphatic nitriles were examined (Scheme I, Table I). The hydrochlorides (2) obtained by filtration from the reaction mixtures and washing with ether were found to be fairly pure. However, further purification of these products was difficult, since they readily change into pyrimidones (3) during recrystallization. They were therefore converted to the pyrimidones (3) by treating them with water, and most of the aliphatic nitriles (**1a–f**) gave 6-chloro-2,5-dialkyl-4(3H)-pyrimidones (3) in good yields regardless of the length of the alkyl chain. The filtrates from **2b** and **2d** were subjected to chromatographic separation, and some oily products were isolated in small yield. These were identified as 4,6-dichloro-2-ethyl-5-methylpyrimidine (**4b**) and 4,6-dichloro-2-butyl-5-propylpyrimidine (**4d**), respectively by comparing their ir spectra with those of the authentic samples prepared by the reaction of **3b** and **3d** with phosphorus pentachloride. It was ascertained that the reaction of 2 or 3 with phosgene in a sealed glass tube gave the corresponding dichloropyrimidines (**4**). It is thus clear that the formation of the dichloropyrimidines (**4**) is due to the further reaction of the initially formed pyrimidones with phosgene (Scheme I).

SCHEME I



a, R = H; **b**, R = CH_3; **c**, R = CH_3CH_2; **d**, R = $CH_3(CH_2)_2$; **e**, R = $CH_3(CH_2)_3$; **f**, R = $CH_3(CH_2)_9$; **g**, R = $(CH_3)_2CH$; **h**, R = Cl; **i**, R = $Cl(CH_2)_2$; **j**, R = $CH_3CH_2O(CH_2)_2$

Pure pyrimidone hydrochlorides (3) could be obtained by treating pyrimidones (2) with dry hydrogen chloride in ether. Analytical details can be reported as being correct for chlorine. The ir absorption bands of all of the hydrochlorides lie in the regions 1700–1730 and 1610–1640 cm^{-1}. Their melting points, however, are the same as those of the corresponding pyrimidones (3) (Table I) except for **2a**. Loss of hydrogen chloride must occur before melting. In addition, it was found that the pyrimidone hydrochlorides (2), when allowed to stand under reduced pressure even at room temperature, lose hydrogen chloride and change into the pyrimidones (3). The pK_a value of **2a** was determined to be 7.91 by a spectroscopic method.[10]

Infrared spectra of the hydrochlorides support the oxo form; the absorptions observed at 1690 and 1600 cm^{-1} in **3a** may be assigned to carbonyl and ring vibrations due mainly to the C=N bond, respectively.[11] If the hydroxy form were preferable, one of these bands should shift to lower frequency. However, **2a** shows these bands with a shift to higher frequency by about 40

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Table I
Pyrimidones Prepared from Nitriles, Phosgene, and Hydrogen Chloride

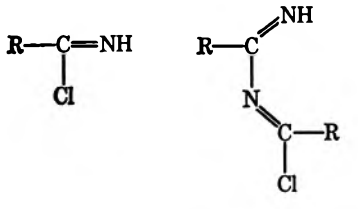
Pyrimidone	Yield, %[a]	Recrystn solvent[b] (v/v)	Mp, °C	Ir,[c] cm^{-1}	Uv,[d] λ_{max}, mμ ($\epsilon \times 10^{-3}$)	Nmr,[e] τ	Mol wt (calcd)	Elemental analyses—Caled, %	Found, %
3a	59[f]	Ac–D (3:1)	235.5–236.5[g]	1685 1600	225 (6.08) 279 (4.33)	(s) 7.60 (3 H), 3.48 (1 H)[h]	143 (144.6)	C, 41.54; H, 3.49; N, 19.38; Cl, 24.52	C, 41.33; H, 3.22; N, 19.54; Cl, 24.3
3b	39[i]	Ac–D (1:1)	203.0–204.5	1670 1600	230 (6.06) 279 (6.83)	(t) 8.65 (3 H), (s) 7.85 (3 H) (q) 7.26 (2 H)	172 (172.6)	C, 48.71; H, 5.26; N, 16.23; Cl, 20.54	C, 48.44; H, 5.22; N, 16.31; Cl, 20.6
3c	56[i]	P	156.0–157.5	1660 1595	232 (5.74) 282 (6.84)	(t) 8.98 (3 H), 8.86 (3 H), 7.29 (2 H) (m) 8.17 (2 H), (q) 7.36 (2 H)	207 (200.7)	C, 53.87; H, 6.53; N, 13.96; H, 17.67	C, 53.99; H, 6.45; N, 13.73; Cl, 17.5
3d[j]	34[i]	Ac–D (1:1)	136.0–137.0	1655 1590	231 (6.67) 281 (7.18)	(t) 9.08 (6 H, 7.40 (2 H), 7.29 (2 H) (c) *ca.* 8.38 (6 H)	220 (228.7)	C, 57.76; H, 7.49; N, 12.25; Cl, 15.50	C, 57.32; H, 7.71; N, 12.47; Cl, 15.4
3e	48[k]	An	95.0–96.0	1670 1590	231 (6.25) 281 (7.44)	(b) 9.12 (6 H), 8.65 (18 H) (e) *ca.* 7.40 (4 H)	308 (312.9)	C, 65.26; H, 9.34; N, 8.95; Cl, 11.33	C, 65.70; H, 9.86; N, 8.92; Cl, 11.2
3f	43[k]	An	82.5–83.0	1675 1595	233 (5.06) 281 (6.55)	(b) 9.12 (6 H), 8.74 (34 H), 7.40 (4 H)	393 (425.1)	N, 6.59; Cl, 8.34	N, 6.50; Cl, 8.56
3g	14[l]	W–E (1:1)	113.0–115.0	1660 1610		(d) 9.00 (6 H), 8.66 (6 H), 7.47 (2 H) (m) *ca.* 7.80 (1 H), *ca.* 6.65 (1 H)		C, 57.76; H, 7.49; N, 12.25	C, 57.77; H, 7.80; N, 12.21
3h	70[m]	B	208.0–211.0	1695 1593	242 (5.13) 289 (5.72)	(s) 5.30[n]	201 (213.5)	C, 28.13; H, 1.41; N, 13.12; Cl, 49.83	C, 28.37; H, 1.26; N, 13.28; Cl, 49.8
3i	19[o]	P–B (1:1)	122.0–123.0	1665 1595		(m) 7.55 (2 H)[n] (t) 6.80 (2 H), 6.68 (2 H), 6.30 (2 H), 6.20 (2 H)		C, 40.10; H, 4.11; N, 10.39	C, 39.80; H, 3.84; N, 10.17
3j[p]	28[q]	W	93.0–94.0	1660 1580		(t) 8.67 (3 H), 8.58 (3 H)[n] (m) *ca.* 7.63 (2 H), *ca.* 6.73 (4 H), *ca.* 6.00 (8 H)		C, 54.07; H, 7.33; N, 9.70	C, 53.90; H, 7.52; N, 9.65

[a] Based on phosgene used. [b] Ac = acetone, D = dioxane, P = petroleum ether, An = acetonitrile, W = water, E = ethanol, B = benzene. [c] KBr disk. [d] The solvent was methanol. [e] s = singlet, d = doublet, t = triplet, m = multiplet, c = complex, b = broad. [f] Reaction time 40 hr. [g] Mp of the hydrochloride is above 240 dec. [h] The solvent was pyridine. [i] Reaction time 110 hr. [j] The filtrate was concentrated and chromatographed on silica gel. Petroleum ether eluted a small amount of **4d**. Ir (neat), 1560 cm^{-1} (ring). [k] Reaction time 100 hr. Reaction time 126 hr. [m] Based on **6** (R = Cl). [n] The solvent was CF_3COOH. [o] Reaction time 19 hr. [p] In the course of the reaction, no precipitates were formed. However, evaporation of the reaction mixture gave a brown solid residue. It was recrystallized and analyzed. [q] Reaction time 68 hr.

cm^{-1}. This is also the case for the other pyrimidones (**3**) (Table I). We observed that the pyrimidone **3a** has two crystal forms; one is needlelike and the other prismatic. Examination of these two crystals, especially structural differences, is in progress.

The reaction of nitriles with phosgene to form pyrimidones has also been extended to 4-chlorobutyronitriles (**1i**) and 4-ethoxybutyronitrile (**1j**), the products being the expected pyrimidones **3i** and **3j**, respectively (Table I). However, attempts to obtain the corresponding pyrimidones from methoxyacetonitrile, malonitrile, ethyl cyanoacetate, 3-chloropropionitrile, 3-alkoxypropionitrile, and 3-diethylaminopropionitrile were all in vain.

Johnson, *et al.*,[12] pointed out that, if imidoyl chloride (I), which may exist in the initial stage of the reaction of nitriles with hydrogen chloride,[13] has a hydrogen atom on the α carbon, it is very unstable and two molecules may condense to form an amidine (II). In addition, nitrile trimerization to 1,3,5-triazine in the presence of hydrogen chloride has been interpreted as a cycloaddition of I to II.[14]



I II

In order to know the reaction mechanism, it is of interest to isolate II and allow it to react with phosgene directly.

Grundmann, *et al.*,[4] have reported that N-(1,2-dichloroethylidene)chloroacetamidine (II, R = $ClCH_2$) is easily isolable by the reaction of chloroacetonitrile with hydrogen chloride in ether.[15] The white amorphous solid prepared according to their method indeed had the same properties as reported, but could not be assigned to II on the basis of elemental analysis.[17] In addition, this product was unstable since its melting point dropped gradually during the storage. Heating it in benzonitrile or chlorobenzene using a sealed tube, however, gave N-(1,2-dichloroethylidene)-chloroacetamidine hydrochloride (**6**, R = Cl), which was identified by elemental analysis and mass spectrum. The amidine hydrochloride (**6**, R = Cl) was also prepared by the direct reaction of chloroacetonitrile with hydrogen chloride in chlorobenzene using a sealed tube and converted to N-chloroacetylchloroacetamide by treatment with water. Treatment of **6** (R = Cl) with phosgene in chlorobenzene did indeed lead to the isolation of 5,6-dichloro-2-chloromethyl-4(3H)-pyrimidone (**3h**) in 70% yield (Table I).

Thus we propose the reaction mechanism given in Scheme II. Speziale[19] has reported that the reaction of N,N-disubstituted acetamidines with oxalyl chloride gives the furanone amines through the intramolecular acylation of α carbon to the $C{=}N^+$ group. Moreover,

(12) A. W. Johnson, C. E. Dalgliesh, and J. Walker, "Chemistry of Carbon Compounds", Vol. 1, Part A, Elseiver Publishing Co., Amsterdam, 1951, p 607.

(13) G. J. Janz and S. S. Danyluk, *J. Amer. Chem. Soc.*, **81**, 3486 (1959).

(14) M. Lora-tamayo and R. Madronero, "1,4-Cycloaddition Reactions," Academic Press Inc., London, 1967, p 134.

(15) Hinkel *et al.*[16] have isolated N-(1-chloroethylidene)-acetamidine hydrochloride by the reaction of acetonitrile with hydrogen chloride, but with difficulty.

(16) L. E. Hinkel and G. J. Treharne, *J. Chem. Soc.*, 866 (1945).

(17) In an earlier report,[18] the reaction product was assigned to chloroacetimidoyl chloride (I, R = $ClCH_2$).

(18) J. Troeger and O. Luening, *J. Pr. Chem.*, **69**, 347 (1904).

(19) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 4361 (1962).

it has been shown[20,21] that the iminium salts react with an electrophile, yielding α-substituted amide derivatives. These reaction mechanisms indicate the probability of the intramolecular C-acylation of the intermediate **8** *via* the enamine **9**.[22]

Experimental Section[23]

Preparation of Pyrimidones (3). General Procedure.—In a 50- or 100-ml glass tube was placed 10 ml of a nitrile–hydrogen chloride solution (0.04–0.06 mol) and 10 ml of a nitrile–phosgene solution (0.04–0.06 mol). The tube was stoppered, cooled in Dry Ice–acetone, sealed carefully, and heated to 60–70° in a water bath. During the course of the reaction, a white crystalline solid precipitated. After the end of the reaction, the reaction tube was chilled in Dry Ice–acetone and opened. The precipitate was filtered, washed with a small portion of the nitrile, and then washed with petroleum ether (bp 35–60°). Further material precipitated on concentration of the filtrate. This was treated in the same way. The precipitates were combined, washed with water, dried in a desiccator over $CaCl_2$ under reduced pressure, and recrystallized (Table I).

6-Chloro-2-methyl-4(3H)-pyrimidone (3a)[1] has two crystal forms: needlelike and prismatic. In the course of crystallization from acetone–dioxane (3:1 v/v), the former precipitated first, and rapid filtration and drying gave the needlelike crystals. On the other hand, when the solution containing the needlelike crystals was allowed to stand for a while, the needlelike crystals were observed to change to the prismatic form. Their ir spectra (KBr disk) are quite different; for example, the former has absorptions at 1670 and 1700 cm^{-1} but the latter has a single absorption at 1685 cm^{-1}. However, they have the same melting point and mixture melting point.

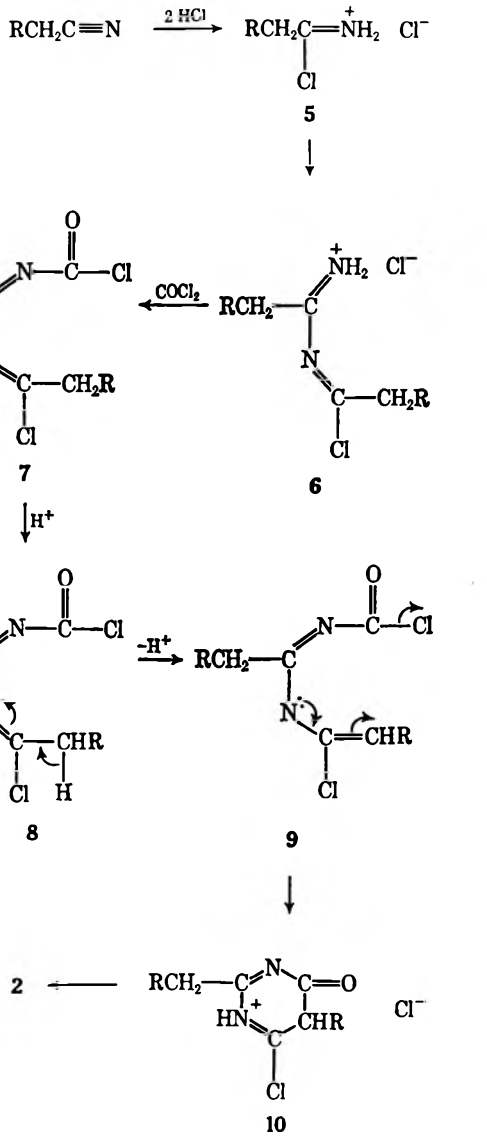
The structure of **3a** was proved by conversion to **4,6-dichloro-2-methylpyrimidine (4a)**. **3a** (7.0 g) was mixed with 10 g of phosphorus pentachloride and heated under reflux for 3 hr, causing evolution of hydrogen chloride, and the temperature was then raised to 140°. Most of the phosphorus oxychloride was removed by distillation under reduced pressure, the residue was poured onto a large amount of ice, and the oily or semisolid product was extracted with ether. After being dried over sodium sulfate, the extract was freed from ether and the residue was chilled to give 7.2 g of volatile **4a**. It was purified by sublimation; mp 45.0–45.5° (lit.[24] 46–48°). Mixture melting point, ir, and nmr showed that it was identical with an authentic sample prepared by the reaction of 2-methyl-4,6(1H, 5H)-pyrimidinedione with phosphorus oxychloride.[24]

6-Chloro-2-ethyl-5-methyl-4(3H)-pyrimidone (3b)[1] was prepared from propionitrile. The tarry product obtained by concentration of the filtrate was chromatographed on silica gel. Petroleum ether eluted 0.5 g of oily liquid, which was identified as **4,6-dichloro-2-ethyl-5-methylpyrimidine (4b)** by glpc and direct comparison of the ir spectrum with that an authentic sample prepared from **3b** and phosphorus pentachloride; ir (neat) 1570 cm^{-1} ring. Glpc was performed with a column of silicone DC 550, 10% on Diasolid L (60–80 mesh, 1-m column, 150°, hydrogen carrier gas, 100 ml/min).

Heating **3b** (1.5 g) and phosgene (2.8 g) in 10 ml of chlorobenzene at 60–65° for 170 hr using a sealed tube and concentration of the filtrate also gave 0.5 g of **4b**.

Preparation of Pyrimidone Hydrochloride (2) from the Free Pyrimidone (3).—Into a solution of the pyrimidones (**3**) in ether, dry hydrogen chloride was bubbled. The precipitates were filtered, washed with ether, and dried to give pyrimidone hydrochlorides (**2**). Their ir spectra (Nujol) were identical with those of the initial products obtained by the reaction of nitriles and phosgene in the presence of hydrogen chloride: compound **2a**, 1730, 1640 cm^{-1}; **2b**, 1700, 1635 cm^{-1}; **2c**, 1700, 1610 cm^{-1}; **2d**, 1700, 1630 cm^{-1}; **2e**, 1700, 1620 cm^{-1}; **2f**, 1700, 1635 cm^{-1}.

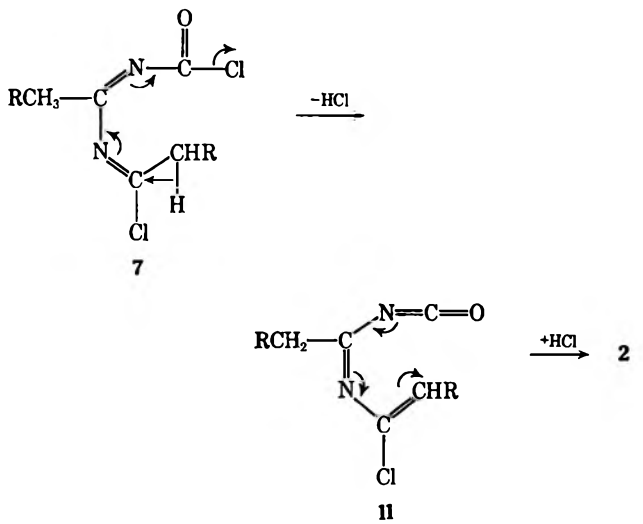
SCHEME II



(20) H. Eilingsfeld, M. Seefelder and H. Weidinger, *Ber.*, **96**, 2899 (1963).

(21) T. Oishi, M. Ochiai, M. Nagai, and Y. Ban, *Tetrahedron Lett.*, 497 (1968).

(22) Another possible mechanism for the formation of the pyrimidones (**2**) is as follows.



However, taking into account the presence of excess hydrogen chloride in the reaction system, the formation of isocyanate **11** would be difficult.

(23) Melting points were determined on a Yanagimoto micro melting point apparatus and were corrected. The nmr spectra were obtained using a Model J. N. M-G-60 spectrometer (Japan Electronic Optics Laboratory Co.); the solvent was deuteriochloroform, except where otherwise noted, with tetramethylsilane as an internal reference. The ir spectra were recorded with a Japan Electroscopic IR-E spectrophotometer. The mass spectra were recorded with a Hitach mass spectrometer Model RMU-6E. The ultraviolet spectra were recorded with a Hitach recording spectrophotometer EPS-3. Molecular weights were determined on a Meehrolab osmometer, Model 301A.

(24) H. R. Henze, W. J. Clegg, and C. W. Smart, *J. Org. Chem.*, **17**, 1320 (1952).

Reaction of Chloroacetonitrile with Hydrogen Chloride.—According to the method of Grundmann,[4] an amorphous solid was obtained. It was placed in a desiccator under reduced pressure to remove adhering hydrogen chloride; mp 142–143° (lit.[4] mp 142°).

Anal. Calcd for $C_4H_6N_2Cl$: N, 12.51; Cl, 63.33. Found: N, 12.21; Cl, 64.5.

During storage, the mp dropped to 131–134° or 126–128°. Water converted it to N-chloroacetylchloroacetamide, mp 190–192° (lit.[4] mp 192°). This solid, when heated with benzonitrile or chlorobenzene in a sealed glass tube at 60–65° for 42 hr, changed to a stable crystalline powder, mp 122–123°; ir (KBr disk) 1695, 1615 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 190 (5), 188 (15), 186 (15) ($M^+ - HCl$), 153 (18), 151 (27) [$ClCH_2$-(=NH)N=C^+CH_2Cl], 76 (77), 78 (25) ($ClCH_2C^+$=NH), 36 (100), 38 (33) (HCl^+).

Anal. Calcd for $C_4H_6N_2Cl_4$: C, 21.45; H, 2.70; N, 12.51; Cl, 63.33. Found: C, 21.20; H, 3.03; N, 12.57; Cl, 63.3.

Water also converts it to N-chloroacetylchloroacetamide. Thus the structure was confirmed as N-(1,2-dichloroethylidene)-chloroacetamidine hydrochloride (**6**, R = Cl).

Reaction of 6 (R = Cl) with Phosgene.—The amidine hydrochloride (**6**, R = Cl) (2.90 g) was added to 10 ml of a chlorobenzene–phosgene solution (2.73 g of $COCl_2$) and heated to 60–65° for 72 hr using a sealed tube. Filtration of the reaction mixture gave 2.32 g of brown solid. Extraction with benzene using a Soxhlet extractor and concentration gave 1.79 g of crude 5,6-dichloro-2-chloromethyl-4(3H)-pyrimidone (**3h**) (70% yield). It was recrystallized and analyzed (Table I).

Reaction of Substituted Acetonitriles and 3-Substituted Propionitriles with Phosgene in the Presence of Hydrogen Chlorides.—In the case of methoxyacetonitrile, no crystalline material could be isolated from the dark brown tar produced. The solid products from the reaction of malonitrile or ethyl cyanoacetate with phosgene in the presence of hydrogen chloride did not have the properties expected of pyrimidones. In the case of 3-chloropropionitrile, a yellow solid, apparently a polymeric substance, was isolated when the reaction mixture was evaporated and treated with water. Since it was insoluble in water and in most organic solvents, further investigation of this substance was not performed. The reaction of 3-methoxypropionitrile with phosgene under the comparable conditions led to the formation of 3-chloropropionitrile, methyl chloroformate, and 3-chloropropionamide.[25] 3-Chloropropionamide was separated from the reaction mixture during the reaction and was obtained in good yield when a small amount of water was previously added to the reaction system; mp 102–103° (lit.[27] mp 102°). Similarly, in the case of 3-ethoxy and 3-butoxypropionitrile, the expected pyrimidones were not isolated. The reaction of 3-diethylaminopropionitrile with phosgene using nitrobenzene as solvent resulted in recovery of the starting materials, even if the reaction temperature was raised to 100°.

Registry No.—Phosgene, 75-44-5; **3a**, 19874-94-3; **3a** (HCl), 20056-12-6; **3b**, 19874-95-4; **3b** (HCl), 20439-58-1; **3c**, 20439-59-2; **3c** (HCl), 20500-54-3; **3d**, 20439-60-5; **3d** (HCl), 20439-61-6; **3e**, 20439-62-7; **3e** (HCl), 20439-63-8; **3f**, 20439-64-9; **3f** (HCl), 20439-65-0; **3g**, 20439-66-1; **3h**, 19875-06-0; **3i**, 20439-68-3; **3j**, 20439-69-4; **6** (R = Cl), 20439-70-7.

Acknowledgment.—The authors are indebted to Reiji Kumagai for technical assistance. The authors also wish to express their appreciation to Dr. Daniel Swern, Temple University, for his encouragement and helpful suggestion.

(25) The easy cleavage of the ether linkage in this reaction is presumably due to the following equilibrium.

$$ROCH_2CH_2C(Cl)=NH_2Cl^- \rightleftarrows ROCH_2CH=C^+(Cl)NH_2Cl^-$$

5′ 5″

5″ has a type of allylic structure, so that reaction with phosgene can readily produce allylic stabilized carbonium ions, giving 3-chloropropionitrile or 3-chloropropionamide, if water is present. Similar equilibrium has been reported by Speziale.[26]

(26) A. J. Speziale and R. C. Freeman, *J. Amer. Chem. Soc.*, **82**, 903 (1960).

(27) C. C. Price and J. Zomlefer, *J. Org. Chem.*, **14**, 213 (1949).

Syntheses of 2-(Chlorinated methyl)-4-methylene-1,3-dioxolanes. Deviations from the Predicted Direction in Competitive Elimination Reactions

HEINZ J. DIETRICH,[1] ROBERT J. RAYNOR, AND JOSEPH V. KARABINOS

Chemicals Division, Olin Mathieson Chemical Corporation, New Haven, Connecticut 06504

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Several cases of competitive elimination and substitution reactions on 1,3-dioxolanes derived from chlorinated acetaldehydes were investigated. It was found that often anion attack occurred at C-4 rather than at the expected more positively charged C-2, demonstrating that eliminations adjacent to electronegative groups do not always follow the predicted pattern. Thus, the novel 4-chloro-2-trichloromethyl-1,3-dioxolane and three 2-(chlorinated methyl)-4-methylene-1,3-dioxolanes were prepared, one of the latter yielding a diene upon further dehydrochlorination. A new synthesis of 4-methylene-2-trichloromethyl-1,3-dioxolane and its allyl-type rearrangement to 4-methyl-2-trichloromethyl-1,3-dioxole is also described.

The title compounds were prepared to serve in a polymerization study which has been reported elsewhere.[2] The conventional syntheses of 4-methylene-1,3-dioxolanes by dehydrochlorination of the corresponding 4-chloromethyl-1,3-dioxolanes[3] were expected to yield preferentially ketene acetal derivatives in cases where chlorine was also available in the 2-methyl position. Reported evidence indicated that the dehydrochlorination in the 2 position is easily accomplished, such as in the syntheses of ketene acetals,[4] or of 2-4-dimethylene-1,3-dioxolane with the *t*-butoxide anion, where no monoolefin had been found.[5] Because of this evidence and also in view of mechanistic considerations it was surprising when preliminary experiments revealed that the 4-chloromethyl position could be quarternized with pyridine without apparent damage to the 2-(*x*-chloromethyl) group.

Results and Discussion

The elimination of hydrogen chloride in the 2 position of 2-(*x*-chloromethyl)-4-chloromethyl-1,3-dioxolanes (*x*

(1) Address correspondence to the author at Corporate Research, Owens-Illinois, Toledo, Ohio 43607.

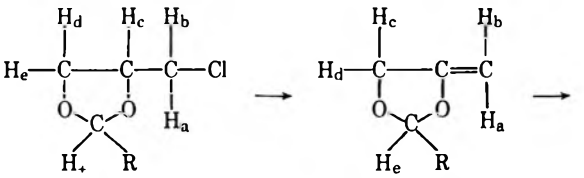
(2) H. J. Dietrich, *J. Polym. Sci., Part A-1*, **6**, 2255 (1968).

(3) H. O. L. Fischer, E. Baer, and L. Feldmann, *Ber.*, **63**, 1732 (1930).

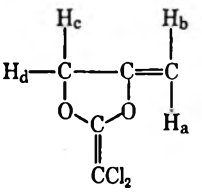
(4) S. M. McElvain and M. J. Curry, *J. Amer. Chem. Soc.*, **70**, 3781 (1948)

(5) B. G. Yagnitskii, S. A. Sarkisyants, and E. G. Ivanyuk, *Zh. Obshch. Khim.*, **34**, 1940 (1964).

= 1–3) was expected to be favored over that in the 4 position by two factors known to control the orientation in base-promoted E2 reactions when steric influences are equal, namely, stability of the olefin (more resonance structures possible) and acidity of the α hydrogen (three negative groups around C-2 *vs.* two around C-4). Contrary to these considerations, the dehydrochlorinations by ethanolic caustic of 2,4-bischloromethyl-1,3-dioxolane (**1**), 2-dichloromethyl-4-chloromethyl-1,3-dioxolane (**2**), and of 2-trichloromethyl-4-chloromethyl-1,3-dioxolane (**3**) proceeded smoothly and with high selectivity in the 4 positions to yield the corresponding 4-methylene derivatives **4**, **5**, and **6**.



1, 2, 3 **4, 5, 6**



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1,4, R = CH_2Cl

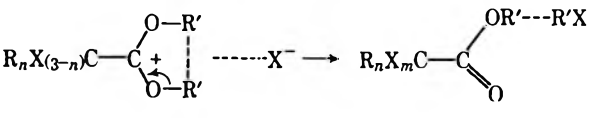
2,5, R = $CHCl_2$

3,6. R = CCl_3

The monomers **4** and **5** were obtained in pure form and **6** in mixture with 2-dichloromethylene-4-methylene-1,3-dioxolane (**7**). The proof of structures is based on the synthesis of **6** by a different route *via* the 2-propynyl hemiacetal of chloral (**13**) and also on the rearrangement of **6** to the dioxole (**12**) (see below). In addition, the ir, mass, and nmr spectra were compatible and established the structural similarity of **4** and **5** with **6**. Small amounts of **7** were formed even at 0–5° and in the presence of an excess of **3**.

The reason why the base anion did not attack the most acidic hydrogen atom (2 H) to form the most stable 2-methylene structure may be related to the stability of an intermediate anion–proton complex. Since no attempt was made to study the transition state, one might only speculate that its stability at C-2 was decreased perhaps owing to electrostatic repulsion of the anion by O-1 and O-3.

A related reaction is the halogenation of ketene acetals[6,7] where the same field effect may be responsible for having blocked the approach of the halide anion X^- to the intermediate carbonium ion (**8**) forcing the acetal to undergo heterolytic cleavage to a 2-halo ester and halo alkyl. Similarly it was found that chlorination of 2-trichloromethyl-1,3-dioxolane (**9**) yielded 4-chloro-2-trichloromethyl-1,3-dioxolane (**10**), besides some 2-chloroethyl trichloroacetate (**11**), *via* an assumed intermediate of the type **8**. The structure of **10** was based on correct



8

R = H, alkyl, or aryl

R′ = alkyl or CH_2 as R′---R′

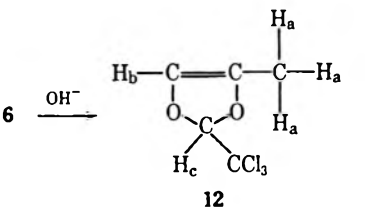
$n = 0, 1, 2$

elemental analysis, its mass fragmentation pattern, and its nmr spectrum (see Experimental Section).

However, the recently investigated[8] homolytic chlorination of 1,3-dioxolane has yielded predominantly 2-chloro-1,3-dioxolane, demonstrating the closeness of competition between 2 and 4 eliminations. Moreover, in the present study it was found that attempted dehydrochlorination of **10** resulted in **11** besides possibly traces (according to ir spectra of distilled reaction product) of either 4-chloro-2-dichloromethylene-1,3-dioxolane or 2-trichloromethyl-1,3-dioxole. This left no doubt that a proton had been shifted from C-2 to C-4 possibly *via* the same intermediate **8** and that little, if any, anion attack at C-5 had occurred.

These results show that a prediction of directing influences on competitive eliminations adjacent to negative centers is still subjected to considerable uncertainty.

Other aspects of the synthesis of **6**, however, were found influenced by steric factors. A study of variables revealed that the dehydrochlorination of **3** stopped at a limited conversion. Nuclear magnetic resonance spectra of starting and recovered dioxolane **3** showed the starting material to be a mixture of *cis* and *trans* isomers regarding the positions of the two methyl substituents relative to the dioxolane ring. Recovered **3** consisted of almost pure *trans* form, indicating that only the *cis* form had undergone dehydrochlorination. The passivity of the *trans* form is attributed to steric hindrance of the backside attacking[9] base anion by the bulky trichloromethyl group. This shielding of the α hydrogen was not observed in the preparation of **4** and **5**. A further complication in the synthesis of **6** was experienced during purification steps. An allyl rearrangement of **6** to 2-trichloromethyl-4-methyl-1,3-dioxole (**12**), as shown, was observed. The strongly exothermic isomerization took place at above 150° with basic catalysts too weak to cause dehydrochlorination at C-2. It was not determined whether this rearrangement was applicable to the synthesis of other members of this al-



12

(6) S. M. McElvain and W. R. Darie, *J. Amer. Chem. Soc.*, **74**, 1816 (1952).

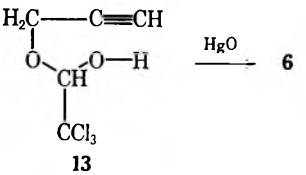
(7) A. S. Atavin, A. N. Mirkova, N. N. Chipanina, and R. A. Preslovskaya, *Zh. Org. Khim.*, **1**, 2077 (1955).

(8) J. Jonas, T. P. Forrest, M. Kratochvil, and H. Gross, *J. Org. Chem.*, **33**, 2126 (1968).

(9) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp 169–173.

most unknown[10] class of aliphatic substituted 1,3-dioxoles.

Since **6** was needed for polymerization studies in sufficient quantity and free from the closely boiling **7**, a different synthesis was devised,[11] based on the addition of the hydroxyl group of chloral 2-propynyl hemiacetal (**13**) to the triple bond, which proceeded in over 65% in-hand yields.



13

A similar reaction has been described for fluorinated carbonyls[12] and the identical synthesis[13] after the first publication of part of this work.[14]

Experimental Section

The following instruments were used in spectral analyses: a grating ir spectrophotometer from Perkin-Elmer, Model 521; a single-focusing mass spectrometer from Consolidated Electrodynamic Corp., Model 21-103-C; and an nmr spectrometer from Varian Associates, Model A-60. The molecular weights were determined in a vapor pressure osmometer from Mechrolab, Inc., Model 302. Melting points are corrected.

2,4-Bischloromethyl-1,3-dioxolane (1).—Chloroacetaldehyde diethyl acetal (1.5 mol), 3-chloro-1,2-propanediol (1.5 mol), *p*-toluenesulfonic acid (5 g), and benzene (500 ml) were distilled slowly until the ethanol–benzene azeotrope was removed. The mixture was neutralized ($NaHCO_3$), dried ($MgSO_4$), and fractionated, yielding 190 g (74%) of **1**: bp 117° (18 mm); $n^{25}D$ 1.4746; ir (neat) 8.8 (COC), 13.2 μ (CH_2Cl); nmr (δ, $CDCl_3$), 3.32–3.78 (4 H, m, H_a, H_b, and CH_2Cl), 3.78–4.68 (3 H, m, H_c, H_d, H_e), 5.17 (0.74 H, t, *cis*-H_f), 5.32 (0.26 H, t, *trans*-H_f).

2-Dichloromethyl-4-chloromethyl-1,3-dioxolane (2).—Dichloroacetaldehyde (1.0 mol) was added dropwise to 3-chloro-1,2-propanediol (1.0 mol) at or below 70°, followed by 196 g of concentrated H_2SO_4 and stirring at 80–90° for 4.2 hr. The mixture was cooled, poured into 1 l. of ice water, and extracted three times with 300 ml of chloroform each. After neutralization (dry Na_2CO_3), filtration, and fractionation, the yield of **2** was 124 g (60.5%): bp 65° (0.30 mm); $n^{25}D$ 1.4930; ir (neat) 8.7–8.95 (COC), 12.6–13.35 μ ($CHCl_2$); nmr (δ, $CDCl_3$), 3.65 (2 H, m, H_a, H_b), 3.80–3.95 (3 H, m, H_c, H_d, H_e), 5.26 (0.4 H, d, J = 3 Hz, *cis*-H_f), 5.40 (0.6 H, d, J = 3 Hz, *trans*-H_f), 5.66 (0.4 H, d, J = 3 Hz, *cis*-$CHCl_2$), 5.64 (0.6 H, d, J = 3 Hz, *trans*-$CHCl_2$). *Anal.* Calcd for $C_5H_7Cl_3O_2$: C, 29.3; H, 3.4; Cl, 51.7. Found: C, 29.26; H, 3.48; Cl, 51.6.

2-Trichloromethyl-4-chloromethyl-1,3-dioxolane (3).—The same method was used as in the preparation of **2**. The yield of **3** after spinning-band distillation was 80.5%: bp 72–74° (0.75 mm); $n^{25}D$ 1.5007; ir (neat) 8.75–8.95 (COC), 12.1–12.5 μ (CCl_3); nmr (δ, $CDCl_3$), 3.56–3.84 (2 H, m, H_a, H_b), 3.88–5.16 (3 H, m, H_c, H_d, H_e), 5.38 (0.52 H, s, *cis*-H_f), 5.49 (0.48 H, s, *trans*-H_f).

2-Chloromethyl-4-methyl-1,3-dioxolane (4).—To a stirred mixture of 1 (0.30 mol) with 100 ml of ethanol in a nitrogen atmosphere was added dropwise at 80° during 2.3 hr a solution of 21.1 g of 85% KOH (0.32 *M*) in 60 ml of ethanol containing 7 ml of H_2O. Refluxing for 1 hr, cooling, neutralization (CO_2), filtration, and fractionation, in a nitrogen atmosphere yielded besides unreacted 1 13.8 g (63.8% of converted 1) of **4**: bp 80° (42 mm); $n^{25}D$ 1.4665; ir (neat) 5.75, 5.90, 6.10 (t, C=C), 8.05, 8.75 (COC), 13.0 μ (CH_2Cl); nmr (δ, $CDCl_3$), 3.94 (1 H, d, J = 2.5 Hz, of t, J = 1.8 Hz, H_a), 4.23–4.77 (3 H, m, H_b, H_c, H_d), 5.45 (1 H, t, J = 4.0 Hz), 3.58 (2 H, d, J = 4.0 Hz, H_f, H_g). *Anal.* Calcd for $C_5H_7ClO_2$: C, 44.6; H, 5.2; Cl, 26.4. Found: C, 44.81; H, 5.31; Cl, 26.1.

2-Dichloromethyl-4-methylene-1,3-dioxolane (5).—The preparation from **2** was identical with that of **4**: yield 74.5% (based on unreacted **2**); bp 94° (32 mm); $n^{25}D$ 1.4814; ir (neat) 5.75, 5.90, 6.1 (t, C≡C), 8.05, 8.75 (COC) 12.65 μ ($CHCl_2$); nmr (δ, $CDCl_3$), 4.04 (1 H, d, J = 3.0 Hz, of t, J = 1.8 Hz, H_a), 4.36–4.90 (3 H, m, H_b, H_c, H_d), 5.6 (1 H, d, J = 3.0 Hz, H_e), 5.55 (1 H, d, J = 3.0 Hz, $CHCl_2$). *Anal.* Calcd. for $C_5H_6Cl_2O_2$: C, 35.5; H, 3.55; Cl, 42.00. Found: C, 34.41; H, 3.85; Cl, 42.4.

2-Trichloromethyl-4-methylene-1,3-dioxolane (6). **Method A.**—A solution of 18.1 g (0.27 mol) of 85% KOH in 7 ml of water and 50 ml of ethanol was added to a mixture of 120 g (0.5 mol) of **3** with 100 ml of methanol at 25° in a nitrogen atmosphere. After standing 2 days at room temperature and heating for 1 hr to 50° the mixture was fractionated in a nitrogen atmosphere yielding 11.8 g of **6** (21% allowing for unreacted **3** and formation of small amounts of **7**).

6. **Method B.**—To a stirred mixture of 56 g (1 mol) of distilled 2-propyn-1-ol and 6.4 g of yellow mercuric oxide in a nitrogen atmosphere was added dropwise with cooling at 5–30° 147 g (1 mol) of distilled chloral over a period of 30 min. Subsequently, the mixture was heated slowly to 100°, using a water bath for removal of the heat of reaction. After the mixture was heated for 5 hr, vpc analysis of periodically withdrawn samples indicated over 80% conversion and no further decrease in starting materials. Fractionation of the mixture yielded 175.7 g (76.5%) of **6**: bp 69–70° (7 mm); $n^{25}D$ 1.4950; ir (neat) 5.90, 6.0, 6.1 (t, C=C), 8.1, 8.8, 9.45 (COC), 12.40 μ (CCl_3); nmr (δ, $CDCl_3$), 4.04 (1 H, d, J = 3.0 Hz, of t, J = 1.8 Hz, H_a), 4.45–5.03 (3 H, m, H_b, H_c, H_d), 5.62 (1 H, s). *Anal.* Calcd for $C_5H_5Cl_3O_2$: C, 29.2; H, 2.46; Cl, 52.40. Found: C, 29.77; H, 2.61; Cl, 52.25.

2-Dichloromethylene-4-methylene-1,3-dioxolane (7).—To 18.1 g (0.27 mol) of 85% KOH in 50 ml of ethylene glycol was added with stirring at 60° within 5 min 0.25 mol of **3** in a nitrogen atmosphere. Heating to 80° and agitation in nitrogen was continued for 18 hr, followed by flash distillation *in vacuo*. The fraction boiling below 100° (13 mm) separated into two layers, the lower one upon redistillation yielding 9 g (39% after recovery of unreacted **3**) of **7**: bp 83–87° (10 mm); mp 48–49°; mass spectrum (70 eV) *m/e* 170 (theoretical, 170) and fragments corresponding to $=CCl_2$ and absence of $—CCl_3$; ir (KBr pellet) 5.75, 5.90, 5.98 (t, C=C), 7.83, 8.4 (COC), 12.0 μ ($=CCl_2$); nmr (δ, $CDCl_3$), 4.33 (1 H, d, J = 3.8 Hz, of t, J = 1.9 Hz, H_a), 4.66–5.22 (3 H, m, H_b, H_c, H_d). *Anal.* Calcd: C, 36.0; H, 2.4; Cl, 42.50. Found: C, 36.03; H, 2.45; Cl, 42.4.

4-Chloro-2-trichloromethyl-1,3-dioxolane (10).—To 1.0 mol of 2-trichloromethyl-1,3-dioxolane (9) (prepared according to McElvain[15]) in 500 ml of carbon tetrachloride was added 0.3 ml of PCl_3, followed by 1.1 mol of Cl_2 gas during 1.3 hr with stirring at 3–4° and continued agitation (3.5 hr) until colorless. After neutralization (86 g of $NaHCO_3$ in 2 l. of ice water), separation, washings, and fractionation, a mixture of **10** and 2-chloroethyl trichloroacetate (11) was obtained, boiling at 114–116° (24 mm). Selective hydrolysis of **11** (3-hr reflux in 300 ml of ether, containing 71 g of triethylamine, filtration, washing five times with water, concentration, and drying to constant weight) gave 105 g (48%) of **10** which was further purified by spinning-band distillations to yield essentially pure *trans* **10**: bp 115–115.5° (24 mm); mp 32°; $n^{25}D$ 1.4945 (supercooled); ir (KBr pellet) 8.4, 8.65 (d, COC), 12.0, 12.4 (d, CCl_3), 12.65 μ (CHCl); nmr (δ, $CDCl_3$), 5.73 (1 H, s, $Cl_3CCH<$), 6.51 (1 H, m, OCHCl), 4.3–4.8 (2 H, m, OCH_2). *Anal.* Calcd for $C_4H_4Cl_4O_2$: C, 21.2; H, 1.77; Cl, 62.9; mol wt, 226. Found: C, 21.13; H, 1.81; Cl, 62.56; mol wt, 229.

Dehydrochlorinations of **10** were attempted at temperatures ranging from 0 to 100° for 0.5 to 24 hr, employing a variety of amines, caustic materials, or basic clays. The only identifiable reaction product was **11**, besides traces of lower boiling distillates showing ir bands indicative of unsaturation.

(10) H. J. Dietrich, J. V. Karabinos, *J. Org. Chem.*, **31**, 1127 (1966).

(11) H. J. Dietrich, R. Raynor, and J. V. Karabinos (to Olin Mathieson Chemical Corp.), U. S. Patent 3,379,736 (April 23, 1968).

(12) H. E. Simmons and D. W. Wiley, *J. Amer. Chem. Soc.*, **82**, 2288 (1960).

(13) A. S. Atavin, A. N. Mirskova, and G. A. Kalabin, *Zh. Org. Khim.*, **3**, 1779 (1967); *Chem. Abstr.*, **68**, 29200e (1968).

(14) H. J. Dietrich, Polymer Preprints, Vol. 8, American Chemical Society, 1967, p 481.

(15) S. M. McElvain, *J. Amer. Chem. Soc.*, **70**, 3781 (1941).

2-Trichloromethyl-4-methyl-1,3-dioxole (12).—Heating of 0.3 mol of 6 with 3.0 g of Linde Molecular Sieve Type 13X in nitrogen to 125° caused an exothermic reaction which raised the temperature to 250°. Cooling during 5 min to 180° and maintaining 180° for 30 min afforded 36 g of distillables consisting of 25% 6 and 75% 12. Spinning-band distillation gave 15 g (24.5%) of 92% pure 12: bp 66–68° (7.8 mm); $n^{25}D$ 1.4815; ir (neat) 5.82 (C=C), 8.15, 8.85 (COC), 11.95–12.45 μ (CCl_3); nmr (δ, $CDCl_3$), 1.90 (3 H, d, J = 1.5 Hz, H_a), 6.18 (1 H, 9, J = 1.5 Hz, H_b), 6.04 (1 H, s).

The elemental analysis of 12 was identical with that of 6.

Registry No.—*cis* **1**, 20286-92-4; *trans* **1**, 20287-07-4; *cis* **2**, 20287-28-9; *trans* **2**, 20287-08-5; *cis* **3**, 20287-29-0; *trans* **3**, 20287-09-6; **4**, 16042-56-1; **5**, 16042-57-2; **6**, 16042-58-3; **7**, 17292-90-9; *trans* **10**, 20302-81-2; **12**, 20287-11-0.

Acknowledgments.—The authors are indebted to W. Harple, H. Hoberecht, and G. Vickers, of Olin Central Analytical Research Department, for determining and interpreting spectral data and to Dr. R. Rittner and his coworkers for performing instrumental and microanalytical work.

1,4-Bis(2-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane Diperchlorate[1,2]

GEORGE R. PETTIT, DYRAL C. FESSLER, AND JOSEPH A. SETTEPANI

Department of Chemistry, Arizona State University, Tempe, Arizona 85281, and Department of Chemistry, University of Maine, Orono, Maine 04473

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Reaction between bis(2-chloroethyl)amine and formalin in ethanol solution was found to yield 1,4-bis(2-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane (1a) dichloride, a novel quaternary ammonium salt. The condensation leading to diazabicyclo[2.2.1]heptane 1a was found generally useful and substances 1b–1f were easily obtained. Hydrogenolysis of, for example, salt 1e was found to yield piperazine 8b. Other pertinent aspects of the chemical and physical (principally proton magnetic resonance) evidence in support of the new ring system have been summarized.

Early in our study of bis(2-chloroethyl)amine in Mannich-type reactions,[3] formation of a water-soluble quaternary ammonium chloride was noted.[4] By allowing bis(2-chloroethyl)amine to react with formalin in ethanol solution followed by addition of perchloric acid, the new compound was conveniently obtained as the less soluble perchlorate salt.

While mass spectral analysis employing a variety of techniques did not give useful information, elemental analytical data and a cryoscopic formula weight determination indicated $C_9H_{18}Cl_4N_2O_8$ for the perchlorate salt. The molecular formula corresponded to combination of 2 mol of bis(2-chloroethyl)amine with 1 mol of formaldehyde. Based on the chemistry of 2-haloethylamines,[5] a number of possible structures (*cf.* 2) were considered. All but a few could be firmly rejected. Of the remaining possibilities, bicyclic structure **1a** and aziridinium salts **3** and **4** seemed most reasonable. Examination of the chemical and physical (*e.g.*, nmr spectra) properties of the new quaternary ammonium salt led to its assignment as 1,4-bis(2-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane diperchlorate (**1a**): a new heterocyclic system.[6]

The rapid alkylation of thiosulfate by aziridinium ring containing compounds and by 2-chloroethylamines capable of cyclizing to such intermediates serves as a means of distinguishing between a piperazinium or aziridinium structure.[7] Using a quantitative technique, salt **1a** was found not to alkylate thiosulfate. Under the same conditions, thiosulfate was consumed as expected by 1-methyl-1-(2-chloroethyl)aziridinium picrylsulfonate,[7a] N-methylbis(2-chloroethyl)amine hydrochloride,[8a] 1,4-bis(2-chloroethyl)piperazine diperchlorate,[5d] and 2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate.[5b,8b] An aziridinium ring was thereby excluded. In addition, aziridinium structures **3** and **4** were eliminated by absence of nmr signals near δ 3.3 in the spectrum of salt **1a**.[9]

The condensation reaction leading to bicyclo[2.2.1]-heptane **1a** was found relatively general for N-alkyl and N-benzyl substituted 2-haloethylamines, and a number of analogous quaternary ammonium salts[10] were prepared. The nmr spectrum of each quaternary salt was easily interpreted in terms of structure **1**. For example, the spectrum of ethyl derivative **1b** displayed a sharp two-proton singlet at δ 5.3 (bridge methylene), an eight-proton singlet at δ 4.3 (piperazine ring), and the char-

(1) Antineoplastic Agents. XXIV. Part XXIII: G. R. Pettit, H. B. Wood, and J. A. Hartwell, *Cancer Res.*, **28**, 2186 (1968).

(2) (a) Based in part on the Ph.D. dissertations of J. A. Settepani, University of Maine, 1963, and D. C. Fessler, Arizona State University, 1968. (b) This investigation was aided in part by Grants T-79B and T-79G from the American Cancer Society and by PHS Research Grant CA-10115-02 from the National Cancer Institute.

(3) G. R. Pettit and J. A. Settepani, *J. Org. Chem.*, **27**, 1714 (1962).

(4) Preliminary communication: G. R. Pettit and J. A. Settepani, *Chem. Ind.* (London), 1805 (1964).

(5) (a) C. R. Dick, *J. Org. Chem.*, **32**, 72 (1967); (b) N. J. Leonard, *Rec. Chem. Progr.*, **26**, 211 (1966); (c) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 1385 (1963); (d) G. R. Pettit and J. A. Settepani, *J. Org. Chem.*, **27**, 2962 (1962); (e) M. F. Sartor, *Chem. Rev.*, **48**, 225 (1951).

(6) Prior examples of the 1,4-diazabicyclo[2.2.1]heptane system have not been confirmed. The 7-thione derivative of **1** has been briefly mentioned in two surveys of thioureas in respect to goitiogenic activity: D. A. McGinty and W. G. Bywater, *J. Pharmacol.*, **84**, 342 (1945) [*Chem. Abstr.*, **40**, 948 (1946)]; R. H. Williams, G. A. Kay and B. Solomon, *Am. J. Med. Sci.*, **213**, 198 (1947) [*Chem. Abstr.*, **41**, 4855 (1947)]. One study was performed at the Parke-Davis laboratories, and these investigators (H. Geer, personal communication, March 11, 1963) kindly identified Union Carbide Co. as their source of the bicyclic compound. Subsequently, it was learned (D. W. Johnson, personal communication, March 26, 1963) that the 1,4-diazabicyclo[2.2.1]heptane-7-thione structure was believed to be in error. For another pertinent report see M. L. Tomayo and R. Madronero, *Rev. Real Acad. Cienc. Exact., Fis. Nat.*, **53**, 1 (1959)

(7) (a) C. Golumbic, J. S. Frutow, and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946); (b) M. Beroza and A. B. Borkovec, *J. Med. Chem.*, **7**, 44 (1964).

(8) (a) G. R. Pettit and J. A. Settepani, *J. Org. Chem.*, **27**, 1714 (1962); (b) We are grateful to Professor N. J. Leonard for providing this specimen.

(9) The nmr spectrum of compound **1a** was initially recorded at Varian Associates, Palo Alto, Calif., by Dr. N. S. Bhacca.

(10) A description of these bicyclo[2.2.1]heptanes has been reported in conjunction with a biological study: D. C. Fessler, G. R. Pettit, and J. A. Settepani, *J. Med. Chem.*, **12**, 542 (1969).

acteristic ethyl triplet and quartet. The two-proton methylene bridge singlet at δ 5.3–5.6 was common to all of the spectra, and a singlet corresponding to the remaining ring protons was observed in all examples of bicyclo[2.2.1]heptane **1** where R was alkyl. Where R was benzyl, the piperazine ring protons no longer appeared as a singlet, but instead appeared as a broad resonance. The broad signal seemed plausible in terms of different spatial relationships between the benzene ring and *exo* and *endo* protons of the bicyclic ring. The resulting chemical shift difference between *exo* and *endo* protons would lead to a signal broadened by coupling.

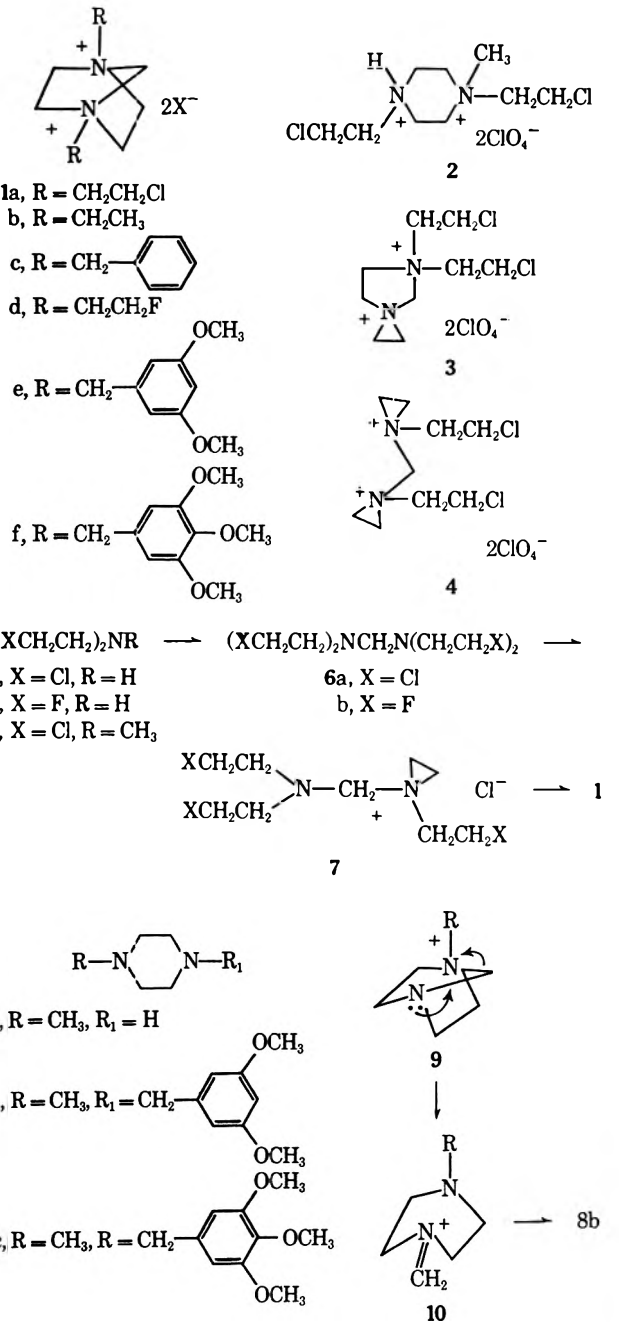
To provide additional support for structure **1**, both an unequivocal synthesis[11] and a degradation of salt **1a** were undertaken. Before a useful alternate synthesis could be developed, the combined spectral and chemical results, which now follow, provided sufficient evidence favoring proposal **1**. The synthetic attempts did, however, serve to emphasize utility of the 2-haloethylamine–formaldehyde route to **1**.

From a chemical standpoint, formation of salt **1a** was easily rationalized as outlined by **5** → **7** → **1**. The first step (**5a** → **6a**), formation of a bis(amino)methane from formaldehyde and a secondary amine, has been well documented.[11b] Conversion of tertiary amine **6a** to **1a** through aziridinium intermediates (**7**)[12a] seems consistent with the known propensity of tertiary nitrogen mustards and bis(2-chloroethyl)amine to form piperazine derivatives by self-condensation. Such a pathway, and hence structure **1**, was supported by isolation of tetrakis(2-fluoroethyl)methylenediamine (**6b**) as an intermediate in conversion of bis(2-fluoroethyl)amine (**5b**) to 1,4-bis(2-fluoroethyl)-1,4-diazabicyclo[2.2.1]-heptane (**1d**) diperchlorate.[10] Other[12b] but less important chemical evidence was obtained as noted below.

Basic hydrolysis of benzyl derivative **1c** was shown to yield dibenzylpiperazine and formaldehyde.[12b] Piperazine derivatives were also formed by hydrogenolysis. One attempt to prepare the parent ring system, 1,4-diazabicyclo[2.2.1]heptane, by catalytic debenzylation of **1c** resulted in formation of 1-methylpiperazine (**8a**) and piperazine. Trace quantities of a component resembling 1,4-dimethylpiperazine was detected but not conclusively identified. Analogous hydrogenolysis of 3,5-dimethoxybenzyl derivative **1e** resulted in absorption of only 2 mol of hydrogen, forming 1-methyl-4-(3′,5′-dimethoxybenzyl)piperazine (**8b**) dihydrochloride. Similarly, perchlorate salt **1f** gave 1-methyl-4-(3′,4′,5′-trimethoxybenzyl)piperazine (**8c**) diperchlorate as the only product of hydrogenolysis. Characterization of piperazine **8c** was completed by comparison with an authentic sample obtained by alternate synthesis.

The hydrogenolysis reaction just described may proceed by loss of a benzyl group to yield tertiary amine **9**, which undergoes ring opening to give an intermediate such as **10**, which rapidly undergoes reduction to, *e.g.*, methylpiperazine **8b**. That ring cleavage occurred only after loss of a benzyl group was suggested by failure of ethyl analog **1b** to undergo hydrogenolysis. The difference in hydrogenolysis products derived from quaternary salts **1c** and **1e,f** may be viewed in terms of some prior experiments[13] where a methoxyl substituent in any position of a benzyl ring was found to greatly retard the rate of hydrogenolysis.

The convenient preparation of bicyclo[2.2.1]heptanes herein described should facilitate entry into future synthetic and theoretical investigations of this interesting bicyclo-ring system.



Experimental Section

Catalytic hydrogenations were accomplished with a slight positive pressure of hydrogen. Melting points were recorded

(11) A number of unsuccessful attempts to construct a methylene bridge between the two nitrogen atoms of piperazine have been reported. Procedures employing cyanic acid (a), phosgene (b), carbon bisulfide (b, c) and formaldehyde (b) have all led to products other than 1,4-diazabicyclo-[2.2.1]heptane: (a) W. L. Mosby, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Vol., XV-2, Interscience Publishers, Inc., New York, N. Y., 1961, pp 1283–1284; (b) W. Herz, *Ber.*, **30**, 1584 (1897); J. F. Walker, "Formaldehyde," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1964, p 359, and W. V. Farrar, *Rec. Chem. Prog.*, **29**, 85 (1968); (c) A. Schmidt and G. Wichmann, *Ber.*, **24**, 3237 (1891).

(12) (a) For a related example refer to H. Böhme and H. Orth, *Chem. Ber.*, **99**, 2842 (1966); (b) see also H. Böhme and H. Orth, *Arch. Pharm.*, **300**, 148 (1967).

(13) R. Baltzly and P. B. Russell, *J. Amer. Chem. Soc.*, **72**, 3410 (1950).

employing a Kofler melting point apparatus and purity was confirmed by thin layer chromatography using silica gel HF_{254} (E. Merck, Darmstadt) on microscope slides. Unless otherwise noted, each chromatogram was prepared using the top layer of water–*n*-butanol–acetic acid (5:4:1) mixture as solvent and developed with iodine vapor. Each analytical sample was colorless.

Infrared spectra were determined in potassium bromide with a Beckman IR-12 by Miss K. Reimer. Nmr spectra were recorded in deuterium oxide (tetramethylsilane as external standard, Varian A-60). Elemental microanalytical data were provided by Dr. A. Bernhardt, Max Planck Institute, Mülheim, Germany.

1,4-Bis(2′-chloroethyl)-1,4-diazabicyclo[2.2.1]heptane Diperchlorate (1a).—A solution of bis(2-chloroethyl)amine (0.20 *M*), 37% formalin (33 ml), and 95% ethanol (66 ml) was left at room temperature for 10 hr. Treating the colorless solution with 70% perchloric acid (15 ml) followed by cooling (ice bath) gave a crystalline solid (32.3 g, 76%) decomposing at 210–211°. Repeated recrystallization from aqueous ethanol afforded a sample as colorless plates: mp 222–223° dec; ν_{max} 1450 (br), 1362, and 1100 cm^{-1}; nmr δ 4.4–3.9 (m, 8 H), 4.45 (s, 8 H), and 5.6 ppm (s, 2 H).

Anal. Calcd for $C_9H_{18}Cl_4N_2O_8$: C, 25.49; H, 4.27; Cl, 33.48; N, 6.60. Found: C, 25.54; H, 4.49; Cl, 33.65; N, 6.37.

The formula weight of 1,4-bis(2-chloroethyl)-1,4-diazabicyclo-[2.2.1]heptane diperchlorate (1a) was determined cryoscopically in water, using a procedure described by Daniels.[14] Both bis(2-chloroethyl)amine (5a) perchlorate (mol wt 242) and N-methylbis(2-chloroethyl)amine (5c) perchlorate (mol wt 256) were used as standards. The results shown in Table I were obtained and are consistent with a $(C_9H_{18}Cl_4N_2O_8)_1$ unit.[15]

TABLE I

	Wt of water, g	Wt of salt, g	Temp, °C	Mol wt	% deviation
Ia	17.72	0.170	0.111	472	+10
Ia	26.12	0.200	0.092	462	+8
5a	18.06	0.205	0.170	246	+1.6
5c	15.94	0.200	0.168	272	+6.2

Nuclear Magnetic Resonance Study of 1,4-Diazabicyclo[2.2.1]-heptanes.—1b, δ 1.5 (t, J = 7.5 cps, 6 H), 3.9 (q, J = 7.5 cps, 4 H), 4.3 (s, 8 H), and 5.3 ppm (s, 2 H); 1c, δ 4.4 (br 8 H), 5.2 (s, 4 H), 5.65 (s, 2 H), and 7.85 ppm (s, 10 aromatic H); 1d, δ 4.33–4.48 (m, 4 H), 4.73 (s, 8 H), 5.65–5.75 (m, 4 H), and 5.77 ppm (s, 2 H); 1e, δ 4.0 (s, 12-OMe H), 4.4 (br, s, 8 H), 5.1 (s, 4 H), 5.65 (s, 2 H), and 7.0 ppm (s, 6 aromatic H); 1f, δ 3.9 (s, 6-OMe H), 3.95 (s, 12-OMe H), 4.35 (br, 8 H), 5.05 (s, 4 H), 5.5 (s, 2 H), and 7.05 ppm (s, 4 aromatic H); 1, R = 3′-chlorobenzyl, δ 4.4 (br, 8 H), 5.25 (s, 4 H), 5.7 (s, 2 H), and 7.9 ppm (m, 8 aromatic H); 1, R = 2-cyclopentylethyl, δ 1.9 (m, 13 H), 3.9 (br, 4 H), 4.2 (s, 8 H), and 5.45 ppm (s, 2 H); 1, R = 2-phenylethyl, δ 3.4 (t, J = 15 cps, 4 H), 4.3 (*t*, J = 15 cps, 4 H), 4.5 (s, 8 H), 5.6 (s, 2 H), and 7.7 ppm (s, 10 aromatic H); 1, R = 2-(3′,4′,5′-trimethoxyphenyl)ethyl, δ 3.25 (br, 4 H), 3.71 (s, 6-OMe H), 3.88 (s, 12-OMe H), 4.25 (br, 4 H), 4.4 (s, 8 H), 5.5 (s, 2 H), and 6.7 (s, 4 aromatic H).

Tetrakis(2-fluoroethyl)methylenediamine (6b).—A solution of bis(2-fluoroethyl)amine (5b) hydrobromide[16] (1.9 g) in water was neutralized with aqueous sodium hydroxide (0.4 g in 2 ml). Addition of 37% formalin (1 ml) followed by cooling in an ice bath resulted in separation of an oil (0.20 g) which was chromatographed on basic alumina (10 g of Brockman activity I). Elution with diethyl ether gave a viscous oil (0.05 g) which was dried *in vacuo* at room temperature.

Anal. Calcd for $C_9H_{18}F_4N_2$: C, 46.96; H, 7.86; F, 33.01; N, 12.16. Found: C, 46.93; H, 8.24; F, 33.05; N, 12.25.

Hydrogenolysis of 1,4-Dibenzyl-1,4-diazabicyclo[2.2.1]heptane (1c) Diperchlorate.—The perchlorate salt (1c, 0.65 g) in water (200 ml) containing suspended 10% palladium on carbon (0.1 g) was hydrogenated at room temperature. After hydrogen (3 mol) uptake had ceased (18 hr), catalyst was removed by filtering the solution through Celite. The filtrate was washed with benzene (10 ml) and freeze dried, yielding a colorless solid (0.4 g) which showed only two singlets (3 H at δ 3.0 and 8 H at δ 3.6) in then mr spectrum. Three components with R_f's identical with those of 1,4-dimethylpiperazine, 1-methylpiperazine, and piperazine were detected on a thin layer chromatogram (chloroform–methanol–17% ammonium hydroxide, 2:2:1). The free bases were separated by preparative layer chromatography (1.5 mm silica gel HF_{254} plate) using the above solvent system. Each of the three bands was eluted with methanol. Treating the eluates of zones corresponding to piperazine and 1-methylpiperazine with methyl iodide led in both cases to a single component identical (by thin layer) with 1,1,4,4-tetramethylpiperazinium iodide. The third zone appeared to be a mixture, and similar treatment with methyl iodide gave inconclusive results.

Hydrogenolysis of 1,4-Bis(3′,5′-dimethoxybenzyl)-1,4-diazabicyclo[2.2.1]heptane (1e) Diperchlorate.—Perchlorate salt 1e (0.6 g) in aqueous (200 ml) solution was hydrogenated for 18 hr at room temperature using 10% palladium on carbon (0.10 g) as catalyst. Isolation of product was accomplished as summarized for 1c to yield **1-methyl-4-(3′,5′-dimethoxybenzyl)piperazine (8b)** diperchlorate (0.45 g, mp 165–168°). A pure specimen was obtained by three crystallizations from ethanol–diethyl ether: mp 190–191.5°; ir ν_{max} 3010, 2800, 1600 (d), 1470 (d), 1120 (br), and 640 cm^{-1}; nmr δ 3.1 (s, 3 methyl H), 3.7 (s, 8 H), 3.95 (s, 6 methoxyl H). 4.4 (s, 2 benzyl H), 6.8 (s, 4 aromatic H).

Anal. Calcd for $C_{14}H_{24}Cl_2N_2O_{10}$: C, 37.25; H, 5.37; Cl, 15.71; N, 6.21. Found: C, 37.18; H, 5.49; Cl, 15.60; N, 6.29.

Hydrogenolysis of 1,4-Bis(3′,4′,5′-trimethoxybenzyl)-1,4-diazabicyclo[2.2.1]heptane (1f) Dichloride.—Using 0.10 g of 5% palladium on carbon, chloride salt 1f, (0.8 g) in water (50 ml) was hydrogenated (7.5 hr) at room temperature. Treatment as with 1c yielded a colorless solid (0.5 g) homogeneous by thin layer chromatography. Three crystallizations from acetone–ethanol–hexane afforded a pure sample shown to be **1-methyl-4-(3′,4′,5′-trimethoxybenzyl)piperazine (8c)** dihydrochloride by infrared spectral comparison and mixture melting point determination with an authentic sample (see below): mp 181–183°; mmp 180–183°.

1-Methyl-4-(3′,4′,5′-trimethoxybenzyl)piperazinium (8c) Dihydrochloride.—A solution of 1-methyl-4-(3′,4′,5′-trimethoxybenzoyl)piperazine[17] (13.0 g) in tetrahydrofuran (50 ml) and a solution of diborane in tetrahydrofuran[18] (160 ml of 1 *M*) were combined at ice bath temperature and allowed to stand for 24 hr at room temperature. The solution was cooled (ice bath) and concentrated hydrochloric acid (20 ml) was added. After removal of tetrahydrofuran at reduced pressure, the resulting white slurry was diluted with ice water, made basic with 50% potassium hydroxide solution, and extracted with diethyl ether (100 ml). The ether layer was washed with water (50 ml) and saturated with hydrogen to yield crude 8c dihydrochloride (2.35 g). Three crystallizations from the same solvent afforded a pure sample as needles: mp 184–185°; ν_{max} 3300 (br), 2610 (br), 1600, 1470, 1430, 1250, and 1130 cm^{-1}; nmr δ 3.1 (s, 3 methyl H), 3.7 (s, 8 H), 3.9 (s, 3 methoxyl H), 3.95 (s, 6 methoxyl H), 4.4 (s, 2 benzylic H), and 6.9 ppm (s, 2 aromatic H).

Anal. Calcd for $C_{15}H_{26}Cl_2N_2O_3$: C, 50.98; H, 7.43; Cl, 20.07; N, 7.93. Found: C, 50.91; H, 7.43; Cl, 19.96; N, 7.85.

Attempted Hydrogenolysis of 1,4-Diethyl-1,4-diazabicyclo-[2.2.1]heptane Diperchlorate (1b).—Perchlorate salt 1b (0.5 g) in water (100 ml) was hydrogenated over 10% palladium on carbon. After 24 hr, no hydrogen had been absorbed. Treatment as for 1c gave starting salt (0.4 g) as evidenced by a nmr spectrum.

Registry No.—1 (R = 3′-chlorobenzyl), 20429-61-2; 1 (R = 2-cyclopentylethyl), 20445-46-9; 1 (R = 2-phenylethyl), 20429-54-3; 1 (R = 2(3′,4′,5′-trimethoxy-

(14) F. Daniels, J. H. Mathews, J. W. Williams, P. Bender, and R. A. Alberty, "Experimental Physical Chemistry," Fifth ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp 68–71.

(15) While it would be possible to use the observed freezing point depression to arrive at a formula weight consistent with a dimer or higher polymer of $C_9H_{18}Cl_2N_2$ (by inserting the larger number of ions per gram formula weight into the van't Hoff equation), such experimental formula weights would be lower than calculated values (by 9% in the case of a dimer). For this reason, higher multiples of the 426 formula weights were considered unlikely.

(16) G. R. Pettit and R. L. Smith, *Can. J. Chem.*, **42**, 572 (1964).

(17) G. Gerbai, G. DiPaco, and G. Dell'Omadarme, *Boll. Chim. Farm.*, **101**, 211 (1962); *Chem. Abstr.*, **59**, 6403*h* (1963).

(18) Employed as received from Metal Hydrides Division, Ventron Corp.

phenylethyl), 20429-55-4; **1a** (diperchlorate), 1020-94-6; **1b** (diperchlorate), 20445-47-0; **1c** (diperchlorate), 15567-89-2; **1d** (diperchlorate), 1083-67-6; **1e** (diperchlorate), 20429-72-5; **1f** (dichloride), 20429-73-6; **8b** (2 $HClO_4$), 20429-60-1; **8c** (2HCl), 20429-59-8.

Novel Reactions of 3-Unsubstituted 3-Isoxazolin-5-ones

DARRELL J. WOODMAN, CORNELIUS H. BORMAN, NARONGSAK TONTAPANISH, AND PETER M. STONEBRAKER

Department of Chemistry, University of Washington, Seattle, Washington 98105

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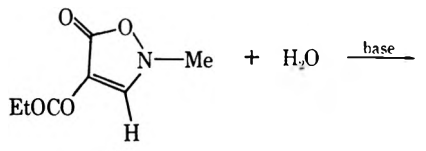
The reaction of 2,4-diphenyl-3-isoxazolin-5-one, **4**, and ethoxide gives ethyl 2-phenylmalonanilate, **7**, while that of 2-methyl-4-carbethoxy-3-isoxazolin-5-one, **2**, with acetate gives an enolic C-acyl derivative, **23** (R = Me). Both reactions may involve rearrangement of the normal ring-opening products.

The base-catalyzed ring opening of 3-unsubstituted 3-isoxazolin-5-ones was shown to involve abstraction of the proton from the 3-position and rupture of the N–O bond by Ulrich, Tilley, and Sayigh,[1] who obtained ethyl N-methylmalonamate, **1**, from the treatment of 2-methyl-4-carbethoxy-3-isoxazolin-5-one, **2**, with aqueous base. An alternative pathway for ring

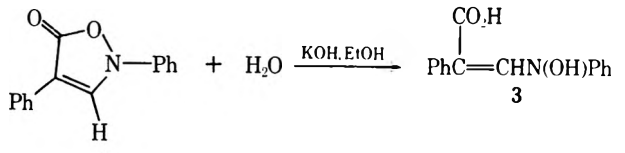


2

CO_2 + $EtOCOCH_2CONHMe$

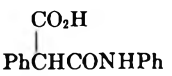
1

opening, cleavage of the ester function, had been proposed earlier by Rupe and Grünnolz,[2] who reported the isolation of 3-(N-hydroxy)anilinoatropic acid, **3**, from the reaction of 2,4-diphenyl-3-isoxazolin-5-one, **4**, with ethanolic potassium hydroxide. Fabbrini, Renzi, and



4 **3**

Speroni[3] accepted this latter pathway for the formulation of the products in a related case, but later DeSarlo and Renzi[4] demonstrated that, in fact, fission of the N–O bond is a general reaction and that the product assigned structure **3** is actually 2-phenylmalonanilic acid, **5**.



5

In the course of an independent study of isoxazolones, we also identified the product from **4** as **5**[5] and found, in addition, that the reactions of **4** and **2** with ethoxide and acetate ions, respectively, give ring-opening products of unexpected structure.

In support of the mode of ring opening they had proposed, Rupe and Grünholz[2] showed that the same compound, which they formulated as **6**, was obtained both from **4** and potassium hydroxide in ethanol and from esterification of the acid they thought to be **3**. In our reexamination of this work, we found, instead, that the product is ethyl 2-phenylmalonanilate, **7**, the ester of **5**.

6 **7**

The possibility that ethoxide actually might attack the 5 position of **4** to give **6** is ruled out by the nmr spectrum of the compound, which lacks the characteristic low-field signals expected for the olefinic and hydroxyl protons of the vinylogous hydroxamic acid function of **6**.[7] Similarly, while the spectral properties are in complete accord with **7**, the tautomers **8** and **9**, which might be obtained directly from the ring opening with N–O bond rupture, are excluded by the absence of any nmr signal or ir band in the regions indicative of the carboxylic acid proton.[9]

8 **9**

Our major interest in the 3-unsubstituted isoxazolones stemmed from the potential synthetic utility of the reaction with carboxylic acid anions. Specifically, the ring opening of **2** with carboxylate, followed by decarboxylation, would be expected to give **10** (or **11**) (Scheme I), which closely resembles the intermediates **12** (or **13**) in the isoxazolium salt method of peptide synthesis.[11]

Facile 6-center intramolecular acyl migrations are

(1) H. Ulrich, J. N. Tilley, and A. A. Sayigh, *J. Org. Chem.*, **27**, 2160 (1962).

(2) H. Rupe and J. Grünholz, *Helv. Chim. Acta*, **6**, 102 (1923).

(3) L. Fabbrini, G. Renzi, and G. Speroni, *Chim. Ind.* (Milan), **43**, 1195 (1961).

(4) F. DeSarlo and G. Renzi, *Tetrahedron*, **22**, 2935 (1966).

(5) J. D. Jacobsen and J. V. Van Ornum,[6] unpublished results.

(6) National Science Foundation Undergraduate Research Participant, 1967.

(7) Both signals appear downfield from the aromatic proton signal in the related compound 3-(N-hydroxy)anilinoacrylophenone.[8] The conceivable nitrone tautomer of **6** also would have a low-field aldehydic signal and would be inconsistent with the NH band in the infrared spectrum.

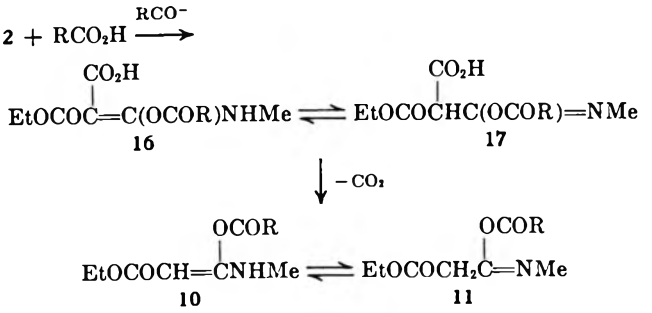
(8) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

(9) The $=NH—^+$ ir band of the possible zwitterionic form of **9** also would appear at long wavelength, comparable with that of the carboxylic acid absorption.[10]

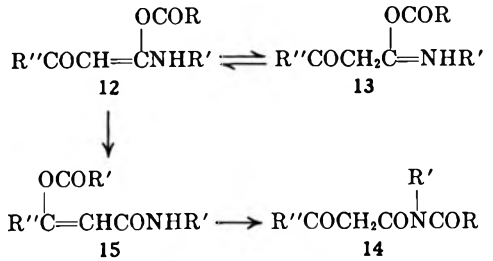
(10) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 39.

(11) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **8**, 321 (1966).

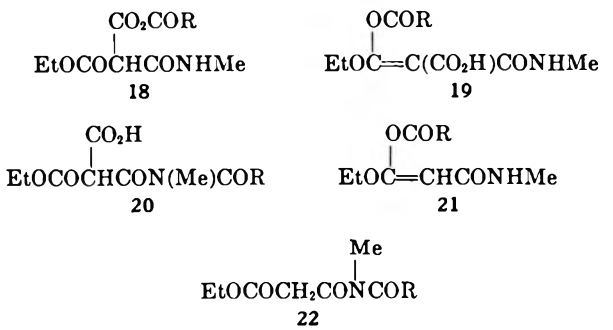
SCHEME I



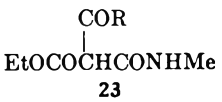
known to convert **12** (or **13**) to the imide **14** *via* the enol ester **15**.[7,12] Comparable rearrangements, beginning



with **16** (or **17**) and decarboxylation, were anticipated to provide routes to **18**, **19**, **20**, **21**, and **22**, and, by analogy with the isoxazolium salt results, the ultimate, most stable product would be the imide **22**.



Ulrich, Tilly, and Sayigh[1] had treated **2** with aqueous sodium acetate, but they obtained **1**, which could have been formed by competitive attack by hydroxide or by hydrolysis of the product from attack by acetate. To avoid either complication, we combined **2** with acetic acid and triethylamine in chloroform. Monitoring by nmr revealed slow conversion of **1** to a single major product. Elemental analysis of the compound showed that decarboxylation had taken place, while hydrolysis to **1** indicated that the product was an acetyl derivative of **1**.[13] Surprisingly, however, the nmr spectrum rules out all of the anticipated structures in which the acyl group is attached to one of the heteroatoms. The spectrum includes the characteristic signals for the ethyl, acetyl, and –NHMe groups, together with a signal at extremely low field indicative of an enolic proton. The absence of an nmr signal for other hydrogen attached to carbon is inconsistent with all of the possible tautomeric forms of all of the candidates **10**,



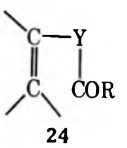
11, **21**, and **22**. The only remaining position for attachment of the acyl group is the central carbon, and an enol of the C-acyl isomer **23** (R = Me) satisfactorily accounts for the spectrum.

The formation of both unusual products **7** and **23** in these reactions can be rationalized as involving subsequent rearrangements of the expected, normal ring-opening products, although alternative mechanisms have not been excluded.

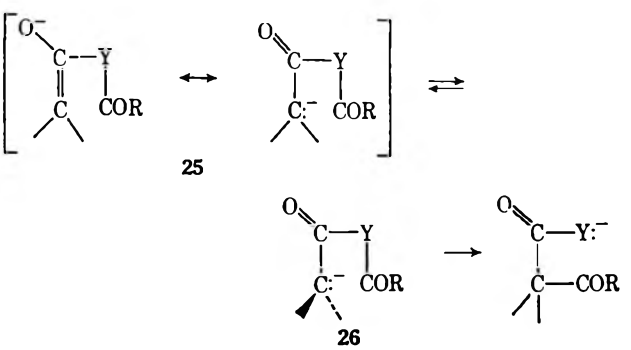
If the reaction of ethoxide and **4** gives **8** or **9** initially, conversion to **7** might be achieved by intramolecular alkylation of the carboxylate ion of either tautomeric intermediate or of the derived zwitterion.

In the case of reaction of **2** with acetate, migration of the acyl group to carbon could be the result of intermolecular processes in which one intermediate serves to acylate the central carbon of an anion from another intermediate or from **1**, although intermolecular reactions of that type are not observed to compete with the intramolecular rearrangements in the closely related reaction sequence leading to **14**.

A second possibility to account for **23** would be 4-center intramolecular acyl migration to carbon. Rearrangement of this type would not be expected for **19** and **21**, because of the stereoelectronic prohibition against acyl migration to terminal carbon in allyloid system **24** (where Y is a heteroatom).[15] However, the



anions available in the basic reaction medium from **10** (or **11**), **16** (or **17**), **18**, **20**, and **22** might circumvent this difficulty, since the electron-withdrawing substituents in the ions (of the type **25**) could afford stabilization of the rotamer **26**, which has the proper geometry for acyl transfer. Again, this reaction was not



observed either to compete with rearrangements leading to **14** in the studies with isoxazolium salts or to occur when **14** itself was subjected to basic conditions. It could be that the 4-center process is especially favorable in the present system, because of the availability of ions from **16** (or **17**), **18**, and **20**, still bearing the carboxyl group, which would have two electron-withdrawing substituents to stabilize **26**. Of these possibilities, **18** is particularly appealing as a precursor of **23**,

(12) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, **7**, 415 (1966).

(13) Selective attack at the acetyl group rather than the amide or ester functions of **23** was expected by analogy with the results of basic hydrolysis of acetylmalonic acid diesters.[14]

(14) G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3855 (1965).

(15) D. Y. Curtin and L. L. Miller, *ibid.*, **89**, 637 (1967).

since it would not be subject to competitive decarboxylation.

Experimental Section

Ethyl 2-Phenylmalonanilate (7).—A catalytic amount of Na metal was added to a suspension of 0.237 g (1.0 mmol) of **4** in 2 ml of absolute EtOH in a dry reaction vessel. The mixture was allowed to stand overnight, giving a yellow-green solution. Evaporation of the solvent and recrystallization of the residue from ethanol–water gave 0.080 g (30%) of the ester **7**, mp 86°; ir (KBr) 3.01 (NH), 5.74 (ester C=O), 6.05 (amide I), and 6.56 μ (amide II); nmr τ 8.76 (t, 3, J = 7.0 Hz), 5.78 (q, 2, J = 7.0 Hz), 5.40 (s, 1), 2.74 (s, 10), and 1.04 (br, 0.96).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; O, 16.94. Found: C, 71.96; H, 5.91; N, 4.96; O, 17.13.

Reaction of 2-Methyl-4-carbethoxy-3-isoxazolin-5-one (2) with Acetic Acid and Triethylamine.—The nmr spectrum was taken at intervals of a solution of 0.171 g (1.0 mmol) of **2**, 0.14 ml (1.0 mmol) of Et_3N, and 0.05 ml (1.0 mmol) of HOAc in 0.80 ml of $CDCl_3$. After several days, no **2** remained, and the spectrum was that of an enol of **23** (R = Me) isolated below. Evaporation of the solvent and sublimation (0.25 mm at 25°) gave a pure sample of the product, mp 32–33°; ir 3.04, 5.97, and 6.38 μ; nmr τ 8.73 (t, 3, J = 7.0 Hz), 7.70 (s, 3), 7.06 (d, 3, J = 4.5 Hz), 5.93 (q, 2, J = 7.0 Hz), 1.42 (br, 1), −7.96 (s, 1).

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; O, 34.19. Found: C, 51.25; H, 7.02; N, 7.30; O, 34.06.

Stirring a sample of the product in water with a slight excess of sodium hydroxide resulted in hydrolysis to **1** (identified by nmr comparison with an authentic sample).

Registry No.—**7**, 20628-57-3; **23** (R = Me), 20628-58-4.

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A Novel Benzimidazole Reaction

ROBERT K. HOWE

Research Department, Agricultural Division, Monsanto Company, St. Louis, Missouri 63166

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Reaction of benzimidazole with ethoxymethylenemalononitrile in ethanol produces **3a** instead of the expected **2** *via* further reaction of **2**. Thermal rearrangement of **4** also produces **3a**. The reaction of benzimidazole with ethoxymethylene compounds was extended to the preparation of **3b** and **3c**, **5a** and **6b**, **7a** and **7b**, and **8a** and **8b**. This reaction illustrates the principle of activation of imidazole rings toward nucleophilic attack by placing sufficiently electron-withdrawing substituents on the ring nitrogen atom.

Reaction of aliphatic and aromatic amines with ethoxymethylenemalononitrile (EMMN) leads to aminomethylenemalononitriles[1] (**1**). In the course of

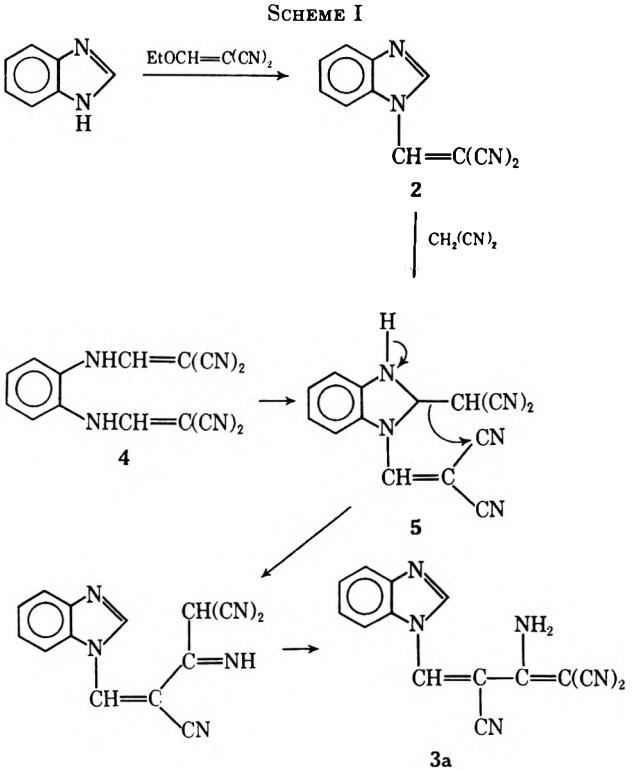
$$RR'NH + EtOCH{=}C(CN)_2 \longrightarrow \underset{\mathbf{1}}{RR'NCH{=}C(CN)_2}$$

synthesis of benzimidazole derivatives for biological studies, we treated benzimidazole with EMMN. This report deals with the unexpected result of this reaction and with the extension of the reaction to a general synthesis of some novel imidazole and benzimidazole derivatives.

Reaction of benzimidazole with 1 equiv of EMMN in hot ethanol produced **3a** (76% yield based on EMMN) instead of the expected (1-benzimidazoyl)methylenemalononitrile (**2**) (see Scheme I). The structure of **3a** was determined by spectral means. The major features of the mass spectrum of **3a** consist of the parent ion at m/e 260, the base ion at m/e 118 (benzimidazole radical cation), and the lower mass region that is remarkably similar to that of benzimidazole itself. The uv spectrum (EtOH) of **3a** reveals the characteristic benzimidazole absorptions at 240 mμ (log ϵ 3.75), 273 (3.89), and 278 (3.50). The uv maxima (EtOH) reported[2] for benzimidazole itself are at 243 mμ (log ϵ 3.68), 272 (3.82), and 279 (3.81). The ir spectrum of **3a** reveals NH_2 and CN absorptions. The nmr spectrum (DMSO) of **3a** reveals the NH_2 signal at τ −1.91 (disappears upon addition of D_2O), the imidazole ring proton as a singlet at 0.42, the benzene ring protons as a multiplet centered at 2.25, and the aliphatic vinyl proton signal at 2.85.

The structure of **3a** was further indicated by an

SCHEME I

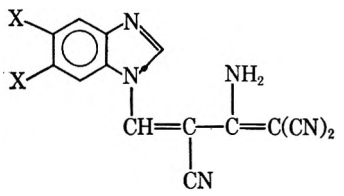


independent synthesis which started with reaction of *o*-phenylenediamine with 2 equiv of EMMN in ethanol at room temperature to give **4**. Thermal cyclization and intramolecular rearrangement of **4** in hot N,N-dimethylacetamide produced **3a** in 69% yield (Scheme I). Reaction of equimolar amounts of benzimidazole, EMMN, and malononitrile in ethanol also produces **3a** (92% yield); this is the preferred method.

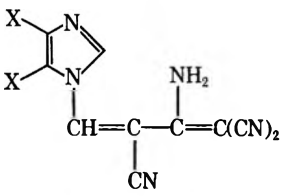
(1) A. A. Santilli, W. F. Bruce, and T. S. Osdene, *J. Med. Chem.*, **7**, 68 (1964).

(2) D. J. Rabiger and M. M. Joullié, *J. Org. Chem.*, **29**, 476 (1964).

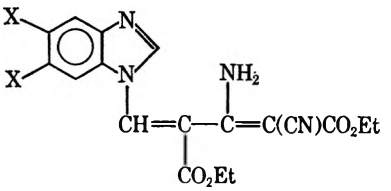
The reaction of benzimidazole with ethoxymethylene compounds and active methylene compounds was extended to the preparations of **3b** and **3c**, **6a** and **6b**, **7a** and **7b**, and **8a** and **8b**. An attempt to extend the reaction to the use of diethyl ethoxymethylenemalonate and diethyl malonate was unsuccessful.[3]



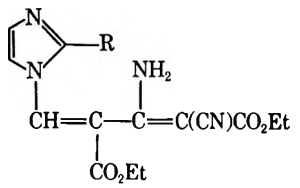
3a, X = H
b, X = CH_3
c, X = Cl



6a, X = H
b, X = C_6H_5



7a, X = H
b, X = CH_3



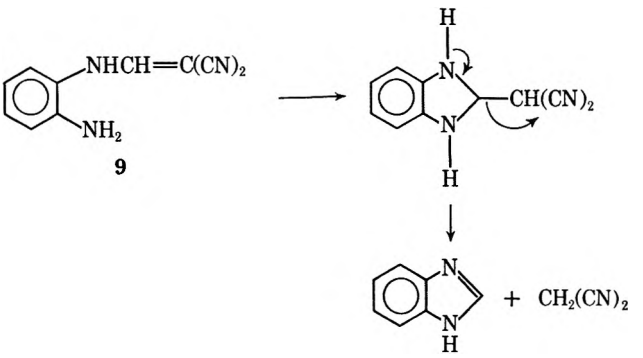
8a, R = H
b, R = CH_3

The most reasonable mechanisms for formation of **3a** from benzimidazole and from **4** are summarized in Scheme I. Evidently, malononitrile and triethyl orthoformate are produced in equilibrium with EMMN in ethanol. Reaction of benzimidazole with EMMN leads initially to **2** which could not be isolated because of its reactivity. The dicyanovinyl group is sufficiently electron withdrawing that the imidazole ring of **2** is strongly activated toward nucleophilic attack by malononitrile anion, which could be generated from malononitrile by proton transfer to unreacted benzimidazole. Intramolecular transfer of the dicyanomethyl group in **5** results in rearomatization and in a ring substituent that is less electron withdrawing. The product, **3a**, is considerably less susceptible to nucleophilic attack; an attempt to add a second molecule of malononitrile to **3a** was unsuccessful.

The first step of the rearrangement of **4** to **3a** *via* **5** parallels the first step of the reported[1] conversion of (2-aminoanilino)methylenemalononitrile (**9**) into benzimidazole (Scheme II). Intramolecular transfer instead of complete expulsion of the dicyanovinyl group in **5** leads to **3a**. An attempt to effect an intermolecular condensation of malononitrile with (3,4-dichloroanilino)-methylenemalononitrile, employing sodium methoxide as a catalyst, was unsuccessful.

(3) The attempt to extend the reaction to diethyl ethoxymethylenemalonate and diethyl malonate was unsuccessful probably because of the relative lack of reactivity of the carbethoxy group to condensation compared with a cyano group.

SCHEME II



Acylation of imidazole and benzimidazole under Schotten–Baumann conditions leads to fission of the imidazole ring *via* nucleophilic attack on the acylated imidazole ring.[4] Alkylation of benzimidazole with chlorotrifluoroethylene results in N-(2-chloro-1,1,2-trifluoroethyl)benzimidazole; this derivative is quite susceptible to nucleophilic attack on the imidazole ring with resultant ring opening followed by subsequent reactions dependent upon the nucleophile.[5] The present work provides another example of activation of imidazole rings toward nucleophilic attack by placing sufficiently strong electron-withdrawing groups on the ring nitrogen atom. This principle lends itself to the synthesis of a whole host of novel compounds through judicious selection of the alkylating or acylating agents and of the nucleophiles.

Experimental Section

Melting points were taken in open capillary tubes with a Mel-Temp apparatus and are corrected. Infrared spectra were determined on the compounds in mineral oil mulls with a Beckman IR-5 spectrometer. Nmr spectra were determined on the compounds in DMSO-d_6 solution with internal tetramethylsilane standard with a Varian A-60 spectrometer.

[*o*-Phenylenebis(iminomethylidyne)]dimalononitrile (4).—A mixture of 100 g (0.926 mol) of *o*-phenylenediamine and 244 g (2.00 mol) of ethoxymethylenemalononitrile in 1500 ml of ethanol was stirred for 2.5 hr at room temperature. The resultant solid, mp 203° dec, was collected and digested with 1.5 l. of hot acetone. The insoluble solid was collected and washed with acetone and ether to give 128 g (53%) of white solid: mp 202–203° dec; nmr τ −0.70 (bs, 2, NH), 1.80 [s, 2, CH=C(CN)$_2$], 2.59 (s, 4, ArH).

Anal. Calcd for $C_{14}H_8N_6$: C, 64.61; H, 3.10; N, 32.29. Found: C, 64.60; H, 3.38; N, 32.02.

2-Amino-4-(1-benzimidazolyl)-1,3-butadiene-1,1,3-tricarbonitrile (3a). Method A.—A solution of 11.8 g (0.10 mol) of benzimidazole, 12.2 g (0.10 mol) of ethoxymethylenemalononitrile, and 6.6 g (0.10 mol) of malononitrile in 200 ml of ethanol was held for 43 hr at reflux and then was allowed to cool. The resultant solid was collected and washed with ethanol to give 24 g (92%) of product: mp 223–224°; ir 3.03, 3.18 (NH), 4.57 (CN), 6.18 (weak), 6.46 μ; uv max (EtOH) 202 mμ (log ϵ 4.5), 240 (3.75), 261 (3.72), 267 (3.84), 273 (3.89), 278 (3.50), 344 (4.51); nmr τ −1.91 (bs, 2, NH_2), 0.42 (s, 1, N=CHN), 2.25 (multiplet, 4, ArH), 2.85 (s, 1, NCH=C).

Anal. Calcd for $C_{14}H_8N_6$: C, 64.61; H, 3.10; N, 32.29; mol wt, 260. Found: C, 64.48, 64.39; H, 3.08, 3.13; N, 32.36, 32.43; mol wt, 259, 262 (osmometry in tetrahydrofuran), 260 (mass spectrometry).

Method B.—A solution of 40 g (0.339 mol) of benzimidazole and 41.5 g (0.340 mol) of ethoxymethylenemalononitrile in 300

(4) K. Hofmann, "Imidazole and Its Derivatives, Part I," Interscience Publishers, Inc., New York, N. Y., 1953, pp 47, 48, 273–276.

(5) W. Reid and H. Lohwasser, *Angew. Chem. Intern. Ed. Engl.*, **5**, 835 (1966).

ml of ethanol was held for 4 days at reflux. The solution was allowed to cool. The resultant solid, 36.1 g, mp 204–215° dec, was crystallized from ethanol to give 33.9 g (76% based on ethoxymethylenemalononitrile) of solid, mp 225–226° dec. The ir spectrum of this material was identical with that of the product obtained by method A.

Method C.—A solution of 60 g (0.231 mol) of [*o*-phenylenebis(iminomethylidyne)]dimalononitrile in 600 ml of N,N-dimethylacetamide was stirred at 100° under nitrogen for 3 hr. The solution was concentrated under vacuum, and the residue was poured into 700 ml of water. The resultant solid, 51.6 g, mp 212–213° dec, was crystallized from 3 l. of hot water (filtration) to give 41.3 g (69%) of product, mp 223–224° dec. The ir spectrum of this material was identical with that of the products obtained by methods A and B.

2-Amino-4-(5,6-dimethyl-1-benzimidazolyl)-1,3-butadiene-1,1,-3-tricarbonitrile (3b).—Reaction of equimolar amounts of 5,6-dimethylbenzimidazole, ethoxymethylenemalononitrile, and malononitrile in ethanol at reflux for 5 days gave white needles, mp 255–256° dec (from ethanol with charcoal treatment), in 75% yield: ir 3.03 sh, 3.20 (NH), 4.58 (CN), 6.20 (weak), 6.46 (C=C) μ; nmr τ −3.95 (s, 2, NH_2), 0.57 (s, 1, N=CHN), 2.42 (s, 2, ArH), 2.93 (s, 1, NCH=C), 7.59 (s, 6, CH_3).

Anal. Calcd for $C_{16}H_{12}N_6$: C, 66.66; N, 4.20. Found: C, 66.50; H, 4.20.

2-Amino-4-(5,6-dichloro-1-benzimidazolyl)-1,3-butadiene-1,1,-3-tricarbonitrile (3c).—*Caution: skin irritant.* By a procedure similar to that employed for **3b** (reaction time, 1 day), the product, mp 268° dec (placed in melting point apparatus at 261°; melting point dependent on rate of heating), was obtained in 71% yield: ir 3.20 (NH), 4.56 (CN), 6.20 (weak), 6.50 μ.

Anal. Calcd for $C_{14}H_6Cl_2N_6$: C, 51.09; H, 1.84; N, 25.53. Found: C, 51.01; H, 1.75; N, 25.57.

2-Amino-4-(1-imidazolyl)-1,3-butadiene-1,1,3-tricarbonitrile (6a).—From equimolar amounts of imidazole, ethoxymethylenemalononitrile, and malononitrile in ethanol solution was obtained, after 18 hr at 23°, a solid product, mp 163–165°, in 46% yield: ir 3.1, 3.2 (NH), 4.58 (CN), 6.35, 6.48 μ; nmr τ −3.75 (bs, 2, NH_2), 0.70 (t, 1, J = 1 Hz, N=CHN), 2.07 (d, 2, J = 1 Hz, HC=CH), 2.82 (s, 1, NCH=C).

Anal. Calcd for $C_{10}H_6N_6$: C, 57.14; H, 2.87; N, 39.98. Found: C, 56.88; H, 2.94; N, 39.79.

2-Amino-4-(4,5-diphenyl-1-imidazolyl)-1,3-butadiene-1,1,3-tricarbonitrile (6b).—A solution of 11.0 g (0.050 mol) of 4,5-diphenylimidazole and 12.2 g (0.10 mol) of ethoxymethylenemalononitrile in 150 ml of ethanol was held for 4 days at reflux. The solvent was removed under vacuum, and the residual solid was crystallized from aqueous ethanol (charcoal) to give 4.3 g (24%) of product: mp 204–205° dec; ir 3.20 (NH), 4.57 (CN), 6.50 μ.

Anal. Calcd for $C_{22}H_{14}N_6$: C, 72.92; H, 3.89. Found: C, 72.82; H, 3.93.

Diethyl 3-Amino-4-(1-benzimidazolylmethylene)-2-cyanoglutaconate (7a).—A solution 11.8 g (0.10 mol) of benzimidazole, 16.9 g (0.10 mol) of ethyl 2-cyano-3-ethoxyacrylate, and 11.3 g (0.10 mol) of ethyl cyanoacetate in 100 ml of ethanol was held for 4 days at reflux and then was allowed to cool. The resultant solid, 28.0 g (79%), mp 193–195°, was collected: ir 3.2 (NH), 4.56 (CN), 5.90, 6.12, 6.20, 6.50 μ; nmr τ −3.19 (bs, 2, NH_2), 0.43 (s, 1, N=CHN), 1.93 (s, 1, NCH=C), 2.25 (multiplet, 4, ArH), 5.90 (q, 4, OCH_2CH_3), 8.80 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.11; N, 15.81. Found: C, 60.77; H, 5.20; N, 15.64.

Diethyl 3-Amino-2-cyano-4-[(5,6-dimethyl-1-benzimidazolyl)methylene]glutaconate (7b).—Prepared by the procedure for **7a** with a reaction time of 19 hr, the product, mp 203–204°, was obtained in 65% yield: nmr τ −3.51 (bs, 2, NH_2), 0.57 (s, 1, N=CHN), 1.94 (s, 1, NCH=C), 2.37 (s, 2, ArH), 5.92 (q, 4, OCH_2CH_3), 7.59 (s, 6, CH_3), 8.82 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{20}H_{22}N_4O_4$: C, 62.82; H, 5.80; N, 14.65. Found: C, 62.55; H, 5.84; N, 15.00.

Diethyl 3-Amino-2-cyano-4-[(1-imidazolyl)methylene]glutaconate (8a).—Prepared by the procedure for **7a**, the product obtained after removal of the solvent was crystallized from water to give a yellow solid, mp 152–154°, in 59% yield: nmr τ −3.62 (bs, 2, NH_2), 0.91 (t, 1, J = 1 Hz, N=CHN), 1.91 (s, 1, NCH=C), 2.31 (d, 2, J = 1 Hz, HC=CH), 5.91 (q, 4, OCH_2CH_3), 8.82 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.14; H, 5.38; N, 18.20.

Diethyl 3-Amino-2-cyano-4-[(2-methyl-1-imidazolyl)methylene]glutaconate (8b).—Prepared by the procedure for **7a**, the product, mp 183–185°, was obtained in 91% yield: nmr τ −2.11 (b, 2, NH_2), 1.91 (s, 1, NCH=C), 2.43 (s, 2, HC=CH), 5.90 (q, 4, OCH_2CH_3), 7.41 (s, 3, CH_3), 8.82 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.62; H, 5.82; N, 17.40.

Registry No.—**3a**, 20406-91-1; **3b**, 20406-92-2; **3c**, 20546-01-4; **4**, 20406-93-3; **6a**, 20406-98-8; **6b**, 20406-94-4; **7a**, 20406-99-9; **7b**, 20406-95-5; **8a**, 20406-96-6; **8b**, 20406-97-7.

The Synthesis of Substituted 2,1-Benzisothiazoles

MICHAEL DAVIS AND ALEX W. WHITE

Department of Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia

Received March 7, 1969

2,1-Benzisothiazole (**3**) and nine substituted 2,1-benzisothiazoles have been synthesized by the reaction of thionyl chloride with an appropriately substituted 2-aminotoluene (*o*-toluidine) in xylene at reflux temperature. Yields as high as 80% may be obtained. Liquid benzisothiazoles are conveniently isolated as picrate salts. The mechanism of formation of **3** is discussed and an intermediate benzylidenesulfinyl compound (**8**) is postulated. Nmr and uv data are presented.

2,1-Benzisothiazole (**3**) and its derivatives have received little attention from chemists in the 70 years since the parent compound was prepared by Gabriel and Stelzner.[1] The original method, reduction by stannous chloride and hydrochloric acid of 2-nitrotoluene-α-thiol, was recently supplemented by a procedure involving the iodine oxidation of an alkaline solution of 2-aminotoluene-α-thiol.[2]

Both of these methods suffer from the disadvantage of requiring relatively inaccessible, air-sensitive thiols, and, although in principle such methods could be extended to the synthesis of many substituted 2,1-benzisothiazoles, in practice such an approach is tedious. In exploratory work, we prepared 5-bromo-2,1-benzisothiazole by the oxidative cyclization of the corresponding aminothiol, but the yield was low. The only substituted 2,1-benzisothiazoles so far reported are those with 3-amino substituents, prepared by peroxide oxidation of 2-aminophenylthioamides.[3,4] By contrast,

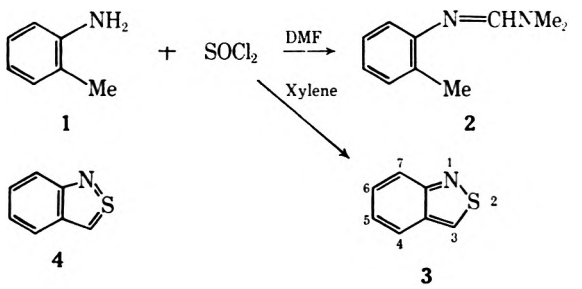
(1) S. Gabriel and R. Stelzner, *Chem. Ber.*, **29**, 160 (1896).
(2) J. Goerdeler and J. Kandler, *ibid.*, **92**, 1679 (1959).
(3) Parke, Davis & Co., Netherlands Patent Application 6408290 (1965); *Chem. Abstr.*, **63**, 17686 (1965).
(4) R. F. Meyer, B. L. Cummings, P. Bass, and H. O. J. Collier, *J. Med. Chem.*, **8**, 515 (1965).

there exists a considerable literature on 2,1-benzisoxazoles[5] and on 1,2-benzisothiazoles.[6]

Recent reports by Naito and coworkers[7,8] on the use, in dimethylformamide solution, of thionyl chloride and sulfur monochloride for construction of the isothiazole ring from compounds containing an amino group and a relatively activated methylene group three carbon atoms removed suggested to us the possibility that 2,1-benzisothiazole might be obtained from a reaction between 2-aminotoluene (**1**) (*o*-toluidine[9]) and thionyl chloride. Although in this latter case the methyl group is not activated, earlier studies in our laboratory[10] on the chemistry and nmr spectrum of 2,1-benzisothiazole had indicated that this compound is surprisingly stable and might well be formed under vigorous reaction conditions.

In view of the current interest in valence-shell expansion in sulfur heterocycles,[11] we note in passing that the properties of 2,1-benzisothiazole indicate a substantial contribution from the tetracovalent sulfur structure **4**.

Reaction between **1** and thionyl chloride in DMF under the general conditions used by the Japanese workers[7,8] afforded the amidine **2** as the main product. No 2,1-benzisothiazole (**3**) could be detected. However, we found that, if xylene were used as the solvent, **3** was formed in reasonable yield, as reported by us in an earlier communication.[12]



We now find that this reaction is a general one, and that substituted 2,1-benzisothiazoles may be prepared from the corresponding substituted 2-aminotoluenes in yields as high as 80%. So far, only 2-amino-5-nitrotoluene has failed to yield the desired product.

The greater basicity of the 2-aminotoluenes and the usually slight solubility of their hydrochlorides in hydrochloric acid can be exploited for a simple separation of the 2,1-benzisothiazoles from the reaction mixtures, which usually contain sulfur and an N-sulfinylarylamine as well as the desired product. 2,1-Benzisothiazoles that are liquids or low-melting solids are conveniently isolated as their picrates. The 2,1-benzisothiazoles and their picrates prepared by the new method are listed in Tables I and II.

TABLE I

MELTING POINTS, BOILING POINTS, NMR DATA, AND MICROANALYSES OF SOME 2,1-BENZISOTHIAZOLES

Registry no.	Substituent	Mp or bp, °C (mm)	τ, H-3[a]	Analyses (calcd, % / found, %) C	H	N	S
271-6-4	None	68 (0.5)[b]	1.07 d	...	...	...	...
20712-04-3	4-Cl	41–42	0.67 d	49.6	2.4	8.2	18.9
20728-40-9 (picrate)				49.8	2.4	8.1	18.7
20712-05-4	5-Cl[c]	72	0.98 d	49.6	2.4	8.2	18.9
				49.7	2.6	8.1	19.0
20712-06-5	6-Cl	71	0.84 d	49.6	2.4	8.2	18.9
				49.7	2.1	8.0	18.6
20712-07-6	5-Br[d]	85	0.91 d	39.3	1.9	6.5	14.9
				39.4	1.9	6.7	14.4
20712-08-7	6-Br[e]	81	0.82 d	39.3	1.9	6.5	14.9
				39.4	1.9	6.7	14.9
20712-09-8	3-CH_3	103	...	64.4	4.7	9.4	21.5
				64.6	4.6	9.1	21.2
20728-41-0	4-CH_3	116 (2)	1.03 d	64.4	4.7	9.4	21.5
20728-42-1 (picrate)				64.3	4.8	9.1	21.0
20712-10-1	7-CH_3	106 (1)	0.91 s	64.4	4.7	9.4	21.5
20728-43-2 (picrate)				64.2	4.7	9.1	21.4
20712-11-2	6-NO_2	149	0.65 d	46.7	2.3	15.5	17.8
				46.8	2.5	15.4	17.5

[a] In $CDCl_3$. [b] Lit.[1] bp 238° (760 mm). [c] Cl: calcd 20.9, found 20.8%. [d] Br: calcd 37.4, found 37.7%. [e] Br: calcd 37.4, found 37.6%.

TABLE II

MELTING POINTS AND MICROANALYSES OF SOME 2,1-BENZISOTHIAZOLE PICRATES

Substituent	Mp, °C	Analyses (calcd, % / found, %) C	H	N	S
None	121[a]	...	...	...	...
4-Cl[b]	99	39.2	1.8	14.1	8.0
		39.5	1.9	13.9	8.0
4-CH_3	135	44.5	2.7	14.8	8.5
		44.6	2.8	14.4	8.2
7-CH_3	98	44.5	2.7	14.8	8.5
		44.5	2.7	14.7	8.8

[a] Lit.[1] mp 123°. [b] Cl: calcd 8.9, found 8.9%.

The known formation of N-sulfinylarylamines from the reaction of arylamines with thionyl chloride[13,14] and evidence of N-sulfinylamines in crude reaction mixtures suggested that 2-methyl-N-sulfinylarylamines, such as (**6**), are intermediates that undergo thermal cyclodehydration. We have found, however, that such compounds, when heated on their own or in high-boiling inert solvents, do not yield 2,1-benzisothiazoles. When heated in the presence of excess thionyl chloride, 2,1-benzisothiazoles are formed, indicating that thionyl chloride—or a product of thermal decomposition of thionyl chloride—is implicated in the cyclodehydration reaction which generates the heterocyclic ring. The following reaction scheme is suggested (Scheme I).

The initial vigorous reaction between **1** and thionyl chloride produces a yellow crystalline compound which is probably the sulfinyl chloride **5**; this, on heating, loses HCl forming the N-sulfinylamine **6**. Continued heating with excess thionyl chloride yields a sulfinyl chloride, **7**, which similarly loses a molecule of HCl. The resulting benzylidenesulfinyl compound **8** eliminates a

(5) K.-H. Wünsch and A. J. Boulton, *Advan. Heterocycl. Chem.*, **8**, 303 (1967).

(6) L. L. Bambas in "The Chemistry of Heterocyclic Compounds," "5-Membered Heterocyclic Compounds with Nitrogen and Sulfur, or Nitrogen, Sulfur, and Oxygen (except Thiazoles)," A. Weissburger, Ed., Interscience Publishers, Inc., New York, N. Y., 1952, p 227.

(7) T. Naito, S. Nakagawa, J. Okumura, K. Takahashi, and K. Kasai, *Bull. Chem. Soc. Jap.*, **41**, 959 (1968).

(8) T. Naito, S. Nakagawa, J. Okumura, K. Takahashi, K. Masuko, and Y. Narita, *ibid.*, **41**, 965 (1968).

(9) The literature betrays some ambiguity in the numbering of substituted *o*-toluidines. We prefer to name all of our compounds as derivatives of 2-aminotoluene to avoid confusion.

(10) M. Davis, B. Ternai, and A. W. White, unpublished results.

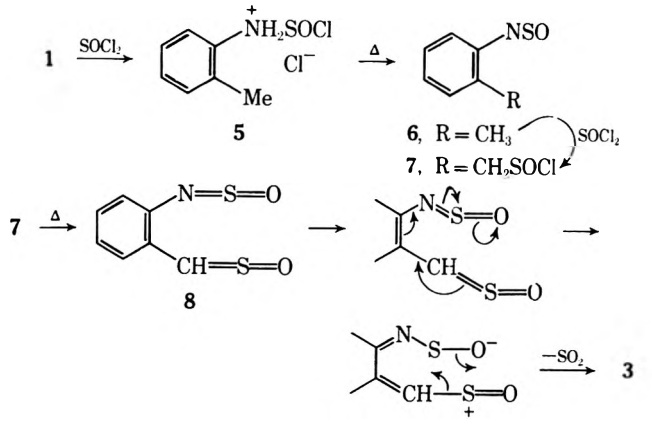
(11) W. G. Salmond, *Quart. Rev.* (London), **22**, 253 (1968).

(12) M. Davis and A. W. White, *Chem. Commun.*, 1547 (1968).

(13) G. Kresze, *Angew. Chem. Intern. Ed. Engl.*, **1**, 89 (1962).

(14) G. Kresze and W. Wucherpfennig, *ibid.*, **6**, 149 (1967).

Scheme I



molecule of SO_2, generating 2,1-benzisothiazole (**3**). This mechanism is supported by the failure of 5-nitro-2-aminotoluene to form a 2,1-benzisothiazole, even under forcing conditions, suggesting that an intramolecular nucleophilic attack of the N-sulfinyl group upon its *ortho*-substituent is the critical reaction. A *p*-nitro group might reasonably be expected to inhibit such an attack.

Optimum yields of 2,1-benzisothiazoles are obtained when the solvent used has a boiling point between 140 and 170°. Below 140° the reaction is too slow, and above 170° the reaction mixture becomes very black and viscous and the product is then difficult to isolate. We have found xylene (mixed isomers, bp 141–144°) convenient, although bromobenzene (bp 155°) and mesitylene (bp 163°) can also be used with success. Even at 140° some thermal decomposition occurs, and by-products isolated include not only sulfur and N-sulfinylamine, but also chlorinated derivatives of the 2-aminotoluene and of the product 2,1-benzisothiazole.

An attempt to form a novel isothiazolopyridine from 2-amino-3-methylpyridine yielded 2-amino-3-methyl-5-chloropyridine as the only isolated product.

Spectral Data.—The nmr spectrum of **3** shows a complex group of lines between τ 2 and 3, derived from the protons on the carbocyclic ring, and a doublet at τ 1.07 from the proton on the heterocyclic ring. This latter proton is weakly coupled with H-7 ($J \approx 1$ Hz). This doublet (or singlet if position 7 is substituted) is a characteristic feature of the spectra of substituted 2,1-benzisothiazoles, and τ values are listed in Table I. Uv maxima (in 95% EtOH) were at 203 nm (ϵ 14,300), 221 (16,400), 288 sh (7600), 298 (9100), and 315 sh (4000).

Experimental Section

All melting points are uncorrected and were obtained with the Büchi apparatus. Nmr spectra were recorded with a Varian A60-D spectrometer system. Analyses were by the Australian Microanalytical Service, Melbourne.

Chemicals.—Reagents prepared by methods in the literature included 2-amino-4-nitrotoluene,[15] 2-amino-5-nitrotoluene,[16] and 2-amino-4-bromotoluene.[17] Other reagents were obtained from Koch-Light Laboratories Ltd., Colnbrook, England.

2-Amino-5-bromobenzyl Alcohol.—This was prepared in quantitative yield by $LiAlH_4$ reduction of an ether solution of 2-amino-5-bromobenzoic acid.[18] It formed colorless needles (from MeOH), mp 112°.

Anal. Calcd for C_7H_8BrNO: C, 41.6; H, 4.0; Br, 39.6; N, 6.9. Found: C, 41.9; H, 4.1; Br, 39.7; N, 6.8.

6-Bromo-2-thio-4H-3,1-benzothiazine.—This was prepared (85% yield) from 2-amino-5-bromobenzyl alcohol by Kitamura's method.[19] It formed pale yellow needles (from EtOH), mp 235–236°.

Anal. Calcd for $C_8H_6BrNS_2$: C, 36.9; H, 2.3; N, 5.3; S, 24.6. Found: C, 36.6; H, 2.3; N, 5.1; S, 24.0.

6-Bromo-2-oxo-4H-3,1-benzothiazine.—The corresponding thio compound (above) was oxidized in alkaline solution with hydrogen peroxide.[20] The product (80% yield) formed colorless needles (from 50% ethanolic DMF), mp 176°.

Anal. Calcd for C_8H_6BrNOS: C, 39.3; H, 2.5; N, 5.7; S, 13.1. Found: C, 39.0; H, 2.5; N, 5.6; S, 13.0.

2-Amino-5-bromotoluene-α-thiol.—This was prepared from 6-bromo-2-oxo-4H-3,1-benzothiazine by alkaline hydrolysis under nitrogen.[19] The product (85% yield) formed colorless fluffy needles (from aqueous EtOH), mp 133°.

Anal. Calcd for C_7H_8BrNS: C, 38.6; H, 3.7; N, 6.4; S, 14.8. Found: C, 38.9; H, 3.7; N, 6.2; S, 15.1.

5-Bromo-2,1-benzisothiazole.—Iodine oxidation of an alkaline solution of 2-amino-5-bromotoluene-α-thiol by the method of Goerdeler and Kandler[2] afforded in low yield (less than 10%) 5-bromo-2,1-benzisothiazole, identical with that prepared from 2-amino-5-bromotoluene by the general procedure A below. Analyses for this and other 2,1-benzisothiazoles are given in Table I.

Reaction between 2-Aminotoluene and Thionyl Chloride in DMF.—Two grams (19 mmol) of 2-aminotoluene was mixed with 10 ml of DMF and 4 ml (55 mmol) of thionyl chloride was added. An exothermic reaction occurred and the mixture solidified. The mixture was left for 2 hr, water was added, and the solution was neutralized ($NaHCO_3$) and extracted with carbon tetrachloride. Evaporation of the dried extract afforded a pale yellow oil (2.4 g) which contained no 2,1-benzisothiazole (vpc). Infrared and nmr spectra indicated that the principal component of this mixture was 2,N,N-trimethylphenylformamidine (**2**).

Reaction of 2-Aminotoluenes with Thionyl Chloride. General Procedure. A. 6-Bromo-2,1-benzisothiazole.—To a solution of 5.8 g (31 mmol) of 2-amino-4-bromotoluene[17] in 15 ml of xylene (bp 141–144°) was added slowly 8 ml (100 mmol) of thionyl chloride. A vigorous reaction occurred and a yellow crystalline mass separated. The mixture was heated under gentle reflux for 24 hr, a further 8 ml of thionyl chloride was added, and heating was continued for another 24 hr. The mixture was cooled and 50 ml of concentrated hydrochloric acid was added. Sulfur dioxide, from the hydrolysis of the N-sulfinylamine,[13] was evolved. After standing for 30 min, with occasional stirring, the pasty mass was filtered through a coarse fritted filter. The aqueous layer was separated, washed with petroleum ether (bp 40–60°), and diluted with water to 250 ml. The resulting crystalline precipitate was recrystallized from aqueous methanol, affording almost colorless long needles of 6-bromo-2,1-benzisothiazole (2.7 g, 42%), mp 81°. The solid on the fritted filter was extracted with boiling water and yielded, after treatment with activated charcoal, colorless crystals (2.6 g, 39%) of the hydrochloride of 2-amino-4-bromotoluene, mp 246° subl, identified by direct comparison.

General Procedure. B. 4-Methyl-2,1-benzisothiazole.—The procedure A, using 6.1 g (50 mmol) of 2,3-dimethylaniline, was followed, but after dilution of the hydrochloric acid solution an emulsion of the 4-methyl-2,1-benzisothiazole was formed. This was extracted with chloroform, the extracts were dried and evaporated, and the residue was dissolved in 70 ml of a saturated solution of picric acid in methanol. The copious yellow precipitate was recrystallized from methanol, affording yellow needles (5.2 g, 28%) of the picrate of 4-methyl-2,1-benzisothiazole, mp 135°. Decomposition of the picrate salt with dilute sodium hydroxide solution yielded an oil, which was distilled, giving the pure free base, a very pale yellow oil, bp 116° (2 mm).

A list of the 2,1-benzisothiazoles and their picrate salts prepared by procedures A and B is given in Tables I and II. 2-Amino-5-nitrotoluene failed to yield a 2,1-benzisothiazole.

2-Methyl-N-sulfinylaniline (**5**).—This was prepared by the

(15) F. Ullman and E. Grether, *Chem. Ber.*, **35**, 337 (1902).
(16) H. J. Page and B. R. Heasman, *J. Chem. Soc.*, 3238 (1923).
(17) N. W. Janney, *Ann.* **398**, 359 (1913).
(18) A. S. Wheeler and W. M. Oates, *J. Amer. Chem. Soc.*, **32**, 770 (1910).
(19) R. Kitamura, *J. Pharm. Soc. Jap.*, **57**, 54 (1937); *Chem. Abstr.*, **36**, 3804[7] (1942).
(20) R. Kitamura *J. Pharm. Soc. Jap.*, **54**, 1 (1934); *Chem. Abstr.*, **30**, 3434[2] (1936).

procedure given by Kresze;[13] it was a pale yellow oil, bp 73° (0.5 mm) [lit.[21] 184° (100 mm)].

Reactions of 2-Methyl-N-sulfinylaniline (5).—The heating of this compound on its own, or in solution, at temperatures between 100 and 200°, failed to yield any 2,1-benzisothiazole. If, however, thionyl chloride was added to a solution of **5** in xylene, or other inert solvent with a boiling point of between about 140 and 170°, and the mixture was heated to reflux, then 2,1-benzisothiazole could be detected in the reaction mixture by vpc within a few minutes. Formation of 2,1-benzisothiazole paralleled the disappearance of thionyl chloride; it ceased when the latter was exhausted, and could be reestablished by further addition of thionyl chloride. In this way, using 3 or more equiv of thionyl chloride, yields of up to 80% (by vpc) of 2,1-benzisothiazole could be produced. However, the increasing viscosity and darkening of the reaction mixture led to difficulties in isolation of the product. 2-Amino-5-chlorotoluene (as its N-sulfinyl derivative) and 5-chloro-2,1-benzisothiazole were also formed in this reaction in yields of a few percent. Doubtless the chlorine came from the thermal decomposition of the thionyl chloride.

(21) A. Michaelis, *Ann.*, **274**, 226 (1893).

Reaction of 2-Amino-3-methylpyridine with Thionyl Chloride.—A mixture of 5.4 g (50 mmol) of 2-amino-3-methylpyridine was treated with thionyl chloride and xylene as in general procedure A. Neutralization of the final dilute hydrochloric acid solution with ammonia solution afforded a yellow oil which crystallized slowly. On recrystallization from hot water, it afforded colorless leaflets (0.8 g, 11%) of 2-amino-5-chloro-3-methylpyridine, mp 66°.

Anal. Calcd for $C_6H_7ClN_2$: C, 50.5; H, 4.9; Cl, 24.9; N, 19.6. Found: C, 50.4; H, 4.8; Cl, 24.9; N, 19.6.

Registry No.—2-Amino-5-bromobenzyl alcohol, 20712-12-3; 6-bromo-2-thio-4H-3,1-benzothiazine, 20712-13-4; 6-bromo-2-oxo-4H-3,1-benzothiazine, 20712-14-5; 2-amino-5-bromotoluene-α-thiol, 20712-15-6; 2-amino-5-chloro-3-methylpyridine, 20712-16-7.

Acknowledgment.—We thank Dr. Bela Ternai and Mr. Nick Cassim for recording the nmr spectra, and Mr. Swee Hin Toh for preparing some of the intermediates used in this work.

2-Alkylidene-2H-indole Intermediates. The Thermolysis of 2-Hydroxydiphenylmethylindole[1,2]

LLOYD J. DOLBY[3] AND PIERRE D. LORD

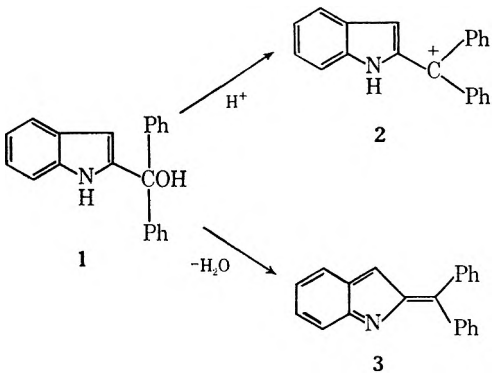
Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received January 21, 1969

The solution thermolysis of 2-hydroxydiphenylmethylindole (**1**) has been studied and, unlike 1-hydroxytetrahydrocarbazole, does not yield a simple "head-to-tail" dimer but affords a mixture of 2 monomers and 3 dimers: 2-diphenylmethylindole (**5**), 11-phenyl-10-H-indolo[1,2-*a*]indole (**7**), 11,11′,10,10′-biindolo[1,2-*a*]indole (**9**), 11-phenyl-10-[3-(2-diphenylmethyl)indolyl]indolo[1,2-*a*]indole (**8**), and 11,11′-diphenyl-10,10′-biindolo[1,2-*a*]-indolylidene (**10**). Monomer **7** appears to have formed from the 2-alkylidene-2H-indole **3**. The composition of the product mixture is concentration dependent. The structures of the monomers were determined by their uv and nmr spectra, and those of the dimers were determined by their uv and mass spectra and chemical transformations. Compound **5** was synthesized by the zinc–acetic acid reduction of carbinol **1** and by the lithium aluminum hydride hydrogenolysis of 2-methoxydiphenylmethylindole (**4**). Dimer **10** was obtained when **7** was treated with N-bromosuccinimide followed by exposure to base.

A number of transformations of substituted indoles can be rationalized by 2-alkylidene-2H-indole intermediates or their conjugate acids. The hydrogenolysis of 2-indolecarbinols by lithium aluminum hydride has been suggested to proceed *via* a 2-alkylidene-2H-indole intermediate[4] and the dimerization of 1-hydroxytetrahydrocarbazole undoubtedly involves such a species or its conjugate acid.[5] Moreover, these intermediates are obviously implicated in the biosynthesis and synthesis of the dimeric *Vocanga* and *Vinca* alkaloids.[5,6]

It was the purpose of the present study to examine the stability and transformations of such species. An attractive compound for such a study appeared to be 2-hydroxydiphenylindole (**1**) since the stability of the derived triarylcarbonium ion (**2**) could be examined directly and the corresponding 2-alkylidene-2H-indole intermediate (**3**) would be expected to be exceptionally stable.



Carbinol **1** was obtained in 78% yield from the reaction of 2-carbethoxyindole with phenylmagnesium bromide. The carbinol affords a highly stable carbonium ion (**2**) (pK_R^+ [7] = −1.50) in aqueous sulfuric acid solution.[8] The solvolysis of **1** in acidic methanol gave 2-methoxydiphenylmethylindole (**4**) in high yield.

(1) This work was supported by the National Institutes of Health (Grant HE 09521) and a Public Health Service career program award 1-K3-NB-28,105 from the National Institute of Neurological Diseases and Blindness.

(2) Taken from the Doctoral Thesis of P. D. Lord, University of Oregon, Dec 1967.

(3) Alfred P. Sloan Fellow, 1965–1967.

(4) L. J. Dolby and S. Sakni, *J. Amer. Chem. Soc.*, **86**, 1890 (1964); L. J. Dolby and D. L. Booth, *J. Org. Chem.*, **30**, 1550 (1965).

(5) G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, **86**, 4631 (1964).

(6) J. P. Kutney, J. Beck, F. Bylsma, and W. J. Cretney, *ibid.*, **90**, 4504 (1968).

(7) N. C. Deno, J. Jaruzelski, and A. Schriesheim, *ibid.*, **77**, 3044 (1955). The pK_R^+ of 4,4′-dimethoxytriphenylmethyl cation is −1.24 compared with −6.65 for triphenylmethyl cation.

(8) K. Hafner and K. Pfeiffer have recently [*Tetrahedron Lett.*, 4311 (1968)] synthesized **1** from 2-benzoylindole and phenylmagnesium bromide which is reported to have a melting point of 155–156°, some 20° higher than that which we have found. These authors have isolated the carbonium ion **6** as the fluoroborate which shows a visible spectrum similar to that which we observed. They also report the ultraviolet spectrum of **3**.

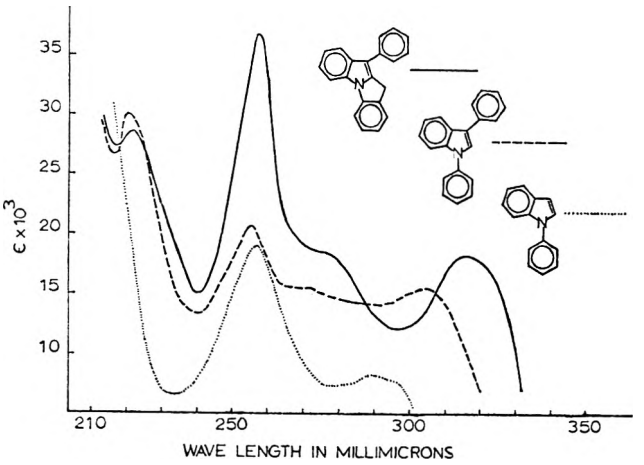
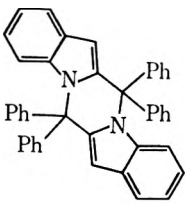


Figure 1.—The uv spectra of 11-phenyl-10H-indolo[1,2-*a*]indole (**7**), 1-phenylindole, and 1,3-diphenylindole.

Ether **4** underwent hydrogenolysis when stirred for 40 min at room temperature with lithium aluminum hydride giving a quantitative yield of 2-diphenylmethylindole (**5**). This reaction probably takes place by an elimination–addition sequence involving intermediate **3**. Carbinol **1** does not undergo any apparent hydrogenolysis under the same conditions or in refluxing ether.

Indole **5**, which was also obtained by the zinc–acetic reduction[9] of **1**, suffers air oxidation quite easily and was characterized as the trinitrobenzene complex. Indole **5** shows λ_{max}^{EtOH} 291 mμ (ε 7100) and its nmr spectrum shows the indole 3 proton at 5.92 and the methine proton at 5.23 ppm. This compound proved to be of importance in resolving the complex reaction mixture obtained in the thermolysis of **1**.

It was originally thought that the thermolysis of 2-hydroxydiphenylmethylindole (**1**) would lead to a "head-to-tail" dimer (**6a**) as in the case of 1-hydroxytetrahydrocarbazole or other simple dimers. No such dimers were obtained in the reaction which instead gave a complex mixture of products.



6a

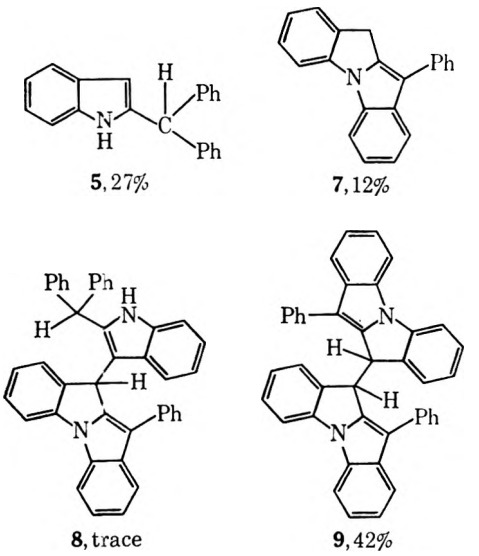
Thermolysis of 2-hydroxydiphenylmethylindole (**1**) in refluxing bromobenzene at various concentrations afforded five compounds: **5**, 11-phenyl-10H-indolo-[1,2-a]indole (**7**), 11-phenyl-10-[3-(2-diphenylmethyl) indolyl]indolo[1,2-*a*]indole (**8**), 11,11′-diphenyl-10,10′-biindolo[1,2-*a*]indole (**9**), and 11,11′-diphenyl-10,10′-biindolo[1,2-*a*]indolidene (**10**). The per cent yields are from a 0.01 *M* reaction (Chart I).

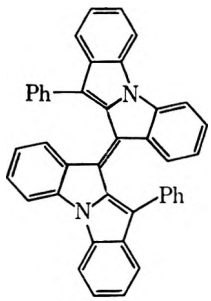
The initial decompositions were carried out in tetralin solution giving a deep blue mixture which showed nine compounds by thin layer chromatography (tlc). However, the reaction mixture was less complex using bromobenzene as solvent.

The indoloindole **7** was first isolated from the early

(9) H. Kauffmann and P. Panwitz, *Ber.*, **45**, 766 (1912).

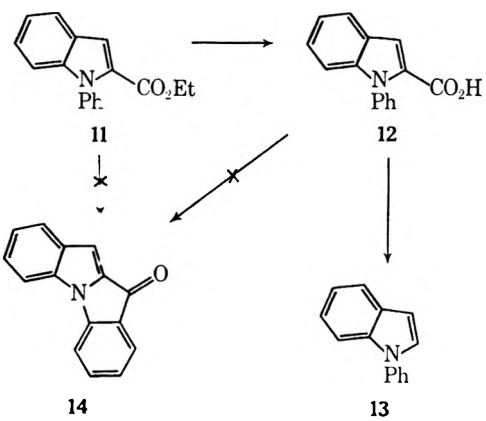
CHART I





10, trace

SCHEME I

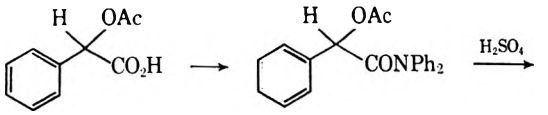


chromatographic fractions of a 0.40 *M* tetralin run and proved to be a key in determining the structures of the dimers. The proposed structure is supported by its ultraviolet (uv) spectrum (Figure 1); its infrared spectrum showing no N–H absorption; and its nmr spectrum which shows a multiplet at δ 6.8–7.9 (13 H) and a singlet at 3.87 (2 H). The nature of the uv chromophore was determined from comparisons with 1-phenylindole and 1,3-diphenylindole.

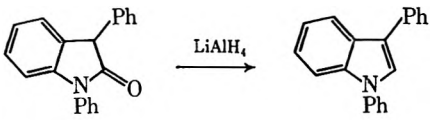
It is hoped that compound **7** could be synthesized independently *via* the ketoindoloindole **14**. However, we were unable to obtain **14** by cyclization of **11** or **12** with polyphosphoric acid[10] (Scheme I).

(10) D. Shirley and P. Roussel, *J. Amer. Chem. Soc.*, **75**, 376 (1963). These authors claim to have isolated **14** in low yield from the reaction of *n*-butyllithium with 1-phenylindole followed by treatment with carbon dioxide. Attempts to synthesize **14** from **12** and its acid chloride failed.

SCHEME II

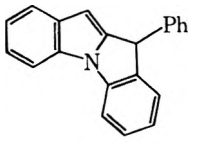


15



16 17

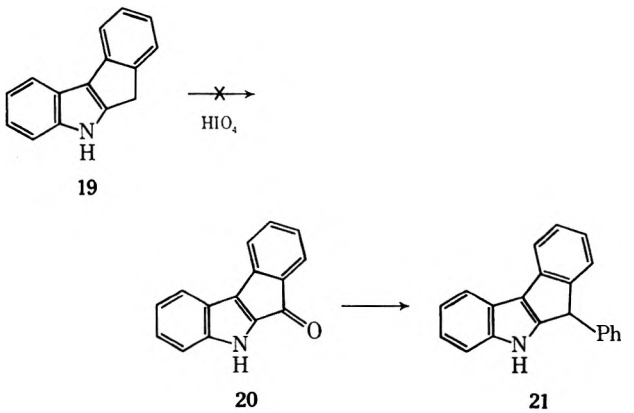
The synthesis of 1,3-diphenylindole was accomplished in a more straightforward manner than found in the literature.[11] Our sequence is outlined in Scheme II. We were unable to detect compound **18**, the double-bond isomer of **7**, in the reaction mixture although the structures of the dimers suggest that **18** is formed.



18

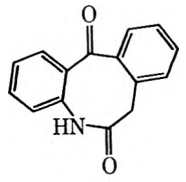
The isolation of compound **7** also suggested that compound **21** might be formed by an alternative cyclization. Hence we attempted to synthesize compound **21** to aid in examining the products from the thermolysis reaction. The attempted sequence is outlined in Scheme III.

SCHEME III



19 20 21

A synthetic sequeuce involving the periodic acid oxidation[12] of the indenoindole **19** to the keto compound **20** followed by reaction with phenylmagnesium bromide and hydrogenolysis by lithium aluminum hydride was thwarted at the initial step. Oxidation of **19** by either periodic acid or sodium metaperiodate gave the dibenzoazocinedione **22** exclusively.



22

Although **21** was not isolated from the thermolysis reaction, the nmr spectrum of **19** showed that the methylene protons appear at δ 3.70 which was further corroboration for the assignment of the methylene protons of **7**.

Dimer **8** was obtained when the residue from a thermolysis reaction was dissolved in benzene followed by dilution with pentane to give crude crystalline **8** in 42% yield.

The uv of pure **8** is strikingly similar to that obtained from a 1:1 mixture of **5** and **7** (see Figure 2).

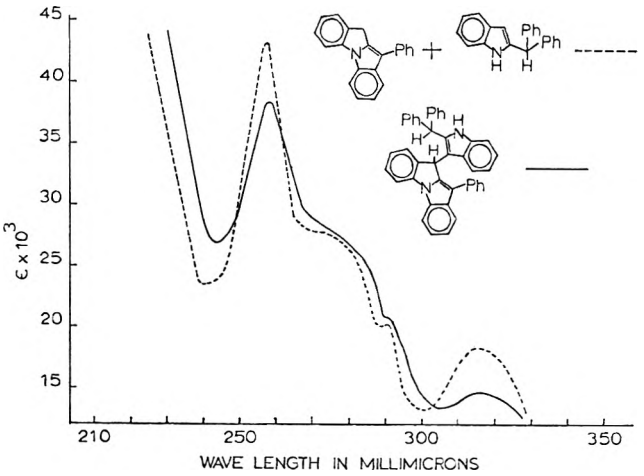
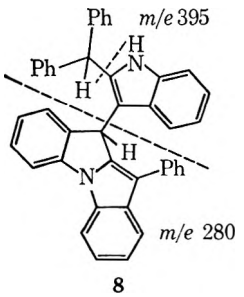


Figure 2.—The uv spectra of 11-phenyl-10-[3-(2-diphenylmethyl)indolyl]indolo[1,2-*a*]indole (**8**) and an equimolar solution of 2-diphenylmethylindole (**5**) and 11-phenyl-10H-indolo-[1,2,*a*]indole (**7**).

The infrared (ir) spectrum of **8** displayed an N–H peak at 2.95 μ and the mass spectrum had peaks at *m/e* 562, 395, and 280.



8

Additional proof of the structure of **8** was obtained when it underwent reductive cleavage by the action of zinc dust in refluxing glacial acetic acid to give a 1:1 mixture of **5** and **7**.[13] Several derivatives of isoindigo have been subjected to similar conditions for brief periods of time to give only the leuco products.[14] However, the reductive cleavage of **8** can be rationalized without difficulty.

(11) E. E. Baroni and K. A. Kovyrzina, *Zh. Obshch. Khim.*, **29**, 3815 (1959); *Chem. Abstr.*, **54**, 19643*h* (1960).

(12) L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).

(13) For reduction of indole by zinc and phosphoric acid, see L. J. Dolby and G. H. Gribble, *J. Heterocycl. Chem.*, **3**, 124 (1966).

(14) H. de Diesbach and E. Heppner, *Helv. Chim. Acta*, **32**, 687 (1949).

Upon closer examination of the reaction mixtures in subsequent runs of the thermolysis in concentrated solution (0.5–0.1 *M*), **5** could be observed in the later chromatographic fractions by the nmr peaks of the methine and 3-indole protons and the characteristic indole absorption in the uv.

Thermolysis of **1** in dilute solution gave a reaction mixture which displayed three spots upon tlc corresponding to **5**, **7**, and **9** and showing only a trace of **8**. The highly insoluble **9** crystallized when an attempt was made to dissolve the reaction mixture.

Dimer **9** was obtained as a high melting white powder whose uv spectrum resembled that of **7** quite markedly. The combustion analysis fit well for $C_{42}H_{28}N_2$ but the highest mass peak in the mass spectrum occurred at *m/e* 558 which is two atomic mass units lower than expected. A very intense base peak at *m/e* 280 appeared to rise from either symmetrical cleavage of the unobserved molecular ion *m/e* 560 or ionization of radicals obtained if **9** undergoes symmetrical thermolytic cleavage.

The possibility that **9** undergoes dehydrogenation and other changes upon being heated under high vacuum was confirmed when attempted sublimation of **9** at 200° and 2.3×10^{-5} mm afforded two other compounds, one of which was blue. The importance of this observation became clear when it was found that treatment of **9** with chloranil in refluxing toluene produced the deep blue crystalline dimer **10** whose mass spectrum exhibited a base peak at *m/e* 558. Dimer **10** was also synthesized when **7** was treated with N-bromosuccinimide and the crude product obtained was stirred with base.[15]

Conclusive proof for the structural assignments of **9** and **10** came from their reactions with zinc and acetic acid. Dimer **9** underwent reductive-cleavage to give **7** only. When **10** was subjected to the same conditions until the blue color was discharged, dimer **9** was obtained and prolonged reaction gave **7**.

Although **10** was never isolated from the thermolysis reaction mixtures, it was the only blue compound obtained in this study. Dimer **10** obtained from **7** and **9** had an identical tlc R_f value with that of the blue compound observed in the reaction mixtures of the thermolysis of **1**.

After isolating and characterizing all of the products of the thermolysis reaction, it became of interest to determine yields of the products as a function of concentration. This was readily accomplished in the case of the reaction in dilute solution where chromatography over Florisil gave a fairly good separation of the products. The product mixture from the thermolysis in concentrated solution was much more difficult to analyze and attempted analysis by preparative tlc and uv spectroscopy gave erratic results. However, one point does emerge, as the concentration is increased the yield of dimer **8** increases at the expense of the symmetrical dimer **9**. Whereas dimer **8** was formed only in trace amounts in 0.01 *M* solution, it was obtained in 22–48% yields from more concentrated (0.1 and 0.5 *M*) reactions. The yield of the symmetrical dimer from more concentrated solutions appeared to fluctuate but was consistently below the yield of 40% observed in the dilute reaction mixture.

A reasonable reaction scheme can be put forward to account for all of the products from the reaction. A particularly interesting feature of the reaction is that intermediate **3** of its conjugate acid can enter into three transformations. One of these species must cyclize to eventually yield compound **7**. It appears that compound **18** must be formed as well although we were unable to isolate it from the reaction mixture or obtain it by isomerization of **7**. However, electrophilic substitution on **18** by intermediate **3** or its conjugate acid would yield dimer **8**. Dimer **9** may be formed by two pathways both involving hydride abstraction by intermediates **2** or **3** which accounts for the large amount of 2-diphenylmethylindole (**5**) formed in the reaction. One pathway to dimer **9** involves hydride abstraction from either compound **7** or **18** followed by electrophilic substitution on **18**. Another likely pathway involves hydride abstraction from dimer **8** followed by internal cyclization to yield **9**. The trace amounts of the blue dimer **10** likely arise by oxidation of dimer **9** either by atmospheric oxygen or one of the several potential hydride abstractors in the reaction mixture.

The complexity of the reaction makes it a difficult one to study. None of the available information demands that 2-alkylidene-2H-indole intermediate **3** be invoked to rationalize the products, although it is attractive to propose this intermediate for several reasons. A major fraction of the products from the thermolysis reaction are derived by internal cyclization of intermediate **3** or its conjugate acid **2**, the triarylcarbonium ion. However, it appears that the triarylcarbonium ion **2** cyclizes only very slowly since quenching its solutions in strong acid affords the starting triarylcarbinol. Thus it seems reasonable to suggest that the internal cyclization proceeds *via* intermediate **3**. The fact that intermediate **3** has been observed directly lends further support to this proposal. However, there is no basis for deciding between intermediate **3** and its conjugate acid as the reactive species in the hydride abstraction reaction or the electrophilic substitution processes.

Experimental Section[16]

2-Hydroxydiphenylmethylindole (1).—To a solution of phenylmagnesium bromide made from 45.59 g (0.291 mol) of bromobenzene and 6.33 g (0.260 g-atom) of magnesium turnings was added a solution of 13.32 g (0.0725 mol) of 2-carbethoxyindole in 150 ml of dry ether over a period of 30 min and the resulting mixture was stirred at room temperature for 6 hr.

The reaction mixture was poured cautiously and with vigorous stirring into 300 ml of chilled saturated ammonium chloride solution. The ether solution was washed with water, dried, and evaporated to give a brown gum. Recrystallization from hot cyclohexane afforded 17.00 g (78.2%) of brown crystals. Recrystallization twice more gave pure **1**: mp 136.0–139.5°; λ_{max}^{EtOH} 292 mμ (ε 6930); nmr ($CDCl_3$) δ 8.24 (N–H, s, 1), 6.07

(15) The latter reaction is analogous to the conversion of 9-bromofluorene of 9-bromofluorene to 9,9′-bifluoreneylidene when treated with base: J. Thiele and A. Wanscheidt, *Ann.*, **376**, 278 (1910).

(16) Melting points are uncorrected. Anhydrous sodium sulfate was used to dry solutions. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and Berkeley Analytical Laboratories, Berkeley, Calif. Ultraviolet spectra were measured with a Cary Model 15 spectrophotometer and infrared spectra were determined with a Beckman IR-5 ir spectrophotometer with chloroform used as solvent unless otherwise indicated. A Varian Associates A-60 spectrometer was used to record nmr spectra and tetramethylsilane was used as an internal standard. Silica gel G (according to Stahl) was used as adsorbent in tlc and benzene–cyclohexane (1:1) was used as solvent. Spots were visualized using a 3% ceric sulfate–10% sulfuric acid solution and heat. The mass spectra were determined by the Morgan-Schaffer Corp., Montreal, Quebec, Canada.

(indole 3-H, d, 1), and 2.95 (O-H, s, 1); ir λ 2.80 μ (O-H) and 2.90 (N-H).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.73; N, 4.68. Found: D, 84.43, 83.73; H, 6.47, 5.75; N, 4.73, 4.73.

Measure of the pK_R^+ of 2-Hydroxydiphenylmethylindole (1).—The pK_R^+ of carbinol 1 was obtained from the absorbance of the ion in the visible region when 5 was dissolved in aqueous sulfuric acid solutions of known composition (per cent by weight). The H_R (C_0) acidity functions were calculated from published data[7] and the pK_R^+ was calculated from the following equation.

$$pK_R^+ = H_R + \log \frac{c_{R^+}}{c_{ROH}}$$

The carbinol was assumed to be entirely dissociated in concentrated sulfuric acid solution. The ion 6 displays λ_{max} 476 mμ (ε 53600) which shifts gradually to 472 mμ until 58.2% acid solution is used and then remains constant.

The average value obtained for the pK_R^+ was found to be -1.50 ± 0.03 ($T° = 26.8 \pm 0.5$). The carbinol could be recovered in 90% yields from 80% acid by dilution with water.

2-Methoxydiphenylmethylindole (4).—A solution of 1 (300 mg, 0.97 mmol), 2 drops of glacial acetic acid, and 10 ml of methanol was refluxed on a steam bath for 30 min. The solution was left to cool at room temperature overnight. Slightly tan, well-formed crystals were obtained and a second crop was combined to give 229 mg (95.2%) with mp 136–140°. A second recrystallization gave material with mp 138–140°; ir 2.88 μ (N-H); nmr (CCl_4) δ 6.45 (indole 3-H, d, 1), 3.10 (OCH_3, s, 3), and 7.85 (N-H, broad s, 1).

Anal. Calcd for $C_{22}H_{13}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.21; H, 6.20; N, 4.36.

2-Diphenylmethylindole (5).—To 500 mg (13.2 mmol) of lithium aluminum hydride in 25 ml of ether was added, with cooling, 1.40 g (4.48 mmol) of 4 in 20 ml of ether. The reaction mixture was stirred at room temperature for 10 min at which point tlc showed only one spot with violet circumference and yellow center. The excess hydride was cautiously destroyed with absolute ethanol and water and the gelatinous mixture was poured into 50 ml of water and 10 ml of concentrated hydrochloric acid. Extraction with ether, followed by washing of the ether layer with 10% hydrochloric acid and saturated salt solution, drying, and evaporation, afforded a quantitative yield of 5 as a pale yellow gum. Attempted distillation at 0.10 mm led to decomposition. The trinitrobenzene complex was obtained as orange needles, mp 167–169°, by heating a 1:1 mixture of 2-diphenylmethylindole and trinitrobenzene in ethanol solution.

Anal. Calcd for $C_{27}H_{20}N_4O_6$: C, 65.32; H, 4.06; N, 11.29. Found: C, 65.15; H, 4.03; N, 11.35.

Pure indole 5 could be obtained by filtration of a solution of the complex over alumina. The compound thus obtained showed λ_{max}^{EtOH} 291 mμ (ε 7100); nmr (CCl_4) δ 5.92 (indole 3-H, d, 1) and 5.23 (methine H, s, 1).

Identical results were obtained when 1 was stirred with zinc dust in refluxing acetic acid for 1 hr.

Isolation of 11-Phenyl-10H-indolo[1,2-*a*]indole (7).—A solution of crude 1 (5.86 g, 0.020 mol) in 50 ml of tetralin was refluxed under nitrogen for 3 hr. Thin layer chromatography showed nine spots, of which only four were large and intense.

The dark green mixture was chromatographed over 300 g of Alcoa alumina packed in petroleum ether (bp 30–60°). The column was eluted with petroleum ether until all of the tetralin was recovered. Elution was continued with benzene–petroleum ether (3:7). Fractions were collected until the intense blue band began to elute. All fractions except one showed the presence of at least two compounds (tlc). Crystallization of the fraction showing one compound from ethyl acetate yielded 135 mg (2.3%) of slightly blue crystalline 7: mp 139–140° (two further recrystallizations removed the blue color but did not change the melting point); uv λ_{max}^{EtOH} 315 mμ (ε 18,300), 275 sh (18,500), 257 (36,800), and 222 (28,600); nmr δ 6.8 to 8.0 (aromatic H, m, 13) and 3.87 (CH_2, s, 2).

Anal. Calcd for $C_{21}H_{15}N$: C, 89.65; H, 5.37 N, 4.98. Found: C, 89.46; H, 5.45; N, 4.89.

N,N-Diphenylacetylmandelamide (15).—A solution of acetylmandelic acid (21.88 g, 0.113 mol) in 35 ml of thionyl chloride was refluxed for 4 hr. The excess thionyl chloride was removed under reduced pressure and the crude acid chloride was added portionwise to a chilled solution of diphenylamine (19.30 g, 0.114 mol) and pyridine (10.30 g, 0.130 mol) in 140 ml of dichloromethane. The reaction mixture was then refluxed for 1 hr.

The cooled reaction mixture was poured into water and the dichloromethane layer was washed with 10% phosphoric acid and water, dried, and evaporated to dryness. The powder obtained was recrystallized from boiling ether to give 24.62 g (63.2%) of amide as well-formed prisms: mp 125–130° (two more recrystallizations raised this to mp 130–133°; ir λ_{max} 5.80 and 6.00 μ (C=O); nmr (CCl_4) δ 6.01 (benzylic H, s, 1) and 2.10 (CH_3C=O, s, 3).

Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55; N, 4.06. Found: C, 76.47; H, 5.44; N, 3.91.

1,3-Diphenyloxindole (16).—To 50 ml of cold, stirring concentrated sulfuric acid was added 5.00 g (14.5 mmol) of 15, portionwise over a period of 20 min. The mixture was stirred at 0° for 2 hr and then poured onto ice. The product was extracted with dichloromethane, washed with saturated salt solution, dried, and evaporated to give a white powder. Recrystallization from ether–petroleum ether (bp 30–60°) gave 2.85 g (68.0%) of crystals, mp 93–96°. Two more recrystallizations raised the melting point to 109–111° (lit.[17] mp 114°).

1,3-Diphenylindole (17).—To a mixture of 250 mg (6.60 mmol) of lithium aluminum hydride in 15 ml of ether was added 679 mg (2.38 mmol) of 16 in 5 ml of ether. The reaction mixture was stirred at room temperature for 4 hr. The excess hydride was cautiously destroyed with ethanol and water. The reaction mixture was worked up in the usual manner and the residue was recrystallized from methanol to give 395 mg (62%) of 17 as fine needles: mp 102–103° (lit.[11] mp 103–104°); uv λ_{max}^{EtOH} 305 mμ (ε 15,500), 255 (20,700), and 221 (15,400). A slight shoulder was observed at 272 mμ (ε 15,400).

1-Phenyl-2-carbethoxyindole (11).—A solution containing 2.32 g (0.020 mol) of ethyl pyruvate, 3.68 g (0.020 mol) of N,N-diphenylhydrazine, and 2 drops of acetic acid in 10 ml of absolute ethanol was heated on a steam bath for 5 min. The mixture was then added to 100 ml of absolute ethanol saturated with hydrogen chloride gas and the ensuing deep red mixture was refluxed on a steam bath for 30 min.

The solvent was evaporated, the milky residue was swirled with water and dichloromethane, and the dichloromethane layer was washed with water and evaporated to a brown oil. Recrystallization from petroleum ether (bp 30–60°) afforded tan plates (4.00 g, 75.5%), mp 59–62°. Sublimation at 100° (0.35 mm) followed by recrystallization from benzene–petroleum ether gave white crystals: mp 63.5–65.0°; uv λ_{max}^{EtOH} 293 mμ (ε 19,700) and 217 (25,800); ir λ_{max} 5.85 (C=O).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.91; H, 5.77; N, 5.16.

1-Phenylindole-2-carboxylic acid (12).—A mixture of 2.65 g (0.010 mol) of 11 in 35 ml of ethanol and 30 ml of 1.00 *N* sodium hydroxide solution was heated on a steam bath for 35 min. The reaction mixture was acidified with concentrated hydrochloric acid, poured into 30 ml of salt solution, and extracted with dichloromethane. The dichloromethane solution was washed with salt solution, dried, and evaporated, leaving 2.27 g (95.8%) of pale tan powder. Recrystallization from ethanol–water gave small tan needles, mp 173–175° (lit.[18] mp 176°).

1-Phenylindole (16).—Under an atmosphere of nitrogen, 478 mg (2.0 mmol) of 12 was heated at 210° for 3 hr. The brown oil obtained (365 mg, 93.5%) could be distilled at 114–117° (0.35 mm): $n^{25}D$ 1.6564; [(lit.[19] bp 179–180° (11 mm); $n^{25}D$ 1.6555)]; uv λ_{max}^{EtOH} 290 mμ (ε 8170) and 257 (19,000).

6H-Indeno[2,1-*b*]indole (19).—To a solution of 4.22 g (31.9 mmol) of 2-indanone and 0.5 ml of acetic acid in 25 ml of absolute ethanol was added 5.00 g (46.2 mmol) of freshly distilled phenylhydrazine. The mixture was stirred for 30 min after which 50 ml of alcohol was added and hydrogen chloride gas was bubbled in for 20 min. The reaction mixture was poured into water and extraction with dichloromethane, followed by washing with 10% sodium carbonate solution and water, drying, and evaporation gave a green solid. Chromatography of the residue over 400 g of alumina with benzene–cyclohexane (3:2) gave 2.29 g (35.0%) of tan solid. Recrystallization from ethanol gave crystals: mp 199° dec (lit.[20] mp 200° dec); uv λ_{max}^{EtOH} 292 mμ sh (ε 17,700), 278 (22,900), 240 (26,600), 235 sh (24,000), and 226 (24,600); nmr ($CDCl_3$) δ 3.70 (CH_2, s, 2).

(17) J. C. Sheehan and J. W. Frankenfeld, *J. Amer. Chem. Soc.*, **83**, 4792 (1961).

(18) E. Fischer and O. Hess, *Ber.*, **17**, 559 (1884).

(19) A. F. Pozharski, B. K. Martsohka, and A. M. Simonov, *Zh. Oshch. Khim.*, **33**, 1005 (1963); *Chem. Abstr.*, **59**, 7515*f* (1963).

(20) J. W. Armit and R. Robinson, *J. Chem. Soc.*, **121**, 838 (1922).

5,6,7,12-Tetrahydrodibenzo[*b*,*e*]azocine-6,12-dione (22). A. By Oxidation of 19 with Sodium Metaperiodate.—A solution of **19** (597 mg, 2.97 mmol) in 6 ml of methanol and 2.5 ml of tetrahydrofuran was added to a stirring solution of sodium metaperiodate (1.38 g, 6.46 mmol) in 11 ml of water. The reaction mixture became turbid and was stirred at room temperature for 5 hr. The mixture was diluted with water and extracted with dichloromethane which, after washing with saturated salt solution, drying, and evaporating, gave a white powder (496 mg, 70.5%). Recrystallization from benzene gave fine white needles: mp 210–212°; uv λ_{max}^{EtOH} 243 mμ; ir λ_{max} 2.95 μ (N—H) and 5.99–6.06 (C=O); nmr ($CDCl_3$) δ 8.30 (N—**H**, broad s, 1) and 3.76 (CH_2, broad s, 2).

Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 75.83; H, 4.51; N, 5.94.

B. By Oxidation of 19 with Periodic Acid.—A solution of **19** 518 mg, 2.53 mmol) in 10 ml of methanol and 1 ml of tetrahydrofuran was added dropwise to a solution of periodic acid (1.42 g, 6.23 mmol) in 8 ml of water over a period of 5 min. The reaction mixture became a deep red during the addition of 22.1 g. Thin layer chromatography showed two spots, the largest corresponding to compound **25** previously obtained.

Dilution of the reaction mixture with water was followed by extraction with ether, washing with 10% sodium thiosulfate solution, water, drying, and evaporation. When *ca.* 1 ml of dichloromethane was added to the residue, a white precipitate was obtained which, upon recrystallization from benzene, gave 295 mg (49%) of **22**.

Isolation of Dimer 8.—To refluxing bromobenzene (65 ml) with nitrogen bubbling through it was added 6.00 g (0.020 mol) of carbinol **1** and the mixture was refluxed for 2 days. The solvent was removed at 100° under reduced pressure and the blue residue was dissolved in ethyl acetate and refrigerated for 5 days.

A gray, crystalline compound (100 mg, 1.8%) was obtained which, upon two more recrystallizations, had mp 224–229° dec; uv λ_{max}^{EtOH} 317 mμ (ε 13,300). 293 (13,300), and 264 (27,400); and mol wt 562 (mass spectrum). The compound gave erratic combustion analyses. This compound, an isomer of **8**, was only found when the thermolysis of **1** was carried out for prolonged periods of time. It showed the same tlc color and R_f value as **8**, and it was later found that when **8** was heated for 2 days in bromobenzene it underwent isomerization to this material.

The residue from the ethyl acetate mother liquor was then eluted over Florisil in a constant-elution chromatography column. Fractions were eluted with cyclohexane, carbon tetrachloride, and carbon tetrachloride–benzene (9:1).

The last fraction contained dimer **8** upon recrystallization of the residue from chloroform–pentane (1.03 g, 18.3%). Two more recrystallizations gave crystals: mp 197–205°; uv λ_{max}^{EtOH} 317 mμ (ε 15,700), 292 (20,400), 285 sh (25,300), 257 (38,400), and 223 (66,300); ir (C_6H_6) λ_{max} 2.88 μ (N—H); mol wt 562 (mass spectrum).

Anal. Calcd for $C_{42}H_{30}N_2$: C, 89.65; H, 5.37; N, 4.98. Found: C, 89.65, H, 5.46; N, 4.88.

Dimer **8** was obtained in higher yield (2.75 g, 41.9%) when 7.00 g (0.023 mol) of **8** was stirred in 500 ml of refluxing bromobenzene under nitrogen for 2 hr. When the residue from the reaction mixture was dissolved in benzene and diluted with pentane until turbid, dimer **8** was obtained as gray crystals. Two further recrystallizations gave material identical with that previously obtained.

Reductive-Cleavage of Dimer 8.—A mixture of 102 mg (0.179 mmol) of **8** and 1.50 g (0.0229 g-atom) of zinc dust was stirred vigorously in 10 ml of refluxing glacial acetic acid under nitrogen for 24 hr. The reaction mixture was filtered and evaporated. The residue was extracted with boiling benzene and evaporated. The residue showed **5** and **7** to be present in a 1:1 ratio (tlc, nmr, and uv).

The residue was dissolved in hot methanol and refrigerated for 5 hr. The crystals obtained (40 mg, 80%), upon a further recrystallization, were identical with **7** in all respects.

The methanol mother liquor was evaporated and then heated with 40 mg (0.19 mmol) of 1,3,5-trinitrobenzene in 5 ml of ethanol and afforded orange crystals which, after two recrystallizations, were identical with the TNB–complex of **5**.

Thermolysis of 1 in Dilute Solution (0.0124 *M*).—To 900 ml of refluxing bromobenzene with a stream of nitrogen bubbling through it was added 3.46 g (0.0116 mol) of **1** in 30 ml of bromobenzene. After 6 hr all of the starting material had reacted and tlc of the reaction mixture showed four spots: the first and fastest moving corresponding to **7**; the second was similar in color to the first; the third corresponded to **5**; and the fourth and faintest occurred at the base of the third spot and corresponded to dimer **8**.

Removal of the solvent followed by swirling the green, gummy residue with hot dichloromethane gave dimer **9** as a fine, white powder (1.28 g, 39.4%).

Dimer **9**, which corresponded to the second tlc spot, was highly insoluble in most solvents but could be recrystallized from boiling toluene to give a white powder: mp 303° dec (sealed tube); uv λ_{max}^{EtOH} 322 mμ (ε 20,000), 258 (46,600), and 222 (41,900). The mass spectrum showed an apparent molecular weight of 558 and a base peak at *m/e* 280. Attempted sublimation at 200° and 2.3×10^{-5} mm gave two different compounds as indicated by tlc of the sublimate; one of these was blue.

Anal. Calcd for $C_{42}H_{28}N_2$: C, 89.97; H, 5.03; N, 5.00. Found: C, 90.04; H, 5.19; N, 5.02.

The dichloromethane filtrate was evaporated and the residue was dissolved in carbon tetrachloride and eluted over 250 g of Florisil. The products were collected in 13 100-ml fractions: fractions 1–9 were eluted with carbon tetrachloride; 10 and 11 were eluted with carbon tetrachloride–benzene 1:1; and the remainder was eluted with benzene.

Fractions 1–3 afforded 0.405 g (12.4%) of **7**. Fractions 4–11 were swirled with boiling methanol and filtered to give an additional 0.091 g of dimer **9** (total yield 42%). Evaporation of the filtrates and combination with fraction 12 gave 0.869 g (26.7%) of crude **5**. The remaining fraction contained a small amount of **5** and **8** but the compounds could not be separated. One reaction at an initial concentration of 0.5 *M* afforded dimer **9** in 34% yield whereas a similar reaction at 0.1 *M* gave **9** in 21% yield.

Chloranil Dehydrogenation of Dimer 9.—A mixture of **9** (442 mg, 0.790 mmol) and chloranil (214 mg, 0.872 mmol) in 30 ml of toluene was refluxed under nitrogen for 24 hr. The solvent was evaporated and the residue dissolved in dichloromethane, washed with water, 10% sodium carbonate solution, and water, dried, and evaporated. Filtration through alumina with benzene afforded 266 mg (60.3%) of dimer **10**. Recrystallization from boiling acetone gave deep blue needles, mp 283–287°. The analytical sample was recrystallized twice from benzene–pentane. The uv showed λ_{max}^{EtOH} 624 mμ (ε 26,800), 480 (7680), 414 (5790), 319 (27,600), 301 (30,700), 285 sh (34,700), 271 (39,000), and 251 (45,900); and the molecular weight was 558 (mass spectrum).

Anal. Calcd for $C_{42}H_{26}N_2$: C, 90.29; H, 4.69; N, 5.02. Found: C, 90.07; H, 4.66; N, 5.23.

Dimer 10 from Indoloindole 7.—A solution of **7** (66.5 mg, 0.236 mmol), N-bromosuccinimide (43.0 mg, 0.244 mmol), and benzoylperoxide (0.4 mg, 0.002 mmol) in 5 ml of carbon tetrachloride was refluxed under nitrogen for 30 min. The hot solution was filtered and evaporated. Thin layer chromatography showed essentially one product with only a trace of **10** being formed. The residue was stirred with 5 ml of dimethyl sulfoxide and 1.0 ml of 1.00 *N* sodium hydroxide solution at room temperature for 4 hr. The reaction mixture was poured into 10 ml of saturated salt solution and extracted with methylene chloride and the methylene chloride solution was washed with saturated salt solution, dried, and evaporated. Filtration through alumina with benzene gave 35.0 mg (53.2%) of deep blue solid which was identical in all respects with dimer **10** previously obtained.

Reductive Cleavage of the Symmetrical Dimer 9.—A mixture of 20 mg (0.036 mmol) of **9** and 500 mg (0.0076 g-atom) of zinc dust was vigorously stirred in 3 ml of refluxing glacial acetic acid for 24 hr under nitrogen. The reaction mixture was worked up as previously described and afforded a quantitative yield of indoloindole **7**.

Reduction of Dimer 10 to Dimer 9.—A mixture of dimer **10** (35 mg, 0.063 mmol) and zinc dust (500 mg, 0.0076 g-atom) in 5 ml of glacial acetic acid was refluxed with vigorous stirring until the blue color was completely discharged (2.5 hr). The reaction mixture was worked up in the usual manner and afforded dimer **9** in 93% yield.

Registry No.—**1**, 20538-21-0; **4**, 20538-22-1; **5**, 20555-27-5; **7**, 20538-23-2; **8**, 20621-44-7; **9**, 20555-19-5; **10**, 20555-28-6; **11**, 20538-24-3; **15**, 20538-25-4; **17**, 20538-11-8; **19**, 7156-31-2; **22**, 20538-09-4; 1-phenylindol, 16096-33-6.

The Preparation and Reactions of 1,4-Dialkoxycarbonyl-1,4-dialkyl-2-tetrazenes

WILLIAM S. WADSWORTH, JR.

Department of Chemistry, South Dakota State University, Brookings, South Dakota 57006

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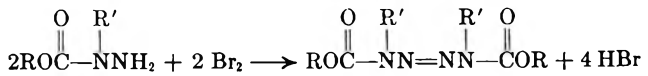
A number of 1,4-dialkoxycarbonyl-1,4-dialkyl-2-tetrazenes have been prepared by the bromine oxidation of 1-alkoxycarbonyl-1-alkylhydrazines. The tetrazenes which have a *trans* configuration react with nucleophiles to give products arising from carbon–nitrogen bond scission. One of the products, 1,4-dimethyltetrazolinone, although thermally stable, undergoes solvent assisted photodecompositions to give isoureas.

Acyclic 2-tetrazenes have been studied by a number of workers.[1] In most cases, those reported have been symmetrically substituted analogs containing nonfunctional groups.[2] It was the purpose of this work to prepare and study the chemistry of the 1,4-dialkoxycarbonyl analogs which might condense with diols or diamines to give interesting polymers.

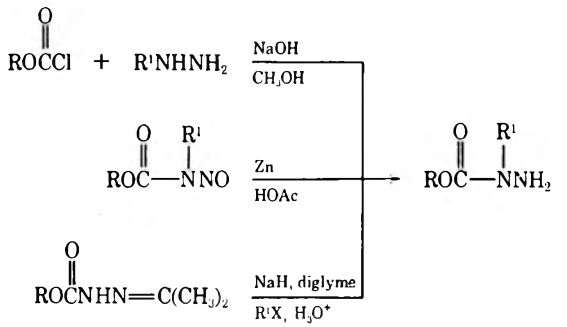
The classical synthesis of 2-tetrazenes involves oxidation of unsymmetrically substituted hydrazines under basic conditions. We have found that, in the case of 1-alkoxycarbonyl-1-alkylhydrazines, bromine oxidation is particularly successful, the 2-tetrazene precipitating from aqueous acid solution in a nearly pure state (Table I).



$$2ROC(=O)NHNH_2 + 2\,Br_2 \longrightarrow ROC(=O)N=NC(=O)OR + 4\,HBr$$

The starting 1-alkoxycarbonyl-1-alkylhydrazines were prepared by one of three different procedures (Scheme I), each of which had its limitations. The

SCHEME I



first[3] was limited by the lack of availability of monoalkylhydrazines. Methyl N-amino-N-cyclohexylcarbamate was prepared in low yield by the zinc–acetic acid reduction of the N-nitroso precursor.[4] The product was not isolated, but was oxidized directly to the 2-tetrazene. The procedure failed when primary N-alkyl substituents were employed. The third method involved the alkylation of an alkylidene hydrazide followed by mild hydrolysis.[5] This method was particularly successful in the preparation of benzyl derivatives.

The 1,4-dialkoxycarbonyl-1,4-dialkyl-2-tetrazenes were prepared by treating an acidified aqueous solution of 1-alkoxycarbonyl-1-alkylhydrazine with liquid bromine. Inverse addition or addition of bromine to an alkaline solution of the hydrazine failed to give a precipitate. Treatment of an alkaline solution of 1-alkoxycarbonyl-1-methylhydrazine with bromine caused a rapid evolution of methyl bromide. Likewise, N-amino-N-methylureas and N-amino-N-methylamides under both acidic and alkaline conditions gave rapid evolution of methyl bromide when their solutions were treated with bromine. Thus, under acidic conditions the presence of an alkoxycarbonyl group has a deciding effect on the course of the oxidation.

Since 2-tetrazene formation takes place under acidic instead of the usual basic conditions used for the formation of 1,1,4,4-tetraalkyl-2-tetrazenes, it would appear that azamines ($R_2\overset{+}{N}=\overset{-}{N}$) postulated as intermediates in 2-tetrazene formation[1e] are not intermediates in this case. Although mechanisms can be given, there is little evidence for their support.

Permanganate was also successful in oxidizing aqueous acid solutions of 1-alkoxycarbonyl-1-alkylhydrazines to 2-tetrazenes, whereas again the aminoamides and ureas underwent decomposition. Rapid gas evolution and small yields of the corresponding N-alkylcarbamate were produced when a dioxane solution of a 1-alkoxycarbonyl-1-alkylhydrazine was warmed with yellow mercuric oxide.

The reaction of 1,4-dialkoxycarbonyl-1,4-dialkyl-2-tetrazenes with a number of nucleophiles (Nu) was studied, and the course of the reaction was found to depend upon the size of the 1,4-dialkyl groups (Scheme II). Whereas I (R = CH_3) gave a high yield of a 1,4-dialkyltetrazolinone,[6] III, when warmed with piperidine, I (R = benzyl) gave less than 1% and I (R = cyclohexyl) gave none. In the latter two, decomposition was primarily *via* route B. The effect of the increased size of the alkyl group may reflect the geometry of the transition state, which, based on least ring strain, would have the N-alkyl groups *cis* and in close proximity. Aqueous sodium hydroxide gave similar results, except that the yield of III was somewhat lower. In neither case was carbon–oxygen bond scission observed. The transition-state energy for carbon–nitrogen bond breakage is lowered by resonance stabilization of the devloping anion, II.

(1) (a) E. Fischer, *Ann.*, **190**, 167 (1878); (b) H. Wieland, *Ber.*, **41**, 3498 (1908); (c) B. L. Erusalimsky, B. A. Dolgoplosk, and A. P. Kravunenko, *J. Gen. Chem. USSR* (Engl. Transl.), **27**, 267 (1957); (d) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1965, p 345; (e) *ibid.*, p 136.

(2) W. E. Thun and W. R. McBride, Abstracts of the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, M 130.

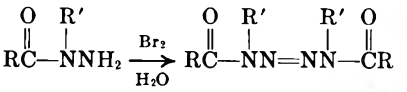
(3) C. Th. Pederson, *Acta Chem. Scand.*, **18**, 2199 (1964).

(4) C. Weygand, "Organic Preparations," Interscience Publishers, Inc., New York, N. Y., 1945, p 241.

(5) (a) G. Cignarella, *Chim. Ind.* (London), **42**, 145 (1966); (b) H. Yamamoto, *J. Org. Chem.*, **32**, 3693 (1967).

(6) 1,4-Dimethyltetrazolinone has been reported to be one of the products formed in low over-all yield by treating 5-hydroxytetrazole with an excess of diazomethane: K. Hattori, E. Lieber, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **78**, 411 (1956).

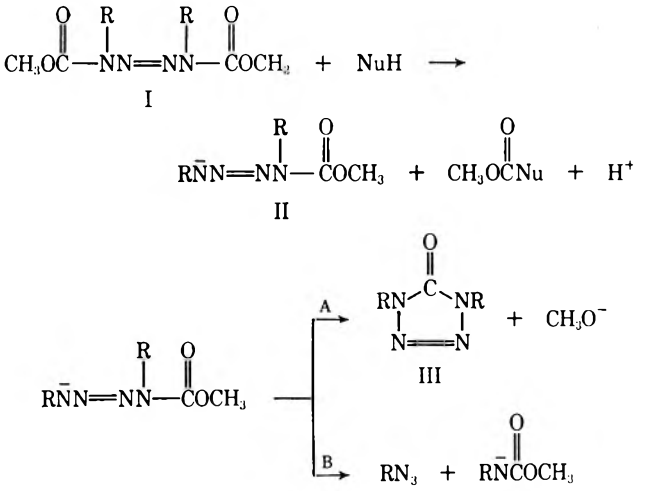
TABLE I



Registry no.	R	R′	Bp (mm) or mp, °C	Registry no.	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
20628-41-5	CH_3O	CH_3	69 (20)	760-81-6	186–187	35.29	5.88	27.45	35.15	5.87	27.42
20628-43-7	C_2H_5O	CH_3	80 (20)	20628-44-8	125–126	41.38	6.89	24.13	41.34	6.92	23.96
...	CH_3O	C_6H_5[a]	69–70	20628-45-9	160 dec	58.53	4.87	17.00	58.47	4.97	16.87
...	CH_3O	C_6H_{11}	...	20628-46-0	101–102	58.69	8.69	15.21	58.71	8.51	15.15
...	C_2H_5O	$C_6H_5CH_2$	...	20628-47-1	114–115	62.50	6.25	14.58	62.44	6.20	14.69

[a] R. Willstatter, *Ann.*, **477**, 161 (1929).

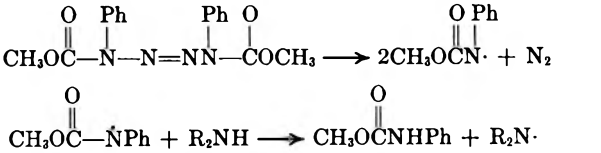
SCHEME II



The cyclization is of further interest, for the starting 2-tetrazene is most probably *trans*.[7] Thus a change in configuration must take place before cyclization. The newly formed negative charge in II is delocalized over three nitrogen atoms, giving some single-bond character to the original double bond and thereby allowing rotation to a *cis* configuration.

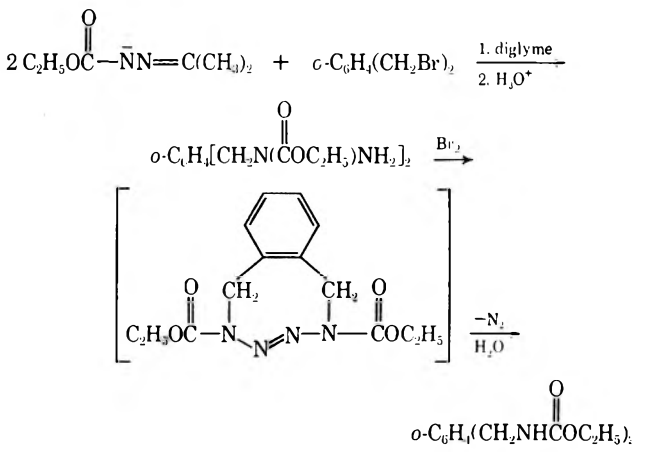
An attempt to prepare a cyclic 2-tetrazene (Scheme III) met with failure. The product, a biscarbamate isolated in high yield, would indicate that the intermediate cyclic tetrazene, if formed, is unstable. Such would most likely be the case if the bromine oxidation of N-aminocarbamates gave 2-tetrazenes with *trans* configurations.

The case of I (R = phenyl) was found to be unique in that, upon treatment with piperidine, the only products isolated were methyl N-phenylcarbamate and a polymeric material. Although no detailed study was made, it was apparent that the 2-tetrazene in this case



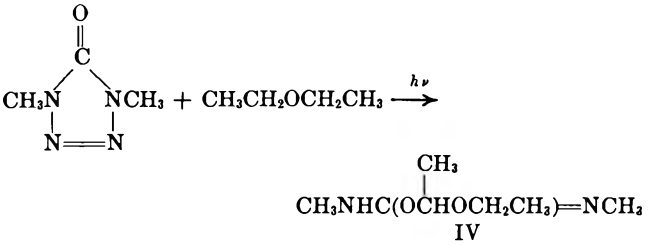
decomposed in solution to give a radical which in turn abstracted hydrogen from the amine. Similar decompositions of 2-tetrazenes are well known.[8]

SCHEME III



The structure of 1,4-dimethyltetrazolinone was determined by spectral and analytical means and through its decomposition products. Unlike other tetrazoles, which decompose on heating,[9] 1,4-dimethyltetrazolinone was found to be thermally stable. Heating a sample to over 300° did not induce decomposition. The possibility that the water-soluble tetrazolinone has an ionic structure and is aromatic cannot be excluded.

In contrast to the lack of nitrogen evolution on heating, 1,4-dimethyltetrazolinone [λ 225 mμ (ε 6200)] does eliminate nitrogen photochemically, giving products arising from solvent incorporation. Photolysis in diethyl ether gave a single product, an isourea, IV,



which partially decomposed upon distillation. The structure of the product was determined by spectral and chemical analysis. A strong imine band at 1620 cm^{-1} and no carbonyl absorption characterized the ir spectrum. The nmr spectrum showed a single absorption for the methyl hydrogens at δ 2.58. The nmr of N,N′-dimethyl-O-benzylisourea, prepared by adding benzyl chloride to the anion of *sym*-dimethylurea, also

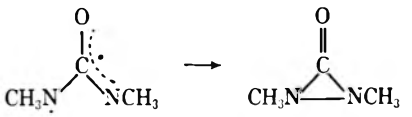
(7) P. S. Forgione, G. S. Sprague, and H. J. Trottkin, *J. Amer. Chem. Soc.* **88**, 1079 (1966).

(8) (a) B. R. Cowley and W. A. Waters, *J. Chem. Soc.*, 1228 (1961); (b) F. O. Rice and C. J. Crelecki, *J. Amer. Chem. Soc.*, **79**, 2679 (1957).

(9) (a) J. E. Baldwin and S. Y. Hong, *Tetrahedron*, **24**, 3787 (1968); (b) F. R. Benson, in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, pp 86–95.

gave a single peak with an identical chemical shift for its methyl hydrogens. The ir and nmr spectra of the crude photolysis product before distillation were nearly identical to the spectra of the purified material. There was no trace of a trialkylurea, $CH_3NH(C{=}O)N(CH_3)$-$CH(CH_3)OCH_2CH_3$, which would easily be detected from its spectra. The hydrogens of the N-methyl groups of the latter would not have identical chemical shifts and one would be split into a doublet. Such is the case for N,N′-dimethyl-N-ethylurea and N,N′-dimethyl-N-benzylurea.

Although a diradical,[10] V, may be an intermediate, there was no evidence of its existence. By direct



V VI

coupling, spin inversion, or bond rotation, the diradical might, as in the decomposition of alkylidenepyrazolines[11] and pyrazolinones,[12] be expected to undergo ring closure to yield in this case a diazacyclopropanone, VI, a single example of which has been reported.[13] No such product was isolated, nor did the ultraviolet spectrum of the mixture give rise to new absorption bonds during the photolysis while the disappearance of the single band at 225 mμ was monitored.

The photodecompositions increased in rate when more efficient hydrogen donor solvents than diethyl ether were used. Thus, in tetrahydrofuran, absorption in the ultraviolet region had disappeared after 40 hr. The ir and nmr spectra of the crude product, which decomposed on heating, verified that it was primarily an isourea. Besides the imine stretching absorption at 1610 cm^{-1} and lack of carbonyl absorption observed in the ir, the nmr spectrum gave a single peak for the methyl hydrogens at δ 2.75. Photodecomposition was complete after only 2 hr when carried out in ethanol or water. In both cases, a mixture of heat-sensitive products were obtained which were not characterized further. When carried out in 2-propanol, nearly quantitative yields of *sym*-dimethylurea and pinacol were obtained.

Experimental Section

Proton nuclear magnetic resonance spectra were determined on a Varian A-60A spectrometer; chemical shifts are reported in δ units (parts per million from tetramethylsilane internal standard). Infrared measurements were made using a Beckman IR-5 instrument. Ultraviolet spectral measurements were made on a Beckman DK-2A recording spectrophotometer. A Hanovia 679A-36 high-pressure mercury lamp with a water-cooled quartz immersion well was used in all photolyses. Photolyses were carried out under an atmosphere of nitrogen at about 15°, in magnetically stirred solutions. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting and boiling points are uncorrected.

1-Methoxycarbonyl-1-methylhydrazine.—Methyl chloroformate (189.0 g, 2.0 mol) was added dropwise with cooling and stirring to a mixture of methylhydrazine (96.0 g, 2.0 mol) and sodium hydroxide (80.0 g, 2.0 mol) dissolved in 500 ml of methanol. After stirring at room temperature for 1 hr, the mixture was filtered, the solvent was removed by distillation, and the residue was distilled to give 90.1 g (43% yield) of liquid, bp 69° (15 mm).

Anal. Calcd for $C_2H_8N_2O_2$: C, 34.61; H, 7.69; N, 26.92. Found: C, 34.57; H, 7.71; N, 26.87.

In a similar manner, using ethyl chloroformate, 1-ethoxycarbonyl-1-methylhydrazine was prepared in 62% yield, bp 82° (15 mm).

Anal. Calcd for $C_4H_{10}N_2O_2$: C, 40.67; H, 8.47; N, 23.72. Found: C, 40.75; H, 8.51; N, 23.64.

1,4-Dimethoxycarbonyl-1,4-dimethyl-2-tetrazene.—To a sample of 1-methoxycarbonyl-1-methylhydrazine (90.1 g, 0.86 mol) was added 500 g of ice, 1 equiv of dilute HCl, and liquid bromine (dropwise with stirring until color persisted). The slurry was stirred at room temperature for 1 hr and filtered. The precipitate was recrystallized twice from ethanol to give 46.9 g of white crystalline product (53.3% yield); nmr (CS_2) δ 3.38 (s) and 1.41 (s), equal intensities.

1,4-Diethoxycarbonyl-1,4-dimethyl-2-tetrazene was prepared exactly as the 1,4-dimethoxycarbonyl analog had been (62.3% yield); nmr (CS_2) 4.32 (q, 4 H), 3.38 (s, 6 H), and 1.39 (t, 6 H).

1,4-Diethoxycarbonyl-1,4-dibenzyl-2-tetrazene.—To a slurry of 50% sodium hydride[14] (9.6 g, 0.2 mol) in 200 ml of freshly distilled diglyme was added dropwise with cooling and stirring a solution of ethyl isopropylidene carbazate (28.8 g, 0.2 mol, mp 65–67° from hexane) dissolved in 50 ml of dry diglyme. After gas evolution had ceased, benzyl chloride (25.4 g, 0.2 mol) was added and the solution was heated at 120° for 3 hr. The solution was cooled, suction filtered, and stripped under reduced pressure. The residue, when distilled, gave 32.4 g (69.1% yield) of 1-ethoxycarbonyl-1-benzyl-2-isopropylidenehydrazine, bp 108–109° (0.4 mm); nmr δ 0.78 (t, 3 H), 1.42 (d, 6 H), 3.78 (q, 2 H), 4.39 (s, 2 H), and 6.95 (s, 5 H). The distillate was dissolved in dilute HCl, the solution was cooled in an ice bath, and liquid bromine was added until color persisted. The precipitate was collected and recrystallized twice from ethanol, yield 15.30 g (57.7%); nmr ($CDCl_3$) 1.40 (t, 6 H), 4.49 (q, 4 H), 5.20 (s, 4 H), and 7.35–7.67 (m, 10 H).

1,4-Dimethoxycarbonyl-1,4-dicyclohexyl-2-tetrazene.—Ethyl N-cyclohexylcarbamate (8.6 g, 0.05 mol) and 3.0 g of $NaNO_2$ were added to 50 ml of H_2O. Concentrated HCl was added dropwise until reaction ceased. The upper oily layer was separated and diluted with 20 ml of acetic acid. The acetic acid solution was added dropwise with rapid stirring to a slurry of 10 g of zinc dust in 100 ml of H_2O held at 0–2°. After the addition, the mixture was allowed to come to 10° and filtered. Liquid bromine was added dropwise to the filtrate until color persisted. After standing overnight, the precipitate was collected and recrystallized from acetonitrile to give 3.8 g of white crystals (41.3% yield).

1,4-Dimethoxycarbonyl-1,4-diphenyl-2-tetrazene.—1-methoxycarbonyl-1-phenylhydrazine (10 g, 0.06 mol) was added to 50 ml of dilute HCl. The solution was cooled to 0°, and liquid bromine was added until color persisted. The percipitate was collected and recrystallized twice from ethanol; yield 4.4 g (44.7%); nmr ($CDCl_3$) 3.75 (s, 6 H) and 7.22–7.71 (m, 10 H).

When a sample (3.3 g, 0.01 mol) of the 2-tetrazene was warmed with 1 equiv of piperidine at 120° for 2 days and distilled, a liquid, bp 150° (20 mm), was obtained which solidified on standing; mp 50°, yield 2.2 g (72%). The ir and nmr of the solid were identical to those of an authentic sample of methyl N-phenylcarbamate obtained by adding methanol to phenylisocyanate. A dark tarry residue remained from the distillation.

1,4-Dimethyltetrazolinone.—1,4-Dimethoxycarbonyl-1,4-dimethyl-2-tetrazene (20.4 g, 0.1 mol) was added to 20 g of piperidine and the solution was gently refluxed overnight. The mixture was stripped of excess piperidine, chilled, and suction filtered. The precipitate was recrystallized twice from ethanol to give 6.75 g (65.8%) of white, water-soluble crystals, mp 116–117°; ir (Nujol) broad band at 1695 cm^{-1}; nmr (CCl_4) 3.50 (s).

Anal. Calcd for $C_3H_6N_4O$: C, 31.58; H, 5.26; N, 49.12. Found: C, 31.65; H, 5.18; N, 48.96.

The filtrate, when distilled, gave 10.3 g (71.5%) of methyl-N-cyclohexylidene carbamate, bp 87–88° (20 mm), identified by comparison with an authentic sample. In a similar manner

(10) Molecular orbital calculations indicate the diradical to have three bonding orbitals. The electron density on oxygen, although less in the excited state than in the ground state, is greater than the electron densities at the two nitrogens. The excited electron is, however, located only on nitrogen and may in part be responsible for the initial abstraction of hydrogen to give IV.

(11) S. D. Andrews and A. C. Day, *J. Chem. Soc., B*, 1271 (1968).

(12) N. J. Turro and W. B. Hammond, *Tetrahedron*, **24**, 6017 (1968).

(13) F. D. Greene and J. C. Stowell, *J. Amer. Chem. Soc.*, **86**, 3569 (1964).

(14) Sodium hydride, 50% in mineral oil, was supplied by Metal Hydrides, Inc.

1,4-diethoxycarbonyl-1,4-dimethyl-2-tetrazene gave a 58% yield of 1,4-dimethyltetrazolinone. The small amount of gas which was evolved during the heating period was condensed in an ice bath. The infrared spectrum of the condensate was identical with that of methyl azide.

1,4-Dibenzyltetrazolinone.—1,4-Diethoxycarbonyl-1,4-dibenzyl-2-tetrazene (7.68 g, 0.02 mol) was added to 10 g of piperidine and the solution was heated overnight at 100°. After removal of excess piperidine under reduced pressure, the residue was distilled. The first cut, 50–54° (0.5 mm), gave 5.70 g of liquid. The infrared spectrum of the liquid was identical to that of an equal mixture of benzylazide and ethyl N-cyclohexylidenecarbamate. The mixture gave two peaks *via* glpc (Carbowax), with retention times identical to those of authentic samples. The second cut, bp 109–110° (0.2 mm), gave 2.8 g of liquid whose infrared spectrum was identical to that of authentic ethyl N-benzyl carbamate. The solid residue which remained from the distillation was recrystallized twice from ethanol to give 0.2 g (3.8% yield) of white crystals, mp 103–104°; ir (Nujol) strong C=O stretching absorption at 1700 cm^{-1}; nmr ($CDCl_3$) 5.08 (s, 4 H) and 7.48 (s, 10 H).

Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.67; H, 5.26; N, 21.05. Found: C, 67.52; H, 5.35; N, 20.87.

Under the same conditions, 1,4-diethoxycarbonyl-1,4-dicyclohexyl-2-tetrazene gave no solid residue upon distillation. Glpc of the distillate gave three peaks in a 1:1:1 ratio whose retention times were identical to those of authentic cyclohexylazide, ethyl N-cyclohexylidenecarbamate, and ethyl N-cyclohexylcarbamate, respectively. The latter precipitated from the distillate on cooling and was found to be identical to an authentic sample. The infrared spectrum of the distillate showed strong azide stretching absorption at 2100 cm^{-1}.

N,N′-Diethoxycarbonyl-*o*-xylyldiamine.—To a slurry of 50% sodium hydride (4.8 g, 0.1 mol) in 100 ml of freshly distilled diglyme was added dropwise with cooling and stirring a solution of ethyl isopropylidene carbazate (14.4 g, 0.1 mol) in 25 ml of dry diglyme. After gas evolution had ceased, α,α'-dibromo-*o*-xylene (13.2 g, 0.05 mol) was added and the mixture was heated at 150° for 24 hr. The solution was cooled and suction filtered, and the solvent was removed under reduced pressure. The residue was taken up in dilute HCl and the solution was treated with liquid bromine until color persisted. The precipitate was collected and recrystallized twice from carbon tetrachloride to give 6.2 g (44.3%) of white crystals, mp 117–118°.

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.14; N, 10.00. Found: C, 59.91; H, 7.20; N, 10.09.

The product was identical with an authentic sample prepared by adding ethyl chloroformate to *o*-xylyldiamine.

Photolysis of 1,4-Dimethyltetrazolinone in Ether.—1,4-Dimethyltetrazolinone (5.7 g, 0.05 mol) was dissolved in 800 ml of freshly distilled diethyl ether. The solution was photolyzed under a blanket of nitrogen with stirring for 48 hr, during which time the 225-mμ band completely disappeared. A small amount of gummy residue collected on the quartz insert during the photolysis. The solvent was removed under reduced pressure and the liquid residue was distilled, bp 95–98° (0.25 mm), to give 4.10 g (51.2%) of N,N-dimethyl-O-(1-ethoxyethyl)isourea; ir (nujol) imine stretching absorption at 1620 and N–H absorption at 3300 and 1520 cm^{-1}; nmr (neat) 6.40 (br, 1 H), 5.49 (q, 1 H), 3.20 (q, 2 H), 2.58 (s, 6 H), 1.04 (d, 3 H), and 0.96 (t, 3 H).

Anal. Calcd for $C_7H_{16}N_2O_2$: C, 52.50; H, 10.00; N, 17.50. Found: C, 52.34; H, 9.98; N, 17.72.

A sample of the distillate, when treated with 2,4-dinitrophenylhydrazine reagent, gave a precipitate, mp 147° (from ethanol), which was identical with an authentic sample of the 2,4-dinitrophenylhydrazone of acetaldehyde.

N,N′-Dimethyl-O-benzylisourea.—To a slurry of 50% sodium hydride (12.0 g, 0.25 mol) in 150 ml of dry diglyme was added *sym*-dimethylurea (22.0 g, 0.25 mol). The slurry was refluxed for 1 hr, after which time gas evolution ceased. Benzyl chloride (31.5 g, 0.25 mol) was added and the solution was refluxed for 1 hr, cooled, and suction filtered. The solvent was removed from the filtrate under reduced pressure and the liquid residue was distilled, giving 22.25 g (50.0%) of product, bp 120° (0.3 mm); ir (neat) imine stretching absorption at 1650 cm^{-1}; nmr (CCl_4) 7.20 (s, 5 H), 6.10 (br, 1 H), 4.25 (s, 2 H), and 2.58 (s, 6 H).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.86; N, 15.72. Found: C, 67.34; H, 7.81; N, 15.81;

Photolysis of 1,4-Dimethyltetrazolinone in 2-Propanol.—1,4-Dimethyltetrazolinone (5.7 g, 0.05 mol) was dissolved in 800 ml of freshly distilled isopropyl alcohol. The solution was photolyzed under a blanket of nitrogen for 2 hr, during which time the 225-mμ band completely disappeared. The solvent was removed under reduced pressure. The residue was distilled, bp 70° (15 mm), giving 46.8 g (81.0%) of pinacol. The residue from the distillation solidified on cooling and was recrystallized from acetonitrile to give 4.0 g (91%) of *sym*-dimethylurea. Both products were identified by comparison with authentic samples.

Registry No.—1-Ethoxycarbonyl-1-benzyl-2-isopropylidenehydrazine, 20628-48-2; 1,4-dimethyltetrazolinone, 13576-20-0; 1,4-dibenzyltetrazolinone, 20628-50-6; N,N′-diethoxycarbonyl-*o*-xylyldiamine, 20628-51-7; N,N-dimethyl-*o*-(1-ethoxyethyl)isourea, 20688-52-8; N,N′-dimethyl-*o*-benzylisourea, 20628-53-9.

Permanganate Oxidation of Tetrasubstituted 2-Tetrazenes[1]

WAYNE E. THUN AND WILLIAM R. MCBRIDE

Chemistry Division, Research Department, Naval Weapons Center, China Lake, California 93555

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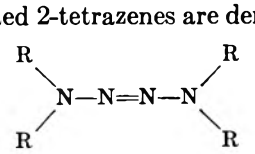
Tetraalkyl-2-tetrazenes, derivatives of the unsaturated hydronitrogen N_4H_4, are oxidized by potassium permanganate in acetone solution to 2-tetrazenes containing a carbonyl group α to a terminal nitrogen of the 2-tetrazene. Further oxidation results in the formation of symmetrically substituted 1,4-diacyl-1,4-dialkyl-2-tetrazenes, confirmed independently by oxidation of an appropriate hydrazine. The oxidation reaction extends to a cyclic derivative containing methylene groups α to the terminal nitrogen. Oxidation of tetrabenzyl- and 1,4-dimethyl-1,4-diphenyl-2-tetrazenes gives 2-tetrazenes containing only a single carbonyl group. Although heat, light, or acid may readily rupture the 2-tetrazene linkage to give nitrogen and other fragments, the permanganate oxidation is an example of a reaction in which the four-membered nitrogen chain remains intact. This stability is attributed to sp^2 hybridization of the terminal nitrogen atoms in the cation radical of the 2-tetrazene; a mechanism involving this species is proposed for the permanganate oxidation. The new hydronitrogen derivative, 1-nitroso-1,4,4-trimethyl-2-tetrazene, is a product of the oxidation of tetramethyl-2-tetrazene with dinitrogen trior tetroxide.

Tetrasubstituted 2-tetrazenes are derivatives of a hydro nitrogen containing a chain of four nitrogen atoms.[2] The most fully explored reaction of this type of compound involves loss of molecular nitrogen from the nitrogen chain. Thus, pyrolysis or photolysis of the free base yield nitrogen and disubstituted amino radicals

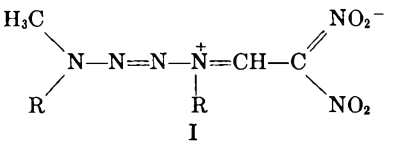


(1) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) L. F. Audrieth and B. A. Ogg, "The Chemistry of Hydrazine," John Wiley & Sons, Inc., New York, N. Y., 1951, pp 3–6.

which may subsequently combine, disproportionate, or abstract hydrogen,[3] or add to an appropriate substrate.[4] Alternatively, decomposition of the conjugate acid of the 2-tetrazene in aqueous solution quantitatively gives nitrogen gas along with other fragments.[5] The reported energy of activation for this aqueous decomposition of tetramethyl-2-tetrazene, 27.1 kcal/mol, is quite similar to 34.6 kcal/mol, obtained from pyrolysis of the neat material.[4]

Several reactions have been reported where nitrogen gas is not evolved and the nitrogen chain of a tetrasubstituted 2-tetrazene remains intact. Fischer[6] found that iodine added to 1,4-dimethyl-1,4-diphenyl-2-tetrazene gives a solid product with the empirical formula $C_{14}H_{16}N_4I_4$. Compounds of this type are generally unstable and can decompose spontaneously. Wieland and Reisenegger[7] added dinitrogen tetroxide to fully substituted 2-tetrazenes containing at least two phenyl groups and obtained the corresponding di-*p*-nitro derivative of the 2-tetrazene. More recently, the reaction of tetraalkyl-2-tetrazenes with tetranitromethane to give dipolar ions of trialkyl-(β,β-dinitrovinyl)-2-tetrazenes (I) has been described.[8] This reaction, to our knowledge, is the first reported in which an alkyl group of a 2-tetrazene was modified without cleavage of the four-membered nitrogen chain. Treatment of the dipolar ion of trimethyl-(β,β-dinitrovinyl)-2-tetrazene (I, R = CH_3) with bromine and then an aqueous solution of potassium hydroxide formed a small amount of material identified as 1-formyl-1,4,4-trimethyl-2-tetrazene in a yield never exceeding 2%. The present paper describes an alternative synthesis for this class of acyl derivatives and considers some aspects of the question concerning the stability of nitrogen chains during oxidative reactions.



I

Experimental Section

Microanalytical work summarized in Table I was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Ultraviolet spectra from absolute ethyl alcohol solutions (Table I) were recorded with a Cary Model 11 MS spectrophotometer. Infrared spectra of the materials in potassium bromide disks were measured with a Perkin-Elmer Model 137 spectrophotometer; the carbonyl stretching frequency, usually the most intense absorption, and several other principal absorptions (Table I) are reported in order of decreasing intensity. Proton magnetic resonance spectra (Table II) were recorded with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained using Hitachi Perkin-Elmer RMU-6E or Bendix Model 12 spectrometers. General methods for the preparation of the tetraalkyl-2-tetrazenes were reported previously.[5] Melting points for the compounds described in the following sections are uncorrected.

1-Formyl-1,4,4-trimethyl-2-tetrazene.—A solution of tetramethyl-2-tetrazene (1.16 g) in 200 ml of acetone was cooled to −78°; potassium permanganate (2.12 g) and calcium sulfate (*ca.* 3 g) were added. The mixture was allowed to warm to room temperature; stirring was continued until the supernatant solution was colorless (16–24 hr). The solid materials were filtered off and washed, and the acetone was evaporated. The resulting solid was recrystallized from pentane, 0.839 g (65% yield). Sublimation of this material gave white crystals, mp 55°. Using the method of Stenstrom and Goldsmith[9] and published H_0 values for hydrochloric acid solutions,[10] the decrease of absorbance of the peak due to the free base with increasing acid concentration was followed; a pK_b value of 14.57 at room temperature was obtained for the 2-tetrazene. The molecular weight was determined with the Bendix mass spectrometer; the most intense peak corresponded to the parent peak at mass 130 (calcd mol wt 130). In addition, a prominent peak corresponding to mass 102 (1-formyl-1,2,2-trimethylhydrazine, formed by loss of N_2 from the parent 2-tetrazene) was observed.

The 2-tetrazene also was prepared by treating 1,1,4-trimethyl-4-(β,β-dinitrovinyl)-2-tetrazene[8] with bromine in carbon tetrachloride. After removal of the solvent, the resulting oil was treated with aqueous potassium hydroxide and the 2-tetrazene was extracted with pentane. Yields from tetramethyl-2-tetrazene by this method did not exceed 2%.

1,4-Diformyl-1,4-dimethyl-2-tetrazene.—Tetramethyl-2-tetrazene (1.16 g) was dissolved in 200 ml of acetone and the solution was cooled to −78°. Potassium permanganate (4.24 g) was added, the mixture was warmed to room temperature, and the solution was stirred overnight. Manganese(IV) oxide was filtered off and the solvent was evaporated to give the diformyl-2-tetrazene, 0.728 g (50%). The material recrystallized from acetone was a white solid, mp 166°. The compound was also prepared in 70% yield by oxidation of 1-formyl-1,4,4-trimethyl-2-tetrazene with potassium permanganate in acetone. Similarly, the material was prepared from 1-formyl-1-methylhydrazine[11] by oxidation with potassium permanganate.[12]

1-Acetyl-1,4,4-triethyl-2-tetrazene.—This material was prepared from tetraethyl-2-tetrazene (1.72 g) and potassium permanganate (2.12 g) in a calcium sulfate buffered acetone solution according to the procedure for 1-formyl-1,4,4-trimethyl-2-tetrazene. The crude product was a yellow oil; no purification of the product was attempted.

1,4-Diacetyl-1,4-diethyl-2-tetrazene.—After 2 days at room temperature, the crude 1-acetyl-1,4,4-triethyl-2-tetrazene was treated with potassium permanganate (2.12 g) in 200 ml of acetone. Concentrated hydrochloric acid (16 drops) was added and the mixture was stirred for 30 min. After filtration and evaporation of the solvent, 0.35 g of solid (18% from tetraethyl-2-tetrazene) was obtained; the product was recrystallized from ether, mp 78°.

1-Propionyl-1,4,4-tripropyl-2-tetrazene.—This material was prepared from tetra-*n*-propyl-2-tetrazene (1.14 g) and potassium permanganate (1.06 g) according to the procedure for 1-formyl-1,4,4-trimethyl-2-tetrazene. The crude product was a yellow oil.

1,4-Dipropionyl-1,4-dipropyl-2-tetrazene.—After a day at room temperature, the crude 1-propionyl-1,4,4-tripropyl-2-tetrazene was treated with potassium permanganate (1.06 g) in 200 ml of acetone. The procedure was similar to that for 1,4-diacetyl-1,4-diethyl-2-tetrazene. The product (about 0.3 g, 25% yield from tetra-*n*-propyl-2-tetrazene) was recrystallized twice from ether, mp 62°.

1,1′-Azoperhydroazepine.—Yellow mercury(II) oxide (10 g) was added to an ether solution of 5 g of 1-aminoperhydroazepine (N-aminohexamethyleneimine or N-aminohomopiperidine, Aldrich Chemical Co., Inc.) at −78° with continuous stirring. The mixture was allowed to warm to room temperature and was left stirring overnight. After filtration and evaporation of the ether, 4.4 g (90% yield) of nearly white crystals were obtained; recrystallization from ethanol gave white needles, mp 64°.

1,1′-Azoperhydroazepin-2-one.—This crystalline material was prepared according to the procedure for 1-formyl-1,4,4-trimethyl-2-tetrazene. The crude product was purified by separation on a column packed with silica gel, mp 70°.

1,1′-Azoperhydroazepine-2,2′-dione.—The direct oxidation of 1,1′-azoperhydroazepine with a small excess of potassium permanganate in acetone (several drops of acetic acid were added after the oxidation had proceeded for several hours) gave the

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(5) W. R. McBride and W. E. Thun, *Inorg. Chem.*, **5**, 1846 (1966).
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(7) A. Wieland and C. Reisenegger, *ibid.*, **401**, 244 (1913).
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TABLE I

ANALYTICAL, ULTRAVIOLET, AND INFRARED DATA

2-Tetrazene	Registry no.	Analyses, % C Calcd	C Found	H Calcd	H Found	N Calcd	N Found	Ultraviolet spectra λ_{max}, mμ	Ultraviolet spectra $\epsilon \times 10^{-4}$	Infrared spectra, ν, cm⁻¹ C=O	Infrared spectra, ν, cm⁻¹ Others
1-Formyl-1,4,4-trimethyl-	20642-57-3	36.91	36.94	7.74	7.76	43.05	43.19	275	1.88	1650	1020, 1350, 738
1,4-Diformyl-1,4-dimethyl-	20642-58-4	33.33	33.61	5.59	5.89	38.87	38.49	270	2.45	1670	1030, 1340, 668
1,4-Diacetyl-1,4-diethyl-	20642-59-5	47.99	48.01	8.05	8.13	27.98	27.92	285	2.40	1680	1380, 1350, 1290
1,4-Dipropionyl-1,4-dipropyl-	20642-60-8	56.22	56.97	9.44	9.70	21.86	22.57	287	2.42	1680	1380, 1065
1,1′-Azoperhydroazepine	16504-24-8	64.24	64.33	10.78	10.78	24.97	24.87	289	1.04	...	2890, 1070, 962
1,1′-Azoperhydroazepin-2-one	20642-61-9	60.47	61.39	9.31	9.43	23.51	23.62	287	...	...	...
1,1′-Azoperhydroazepine-2,2′-dione	20642-62-0	57.12	56.85	7.99	7.96	22.21	22.12	283	1.7	1670[a]	1125, 1380, 958
1-Formyl-4-methyl-1,4-diphenyl-	20642-63-1	66.13	65.83	5.55	5.33	22.04	22.06	314	1.0	1690	1365, 1325, 720
1-Benzoyl-1,4,4-tribenzyl-	20642-65-3	77.39	77.47	6.03	5.91	12.89	13.01	294	1.5	1625	697, 1380
1-Nitroso-1,4,4-trimethyl-[b]	20642-64-2	...	...	...	...	...	...	310	1.3	1470[c]	1325, 980, 1090

[a] Third most intense peak. [b] Infrared spectrum of CCl_4 solution. [c] Absorption due to N=O, second most intense peak.

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA

2-Tetrazene	Shift, ppm; J, Hz N—CH_2—	Aryl- or —CH_2CH_3—	—$COCH_2$— or —COH
1-Formyl-1,4,4-trimethyl-	3.03 (s, 6 H) 3.16 (s, 3 H)		8.73 (s, 1 H)
1,4-Diformyl-1,4-dimethyl-	3.35 (s, 6 H)		8.96 (s, 2 H)
1,4-Diacetyl-1,4-diethyl-	4.06 (q, 4 H); J = 7.1	1.13 (t, 6 H); J = 7.1	2.37 (s, 6 H)
1,4-Dipropionyl-1,4-dipropyl-	3.97 (t, 4 H); J = 7.2	0.89 (t, 6 H); J = 7.2 1.20 (t, 6 H); J = 7.4 1.55 (m, 4 H)	2.71 (q, 4 H); J = 7.4
1,1′-Azoperhydroazepine	3.24 (m, 8 H)	1.38 (m, 16 H)	
1,1′-Azoperhydroazepin-2-one	3.71 (m, 4 H) 3.98 (m, 2 H)	1.72 (m, 14 H)	2.62 (m, 2 H)
1,1′-Azoperhydroazepine-2,2′-dione	4.30 (m, 4 H)	1.81 (m, 12 H)	2.80 (m, 4 H)
1-Formyl-4-methyl-1,4-diphenyl-	3.52 (s, 3 H)	7.19 (m, 10 H)	9.01 (s, 1 H)
1-Benzoyl-1,4,4-tribenzyl-	4.38 (s, 4 H) 5.41 (s, 2 H)	6.83 (m, 5 H) 7.31 (m, 15 H)	
1-Nitroso-1,4,4-trimethyl-	3.32 (s, 6 H) 3.44 (s, 3 H)		

desired product which was recrystallized from ethanol–water, mp 213°.

1-Formyl-4-methyl-1,4-diphenyl-2-tetrazene.—Dimethyldiphenyl-2-tetrazene (1.82 g) was dissolved in 300 ml of acetone at room temperature, potassium permanganate (1.62 g) was added, and the mixture was stirred until homogeneous; then glacial acetic acid (3 ml) was added. Although the color of the permanganate was depleted in about 30 min, stirring was continued overnight. The solvent was partially evaporated after filtration. The first fraction (0.43 g) was primarily starting material (23% yield), but the second fraction (0.82 g) contained the desired product (*ca.* 40% yield). Recrystallization from acetone gave a solid, mp 94°.

1-Benzoyl-1,4,4-tribenzyl-2-tetrazene.—Tetrabenzyl-2-tetrazene (2.14 g) and potassium permanganate (1.08 g) were dissolved in 400 ml of acetone containing glacial acetic acid (1 ml) and the solution was stirred overnight. After the manganese(IV) oxide was filtered off, the solvent was evaporated, leaving a crude product, 1.61 g (73%). Separation on a silica gel column with methylene chloride–*n*-hexane (50:50) gave a central fraction, 0.49 g, mp 87°.

1-Nitroso-1,4,4-trimethyl-2-tetrazene.—An excess of dinitrogen tetroxide or dinitrogen trioxide was bubbled into a solution of tetramethyl-2-tetrazene in chloroform or carbon tetrachloride, cooled to about −20°. Most of the solvent was evaporated and a nearly white solid was collected on a sintered glass disk, mp 38–40°. However, in some cases a dark oil was the product of the reaction. The oil was washed several times with a total of 300 ml of pentane, and the pentane solution was evaporated to a volume of 50 ml and cooled to −78° to precipitate the product prior to filtration. Further purification by sublimation gave a slightly yellow solid, mp 40°. A parent peak corresponding to *m/e* 131 and prominent peaks corresponding to *m/e* 43, 59, 28, and 15 were observed in the mass spectrum. A precise mass determination of the parent peak was 131.0813; calcd for $C_3H_9N_5O$, 131.0807. A broad unsymmetrical absorption at 1480–1440 cm^{-1} and absorption at 1045 cm^{-1} were observed in the infrared region, corresponding to the N=O and N–N stretching frequencies, respectively.[13] The analysis for the nitroso functional group was determined by adding acid to a solution of the material in an inert atmosphere to form nitrous acid. The nitrous acid thus produced liberated iodine from iodide and the iodine was titrated with thiosulfate.[14] *Anal.* Calcd wt of samples from thiosulfate titration: 0.0623 and 0.1323 g. Found: 0.0626 and 0.1279 g, respectively. *Caution!* This material is sensitive to friction and impact. Preliminary results indicate a kilogram weight dropped onto the solid from 7 cm will initiate detonation.

Results

Tetramethyl-2-tetrazene.—Oxidation of 1,1,4,4-tetramethyl-2-tetrazene with potassium permanganate in acetone solution and at room temperature provides a good synthesis for 1-formyl-1,4,4-trimethyl-2-tetrazene. The latter compound, pK_b = 14.57, is a much weaker base than tetramethyl-2-tetrazene, pK_b = 7.80.[15] This new synthesis gives material identical with that obtained from the reaction of trimethyl(β,β-dinitro-

(13) (a) E. Müller and H. Haiss, *Chem. Ber.*, **95**, 1255 (1962); (b) R. N. Haszeldine and B. J. H. Mattinson, *J. Chem. Soc.*, 4172 (1955).

(14) (a) F. Sutton, "A Systematic Handbook of Volumetric Analysis," Butterworth and Co. Ltd., London, 1955, pp 398–400. (b) For a more recent procedure which may be useful, see J. Gal, E. R. Stedronsky, and S. I. Miller, *Anal. Chem.*, **40**, 168 (1968).

(15) W. R. McBride and H. W. Kruse, *J. Amer. Chem. Soc.*, **79**, 572 (1957).

vinyl)-2-tetrazene with bromine and aqueous potassium hydroxide. The time required for the oxidation, as judged by the disappearance of the permanganate, varies according to the amount of moisture in the acetone; greater amounts of moisture necessitate shorter reaction times. Although acidic aqueous solutions accelerate the completion of the oxidation to a few minutes, yields are lower and evolution of nitrogen indicates an alternative reaction resulting in the cleavage of the nitrogen chain. 1-Formyl-1,4,4-trimethyl-2-tetrazene is a product of the permanganate oxidation of tetramethyl-2-tetrazene over the pH range from 1 to 13; in fact, the product can be detected even from oxidation in acetic acid. In one experiment, an electron paramagnetic resonance spectrum of a slightly acidic solution at room temperature indicated both absorption due to Mn^{2+} and a more complex spectrum, attributed to the tetramethyl-2-tetrazene cation radical. The epr spectrum of this latter species, however, is better resolved under different conditions.[16]

Further oxidation of tetramethyl-2-tetrazene (or 1-formyl-1,4,4-trimethyl-2-tetrazene) with potassium permanganate in acetone at room temperature forms 1,4-diformyl-1,4-dimethyl-2-tetrazene in good yield. The latter compound was prepared independently by oxidation of 1-formyl-1-methylhydrazine directly to the 2-tetrazene. 1,4-Diformyl-1,4-dimethyl-2-tetrazene is a weaker base than 1-formyl-1,4,4-trimethyl-2-tetrazene; a pK_b value at 25° for the diformyl derivative is estimated at 18. The formyl-2-tetrazenes differ from tetramethyl-2-tetrazene not only because they exist as free bases rather than as conjugate acids in dilute acid, but also because they decompose in moderately basic solution. Preliminary studies of formyl-2-tetrazenes in dilute aqueous solution at 20° established that the decomposition is initially pseudo first order and that the decomposition rate for a given tetrazene is 4 to 6 times faster at pH $\sim$ 13 than at pH $\sim$ 1, indicating decomposition due to hydrolysis of the formyl group.[17]

The usual reduction product of permanganate in these reactions is manganese(IV) oxide. Since Henbest and Thomas[18] were able to oxidize dimethylaniline to formylmethylaniline in 80% yield with a fiftyfold excess of "activated" manganese dioxide, conditions similar to those they described were used to oxidize tetramethyl-2-tetrazene. Yields of several per cent of formylmethyl-2-tetrazenes were recovered from such reactions, but, because of the poor yields and the excessive amount of manganese dioxide employed, we conclude that permanganate is the principal oxidant in our reaction.

At room temperature, tetramethyl-2-tetrazene can be oxidized to 1-formyl-1,4,4-trimethyl-2-tetrazene within 10 min in solutions buffered at pH 5; under these conditions, there is negligible oxygen exchange between the permanganate ion and water.[19] The mass spectral data for the formyl-2-tetrazene reveal that ^{18}O is incorporated in the 2-tetrazene when $Mn^{16}O_4^-$ is the oxidant and $H_2{}^{18}O$ is the solvent, but not *vice versa*. Thus, it is highly unlikely that any kind of manganate ester is involved in the oxidation mechanism.

Tetramethyl-2-tetrazene was also oxidized by nitrogen oxides during the present investigation. Again, an epr spectrum of the cation radical of tetramethyl-2-tetrazene[16] is observed on the addition of gaseous dinitrogen tetroxide to an aqueous solution of the 2-tetrazene. If the reaction is performed in chloroform or carbon tetrachloride with dinitrogen tri- or tetroxide, an easily sublimable, explosive material, 1-nitroso-1,4,4-trimethyl-2-tetrazene, is obtained.

Classes of Tetrasubstituted 2-Tetrazenes.—The permanganate oxidation is a general reaction of tetraalkyl-2-tetrazenes. With tetraethyl- and tetra-*n*-propyl-2-tetrazene, the monoacyl derivatives were obtained only as light yellow oils and were not purified for chemical analysis. However, further oxidation of these oils gave solid diacyl derivatives. In all cases, a methyl or methylene group alpha to a terminal nitrogen (the 1,4 positions) of the 2-tetrazene chain is oxidized to a carbonyl group; under the conditions employed, the oxidation is terminated on the formation of the symmetrical diacyl-substituted 2-tetrazene. The generality of the synthesis was extended to cycloalkyl derivatives of 2-tetrazenes containing a methylene group α to the 1,4 nitrogens. 1,1′-Azoperhydroazepine (1,1,4,4-dihexamethylene-2-tetrazene) was used as the model compound for the permanganate oxidation.

Tetrabenzyl- and 1,4-dimethyl-1,4-diphenyl-2-tetrazenes were chosen as being representative of 2-tetrazenes containing pseudoalkyl and alkyl–aryl substitution. In these examples, oxidation with permanganate proved to be more difficult than with the alkyl- or cycloalkyl-substituted 2-tetrazenes; only the monoacyl-substituted 2-tetrazenes were successfully isolated as products. Elemental analyses and various spectral data indicated further oxidation to diacyl-substituted derivatives, but these products, in low yield, were not obtained in satisfactory purity for good elemental analysis.

Methylated Hydrazines.—The permanganate oxidation was extended to another class of substituted hydro nitrogens, methylated hydrazines. Formylmethyl-2-tetrazenes were recovered in very low yield by the direct oxidation of 1,1-dimethylhydrazine. It is not presently known whether the reaction proceeds *via* formation and oxidation of tetramethyl-2-tetrazene or *via* oxidation of 1,1-dimethylhydrazine to 1-formyl-1-methylhydrazine and subsequent formation of formylmethyl-2-tetrazenes. Tetramethylhydrazine was oxidized to both formyltrimethylhydrazine and 1,2-diformyl-1,2-dimethylhydrazine. Qualitative identification of formyltrimethylhydrazine was made from mass spectral data, and diformyldimethylhydrazine was identified from comparison of glpc elution time and mass, nmr, and ir spectra with data from an authentic sample of diformyldimethylhydrazine.[20]

Discussion

The most unusual feature of the oxidation of tetrasubstituted 2-tetrazenes—whether with potassium permanganate, nitrogen oxides, or tetranitromethane—is the retention of the four-membered nitrogen chain. Electron impact data indicate that the bond dissociation energy of the nitrogen–nitrogen single bond in

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(17) S. Langlois and A. Broche, *Bull. Soc. Chim. Fr.*, 812 (1964).
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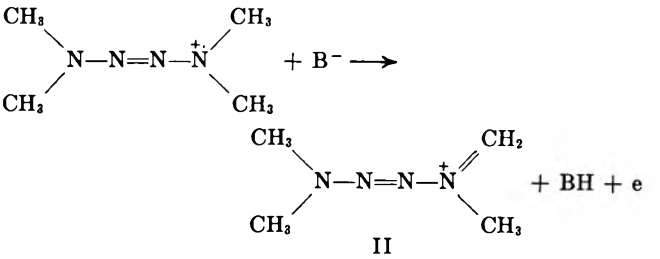
(19) G. Zimmerman, *J. Chem. Phys.*, **23**, 825 (1955).
(20) J. Thiele, *Chem. Ber.*, **42**, 2575 (1909).

tetramethyl-2-tetrazene is 16.5 kcal/mol.[21] Only the nitrogen oxides, dinitrogen tri- and tetroxide, have weaker nitrogen–nitrogen single bonds.[22] It is therefore somewhat surprising that an alkyl group of the 2-tetrazene is altered without rupture of the relatively weak nitrogen–nitrogen bonds.

Experimentally, it has been observed that each of the oxidants mentioned above can react with tetramethyl-2-tetrazene to form the cation radical, a species with one electron removed. It now seems obvious that most, if not all, of the oxidation reactions leading to the retention of the 2-tetrazene nitrogen chain occur *via* a cation radical. From the published epr spectrum of the tetramethyl-2-tetrazene cation radical, relatively small nitrogen coupling constants[16] were determined for the 1,4 positions compared with those predicted for tetrahedral nitrogen atoms. This evidence supports sp^2 hybridization on the terminal nitrogen positions.

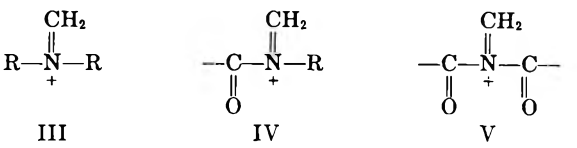
The sp^2 hybridization in the tetramethyl-2-tetrazene cation radical should both strengthen the nitrogen–nitrogen single bond and reduce the likelihood of an elimination reaction of the stable diatomic nitrogen molecule. Although pertinent bond dissociation energy data are not available, this point may be crudely illustrated from bond energies. Bond energies for the nitrogen–nitrogen single and double bonds are 37 and 61 kcal/mol, respectively, and that for the carbon–nitrogen single bond is 66 kcal/mol.[23] During the formation of 1-nitroso-1,4,4-trimethyl-2-tetrazene, a carbon–nitrogen single bond in the 2-tetrazene is replaced by a nitrogen–nitrogen single bond. This would suggest that the stabilization energy of the nitrogen chain in the cation radical is greater than 29 kcal/mol, the difference between the carbon–nitrogen and nitrogen–nitrogen single-bond energies. Recent results from infrared spectra of hydrazine derivatives indicate that, as the configuration on the nitrogen atom changes from sp^3 to sp^2, a corresponding decrease in repulsion between lone pairs occurs, accompanied with a shortening and strengthening of the nitrogen–nitrogen single bond.[24]

If the chemical oxidation of these substituted 2-tetrazene hydro nitrogens is similar to the electrochemical oxidation of primary aliphatic amines,[25] the initial step in the oxidation is the removal of an electron from a nitrogen atom. It is proposed that such a mechanism indeed does extend to the tetrasubstituted 2-tetrazenes currently studied. In a reaction analogous to the electrochemical oxidation of dimethylaniline[26] and the permanganate oxidation of tertiary aliphatic amines,[27] electron abstraction gives a cation radical as the first step. A basic medium assists in deprotonation of the cation radical, and this is rapidly followed by loss of a second electron. The resultant cation (II), like those derived from substituted amides[28] (IV), is hydrolyzed



II

to a primary alcohol which can then be readily oxidized by permanganate to formyltrimethyl-2-tetrazene. The stabilization by conjugation of the iminium cations II and IV possibly precludes the direct hydrolysis[29] of II to formaldehyde and other fragments. Cations containing structures III, IV, and V can hydrolyze and sub-



III IV V

sequently lose a proton to give corresponding N-hydroxymethyl compounds; the order of stability toward hydrolysis is V > IV > III. The importance of both moisture and a basic medium has been recognized in the permanganate oxidation of a benzyl to a benzoyl group in aryl-substituted amines,[30] compounds possibly capable of forming cation radicals.[31] Although the optimum medium and pH for the oxidation of tetrasubstituted 2-tetrazenes were not definitely established, it is clear that extremes in pH should be avoided. A strongly basic medium contributes to the rapid hydrolysis of the desired product, while strongly acidic conditions accelerate the decomposition of the starting 2-tetrazene; qualitatively, permanganate catalyzes this latter reaction.

Oxidation of pseudoalkyl- and alkyl–aryl-substituted 2-tetrazenes can be complicated by competitive reactions. This is noted in the oxidation of dimethylaniline upon removal of an electron; redistribution of the free electron density in the phenyl group leads to other reaction products.[26] Choice of experimental conditions can become most important. Thus, benzoyldibenzylamine was obtained by the permanganate oxidation of tribenzylamine in a slightly basic medium[30] but not in a neutral medium.[32] Other reactions might involve hydrogen instead of electron abstraction in the first step[27] and hydrolysis of the cation in a different manner[29] owing to acyl substitution in the 2-tetrazene.

The formation of 1-nitroso-1,4,4-trimethyl-2-tetrazene is believed to involve a free-radical mechanism similar to one proposed for the oxidation of tertiary amines[33] and the transient formation of trimethyl-2-tetrazene; 1-nitroso-1,2,2-trimethylhydrazine is pre-

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pared from trimethylhydrazine and nitrous acid.[34] A 1,4-disubstituted 2-tetrazene has been proposed as an intermediate in the reaction of *p*-toluenesulfonyl azide with a halomagnesium salt of aniline.[35] Thermally, 1-nitroso-1,4,4-trimethyl-2-tetrazene is more stable than similar 1-nitroso-1,3-diaryltriazenes.[13]

The permanganate oxidation was extended successfully to the alkyl-substituted hydronitrogen, tetramethylhydrazine. According to electron-impact studies, this material has a relatively strong nitrogen–nitrogen single bond,[21] but it is quite easily oxidized to a cation–radical.[36] This latter fact accounts for the analogous reaction. Although the permanganate oxidation of tetra-*n*-propylhydrazine to 1,2-dipropionyl-1,2-dipropylhydrazine has been reported,[37] tetra-*n*-propylhydrazine was not isolated, but was only proposed as an intermediate in the oxidation of dipropylamine, a supposition not consistent with a more recent investigation.[32]

In contrast with degradation reactions commonly associated with oxidation of amines,[38] Davis and Rosenblatt[39] recently oxidized an N-methyl to an N-formyl group in tertiary amines with oxygen and a platinum catalyst at room temperature. Tertiary amines containing aryl groups were more difficult to oxidize; under similar conditions, an N-benzyl group was not oxidized. Both the oxidizing species and the structure of the amine are especially important where dual mechanisms of electron and hydrogen abstraction are possible.[27] Dual oxidation mechanisms were discussed recently in a review of the electrochemical oxidation of amines.[40] While oxidation at low potentials forms a cation radical, at higher potentials another electron and a proton are lost rapidly to form an iminium salt. With amines, oxidants such as chlorine dioxide react according to the low-potential mechanism; oxidants such as permanganate yield products expected from oxidation at higher potentials. Since a cation radical which is more stable than the corresponding radical from amines is formed during the oxidation of the 2-tetrazenes, it is not surprising in retrospection that some chemical oxidants associated with the higher potential reaction for amines would react according to the low-potential mechanism during the oxidation of the tetrasubstituted 2-tetrazenes.

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The Fischer Indole Cyclization of Several *ortho*-Substituted Phenylhydrazones[1,2]

WALTER F. GANNON, JOSEPH D. BENIGNI, DONALD E. DICKSON, AND RALPH L. MINNIS

Regis Chemical Company, Chicago, Illinois 60610

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Fischer indole cyclization of ethyl pyruvate *o*-methoxyphenylhydrazone in ethanolic hydrogen chloride gave 2-carbethoxy-6-chloroindole as the main product. Minor products included 2-carbethoxy-3-chloroindole, the expected 2-carbethoxy-7-methoxyindole, and several indolic dimers. Similarly, ethyl pyruvate *o*-benzyloxyphenylhydrazone gave 2-carbethoxy-6-chloroindole. Cyclization of cyclohexanone *o*-methoxyphenylhydrazone in dilute sulfuric acid yielded 8-methoxy-1,2,3,4-tetrahydrocarbazole as the major product. The only isolated by-product, previously reported to be "12-methoxy-1,2,3,4-tetrahydroisocarbazole," has now been shown to have a dimeric structure. When the reaction was run in ethanolic hydrogen chloride, the dimer hydrochloride became the main product and 8-methoxy-1,2,3,4-tetrahydrocarbazole is formed in lower yield. The structure of the dimers and the reaction mechanism are discussed.

The simplest approach to 7-methoxyindole, an intermediate in a synthetic program on indole chemistry, appeared to be the Fischer indole cyclization of ethyl pyruvate *o*-methoxyphenylhydrazone (**1**). The transformation of *o*-anisidine to 2-carbethoxy-7-methoxyindole (**2**), *via* the hydrazone (**1**), has been reported[3] to proceed in 30% over-all yield; the preparation of the ethoxy analog of **2** by cyclization of the corresponding phenylhydrazone has also been described.[4] However other workers[5] found that cyclization of **1** with ethanolic hydrogen chloride gave an unidentified indole, mp 168°, different from **2**. Our results on the Fischer cyclization of **1** and related compounds are described.

While the reaction of diazotized *o*-anisidine with ethyl α-methylacetoacetate afforded the hydrazone **1** as an oil, use of ethyl α-ethoxalylpropionate[6] yielded crystalline **1**. The latter could be separated into two forms which are presumably the *syn* and *anti* isomers as indicated by analytical and spectral properties and the fact that the mixture and both forms yielded the same product mixtures when cyclized in acid media.

Cyclization of the isomeric hydrazone mixture **1** in ethanolic hydrogen chloride gave a mixture of polar and faster moving components. Fractional crystallization yielded a single compound, mp 177–178°, whose empirical formula corresponded to $C_{11}H_{10}ClNO_2$ (yield 36%). The melting point suggested that the product was 2-carbethoxy-6-chloroindole (**3**),[7] and this was verified by comparison of the product (**3**) and its corresponding acid (**4**) with authentic samples prepared by

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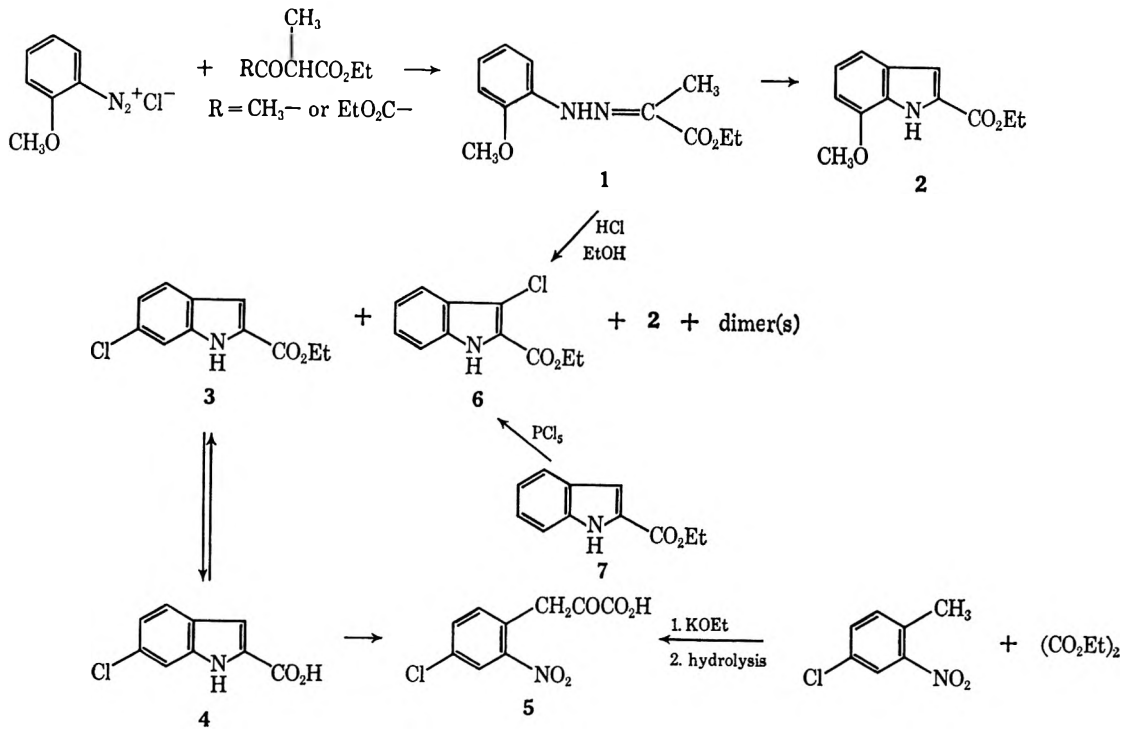
SCHEME I



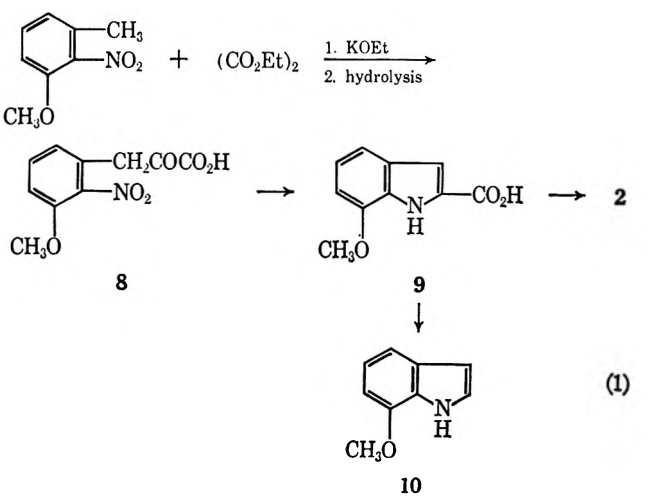
cyclization of the Reissert product (**5**) obtained from 4-chloro-2-nitrotoluene[8] (see Scheme I). It now seems reasonable to assume that the unknown indole obtained previously[5] under these conditions is in fact 2-carbethoxy-6-chloroindole.

Chromatography of the recrystallization mother liquors separated the indolic materials from more polar substances (total yield of indoles was 53%). Examination (tlc) of the indolic mixture indicated the presence of additional 2-carbethoxy-6-chloroindole (**3**), the expected 2-carbethoxy-7-methoxyindole (**2**), and an unknown compound. Fractional crystallization first yielded a mixture of only **3** and the unknown. Further treatment allowed the isolation of a 0.9% yield of the unknown which was shown to be 2-carbethoxy-3-chloroindole (**6**) by comparison with an authentic sample.[9] Comparison of the nmr spectra of the pure 3-chloro compound and the mixture of the 3- and 6-chloro compounds showed that the 3-chloro isomer was present in the greater amount.

The combined mother liquors from the recrystallizations gave an oily solid which showed only 2-carbethoxy-7-methoxyindole (**2**) and 2-carbethoxy-3-chloroindole (**6**) by tlc. The mass spectrum of this solid confirmed these assignments, but in addition showed a parent peak at *m/e* 233 for which we suggest 2-carbethoxy-6-ethoxyindole. The nmr spectrum of this mixture is consistent with these structures. Further attempts to isolate individual components were unsuccessful.

The polar mixture obtained from the alumina column was rechromatographed, whereby a single component, mp 233–235°, was isolated. The nmr spectrum of this compound indicated the presence of CO_2Et, OCH_3, and aromatic protons. The mass spectrum showed a parent peak at *m/e* 406. Lack of material precluded further work on this compound, but the data available, together with results to be discussed later, prompt us to suggest a dimeric structure consisting of 2-carbethoxy-7-methoxyindole coupled to a molecule of the same type wherein the methoxy group has been lost.

The authentic 7-methoxyindole (**10**) was eventually prepared *via* the Reissert synthesis illustrated in eq 1.[10] Conversion of the intermediate acid (**9**) into the ester (**2**) provided comparison material used in the Fischer study.



Cyclization of the hydrazone mixture **1** in mixed acetic and sulfuric acids gave a 4.2% yield of 2-carbethoxy-7-methoxyindole (**2**) as the only isolable indolic product (similar to the previously described results[5]). Attempted cyclization with polyphosphoric acid gave no indication of reaction up to 95°, at which point extensive darkening occurred. No products could be isolated.

We also attempted the cyclization of ethyl pyruvate *o*-benzyloxyphenylhydrazone in ethanolic hydrogen chlo-

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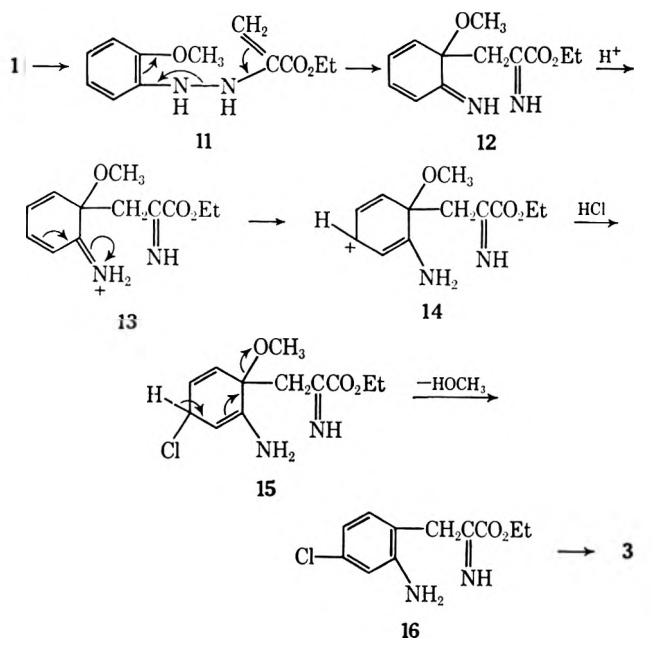
ride. Ek and Witkop[11] abandoned attempts to prepare analogs of this compound when they found that ethyl pyruvate *o*-tosyloxyphenylhydrazone "could not be brought to cyclize." Our reaction became quite dark and was quenched shortly after starting. Tlc of the reaction mixture showed a complex mixture which contained hydrazones and 2-carbethoxy-6-chloroindole (**3**). Column chromatography yielded a solid which was shown to be one of the hydrazone isomers.

We have subjected 2-carbethoxy-7-methoxyindole to refluxing ethanolic hydrogen chloride and recovered it unchanged, implying that the novel reaction leading to the main product (**3**) occurs prior to indole formation. A possible interpretation is illustrated below (Scheme II). Carbon–carbon bond formation of the ene–hydrazine intermediate (**11**) at the occupied *ortho* position gives **12** which by protonation of the ring imino nitrogen and shift of the double bonds subsequently leads to the introduction of chlorine as in **15**. Loss of methanol produces **16** which can then cyclize in normal fashion[12] to give 2-carbethoxy-6-chloroindole (**3**). Admittedly an additional shift of the second ring double bond in species **13** would lead to a carbonium ion in the incipient 4-indole position, but we have been unable to detect any 2-carbethoxy-4-chloroindole in the reaction mixture. Further, it is noteworthy that attack at an occupied site predominates over normal Fischer cyclization at the unoccupied position.

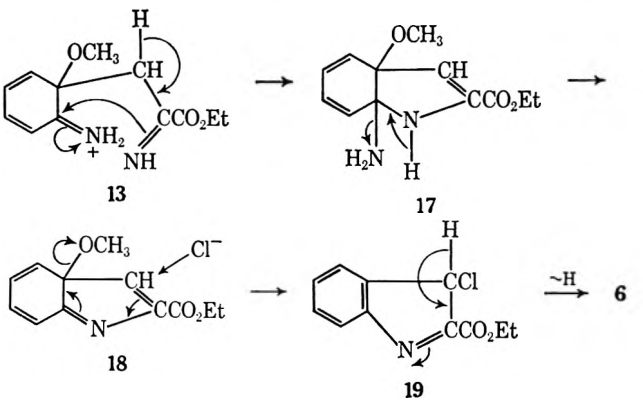
SCHEME II



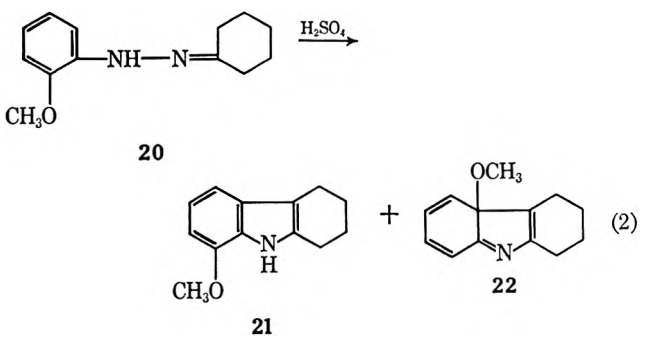
The formation of the by-product **6** may be visualized as shown in Scheme III. Cyclization of structure **13** (see Scheme II) in the "abnormal" Fischer sense[12] would give **17** which, by loss of ammonia, could give rise to structure **18**. Attack of chloride, concurrent with the loss of methanol, and subsequent aromatization could lead to 2-carbethoxy-3-chloroindole (**6**).

While there has been a report[13] of a Fischer indolization wherein a by-product containing a new aromatic substituent was obtained in low yield, the reaction shown in Scheme I is, to our knowledge, the first reported instance of such an exchange determining the main product.

SCHEME III



In connection with these studies we noted that the cyclization of cyclohexanone *o*-methoxyphenylhydrazone (**20**) in dilute sulfuric acid has been reported[13a] to give as major products the normal Fischer product, 8-methoxy-1,2,3,4-tetrahydrocarbazole (**21**) and the unlikely 12-methoxy-1,2,3,4-tetrahydroisocarbazole (**22**) (eq 2). We repeated the published procedure and did indeed obtain compound **21** in 64% crude yield and a quantity (now considered to be 20%) of a solid (A) whose melting point was close to that reported for structure **22**.



Initial evidence indicated that neither compound **22** nor any simple tetrahydrocarbazole structure could fit the data for the reaction by-product. Analysis is consistent with the empirical fromula $C_{25}H_{26}N_2O$ and the mass spectrum displays a parent peak at m/e 370. The nmr spectrum shows one NH, one OCH_3, six to seven aromatic protons in a complex system, and an unresolved area of multiplets in the aliphatic region.

When the cyclization of **20** was conducted in ethanolic hydrogen chloride, the normal product (**21**) was isolated in only 9% yield and a new compound (B) was obtained as the major product (28%), $C_{25}H_{29}ClN_2O$. The spectral data are reminiscent of, but not identical with, the first product (A). Treatment of the latter with ethanolic hydrogen chloride gave the new compound B; conversely passage of the chloro compound B over an alumina column or treatment with base returned A. While B appears to be a hydrochloride hydrate of A it is noteworthy that A failed to form a crystalline derivative with picric, sulfuric, or fumaric acids.

(11) A. Ek and B. Witkop, *J. Amer. Chem. Soc.*, **76**, 5579 (1954).

(12) For a review of the Fischer indole synthesis, see B. Robinson, *Chem. Rev.*, **63**, 373 (1963).

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While the data rule out structure 22 for the reaction by-product A, they do not permit an unambiguous structural assignment. Similar to the polar compound isolated from the cyclization of ethyl pyruvate *o*-methoxyphenylhydrazone, we suggest for compound A a dimeric structure composed of 8-methoxy-1,2,3,4-tetrahydrocarbazole (21) coupled to a molecule of 21 which has lost the methoxy group. However additional information would be required to determine the point at which the two ring systems are joined and the disposition of double bonds.

Experimental Section[14]

Ethyl Pyruvate 2-Methoxyphenylhydrazone (1).—To a solution of 28.5 g (0.23 mol) of *o*-anisidine in 46 ml of hydrochloric acid and 68 ml of water cooled to 5–7° was added a solution of 16.8 g (0.24 mol) of sodium nitrite in 30 ml of water. The addition took 20 min, and the resulting solution was stirred for an additional 20 min.

This diazonium solution was added dropwise below the surface at 5–7° over 25 min with stirring to a solution of 174 g (2.10 mol) of sodium acetate, 460 ml of water, and 70 ml of alcohol. To the resulting suspension was added 50 g (0.25 mol) of ethyl α-ethoxalylpropionate dropwise over a period of 1.0 hr at 5–7°, and the suspension was stirred at 7–10° for 2 hr. After the water had been decanted the resulting oil was crystallized from 50% aqueous ethanol to give 44.0 g (82.2%) of product, mp 66–80°.

Separation of Isomers.—The crude hydrazone was recrystallized twice from ethanol to give a solid: mp 87–90°; tlc (silica gel, benzene), single spot, R_f 0.52; ir ($CHCl_3$) 5.99 μ (ester carbonyl).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.94; Y, 6.76; N, 12.16.

The mother liquors were concentrated and cooled slowly to return 5.8 g of the other isomer: mp 68–70° (recrystallization from alcohol did not raise the melting point); tlc (silica gel, benzene), single spot, R_f 0.61; ir ($CHCl_3$) 5.95 μ (ester carbonyl).

Anal. Found: C, 60.76; H, 6.55; N, 11.81.

Fischer Cyclization of 1 (Mixture).—A solution of 50.0 g (0.212 mol) of 1 in 1.0 l. of saturated ethanolic hydrogen chloride was heated to reflux for 25 min. The mixture was cooled and poured into ice–water; the resulting solid was collected, washed well with water, and dried to give 35.3 g of material melting at 115–145°. The solid was recrystallized from benzene–hexane (9:5) to give in two crops 17.2 g (36.1%) of 2-carbethoxy-6-chloroindole, mp 169–173°. The product was recrystallized from benzene–hexane to a constant melting point of 177–178° (lit.[5] mp 177–178°). It was found to be identical with authentic 2-carbethoxy-6-chloroindole prepared as previously described[8] with respect to melting point, mixture melting point, tlc, and ir.

Saponification of the ester obtained from the reaction in the usual manner yielded 64.4% 2-carboxy-6-chloroindole, which, after purification, melted at 244–245° dec: ir (KBr) 5.97 μ (C=O of acid); tlc [silica gel H, methanol–water (1:1)], single spot, R_f 0.75. This compound was identical with authentic 2-carboxy-6-chloroindole prepared as previously described[8] with respect to melting point, mixture melting point, tlc, and ir.

Anal. Calcd for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.41; H, 3.32; N, 7.23.

The mother liquors were taken to dryness, and the resulting 17 g of oil was dissolved in 30 ml of benzene–hexane (3:1) and chromatographed through a dry packed alumina column 1 × 24 in. The column was eluted with benzene–hexane (3:1). Thin layer chromatography (silica Gel H, benzene) showed the first 10 fractions of 80 ml to be identical, a mixture of 2-carbethoxy-6-chloroindole and two other compounds having lower R_f values. The combined fractions were taken to dryness to yield 7.8 g of solid, which was recrystallized from hexane–benzene (9:1) to yield 3.2 g of solid, mp 130–145°. Thin layer chromatography showed the presence of 2-carbethoxy-6-chloroindole and only one other compound having a lower R_f value.

The solid was dissolved in 27 ml of methanol and cooled very slowly to room temperature. There resulted 0.42 g of crystals, mp 153–156°, which was recrystallized from methanol and then from hexane to give long white needles: mp 156–157°; ir ($CHCl_3$) 2.98 (NH) and 5.89 μ (C=O); tlc (silica gel, benzene), single spot, R_f 0.52. This compound was identical with authentic 2-carbethoxy-3-chloroindole prepared by the literature method[9] with respect to melting point, mixture melting point, tlc, and ir.

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.23; Cl, 15.86. Found: C, 59.19; H, 4.67; N, 6.32; Cl, 15.72.

The mother liquors, from which the mixture of the two esters was taken, was concentrated to dryness. Tlc showed the presence of 2-carbethoxy-3-chloroindole, 2-carbethoxy-6-chloroindole, and 2-carbethoxy-7-methoxyindole. Continued crystallization from benzene–hexane left a near-solid which showed only 2-carbethoxy-3-chloroindole and 2-carbethoxy-7-methoxyindole by tlc: nmr δ 1.42 and 1.52 (overlapping triplets, CH_3 of ester), 3.93 (s, OCH_3), 4.38 (q, CH_2) 6.62–7.67 ppm (m, aromatic); mass spectrum *m/e* 223, 229 ($C_{11}H_{10}ClNO_2$), 219 ($C_{12}H_{13}NO_3$), and 233 ($C_{13}H_{15}NO_3$).

The chromatography column was finally eluted with ethanol to give 7.5 g of semisolid which was rechromatographed. Elution with chloroform–benzene (9:1) gave 0.04 g, which was recrystallized from benzene: mp 233–235°; nmr δ 1.35 (broad m, ester CH_3), 4.09 (s, OCH_3), 4.34 (broad m, CH_2 of ester), and 7.13–7.55 ppm (broad m, aromatic); mass spectrum *m/e* 406–407.

Fischer Cyclization of *syn*- and *anti*-Hydrazones Separately.—A solution of 5.0 g (0.21 mol) of ethyl pyruvate *o*-methoxyphenylhydrazone (mp 68–70°) in 200 ml of alcoholic hydrogen chloride was heated to 50° for 30 min. Tlc showed that the starting material had been completely consumed. The mixture was concentrated to half its volume, cooled, and poured into cold water. The resultant solid was collected, air dried, and recrystallized from benzene–hexane to give 1.1 g (23.2%) of 2-carbethoxy-6-chloroindole, mp 166–171°. A sample was recrystallized to a constant melting point of 177–178°, and was identical in all respects with the authentic sample of 2-carbethoxy-6-chloroindole.

Concentration of the filtrate gave an oil which could not be induced to crystallize; tlc [silica gel, benzene–ethyl acetate (19:1)] shows additional 2-carbethoxy-6-chloroindole at R_f 0.52 as well as several other components.

When a 5.0-g sample of the second hydrazone isomer (mp 88–90°) was subjected to the same conditions, a 1.18-g (24.7%) yield of 2-carbethoxy-6-chloroindole was obtained; tlc of these mother liquors was essentially the same as that described above.

2-Carbethoxy-7-methoxyindole (2).—Authentic 2-carboxy-7-methoxyindole prepared by the literature method[10] was treated with ethanol and sulfuric acid in the usual manner to give a 62% yield of product: mp 114–115° (recrystallization from hexane did not change the melting point); tlc [silica gel, benzene–ethyl acetate (19:1)], single spot, R_f 0.47.

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.91; N, 6.39. Found: C, 66.01; H, 6.17; N, 6.66.

The indole itself was prepared by decarboxylation of the 2-carboxy derivative.[10]

Attempted Reaction of 2 under Fischer Cyclization Conditions.—A solution of 0.25 g (0.0011 mol) of 2 in 10 ml of ethanolic hydrogen chloride was stirred and heated at 50° for 0.5 hr. The solvent was removed and the residue was recrystallized from alcohol to give 0.18 g (72%) of unchanged ester, mp 114–115°. The mother liquors showed no trace of 2-carbethoxy-6-chloroindole by tlc.

Ethyl Pyruvate 2-Benzyloxyphenylhydrazone.—A mixture of 50.0 g (0.25 mol) of *o*-benzyloxyaniline,[11] 50 ml of concentrated hydrochloric acid, and 50 ml of water was heated and stirred at 70° for 10 min. The suspension was cooled to 7° and to the mixture was added dropwise over 10 min a solution of 18.3 g (0.265 mol) of sodium nitrite in 50 ml of water. Stirring and cooling were continued for 0.5 hr.

To a slurry made from 190 g (2.26 mol) of sodium acetate, 75 ml of alcohol, and 500 ml of water at 5–7°, a 54.0-g (0.267 mol) portion of ethyl α-ethoxalylpropionate was added. To the

(14) Melting points were taken on a Thomas–Hoover Uni-Melt capillary apparatus and are corrected. Ultraviolet spectra were measured on a Perkin-Elmer recording spectrophotometer, Model 202, in ethanol solution. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137. Nuclear magnetic resonance spectra were measured on a Varian A-60 spectrometer in deuteriochloroform solution at the Simon Research Laboratory, Elgin, Ill., or at the National Institutes of Health, Bethesda, Md. Mass spectra were also run at the latter address. Elemental analyses were performed by either Midwest Microlab, Inc., Indianapolis, Ind., or Micro-Tech Laboratories, Skokie, Ill.

stirred suspension (5–7°) was added dropwise over 1 hr the diazonium solution prepared above. Stirring was continued for 1 hr more at room temperature. The suspension was extracted with 700 ml of ether; the extract was dried and concentrated to 100 ml. On cooling, a yellow solid crystallized. It was collected, washed with ether, and dried to yield 43.0 g (55.0%) of isomeric hydrazone esters, mp 50–65°.

A sample was recrystallized from hexane twice and dried at 27° under vacuum for 6 hr for analysis: ir ($CHCl_3$) 5.93 (ester C=O), 7.89 μ (ether); tlc (silica gel, benzene), two spots, R_f 0.29 and 0.80.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.49; H, 6.66; N, 8.70.

Fischer Cyclization of Ethyl Pyruvate 2-Benzyloxyphenylhydrazone.—A solution of 20.0 g (0.64 mol) of ethyl pyruvate 2-benzyloxyphenylhydrazone in 140 ml of saturated ethanolic hydrogen chloride was heated to reflux for 6 min. The suspension, which became quite dark, was cooled and poured into water. The products were extracted with ethyl acetate; the organic layer was dried and taken to dryness. The oil was dissolved in benzene–hexane (4:1) and poured over an alumina column 0.5 × 12 in. The first 20 ml from the column was taken to dryness and crystallized from hexane to give 0.50 g of solid, mp 76–79°. It was recrystallized from hexane to a constant melting point of 77–79°. It was dried then at room temperature 4 hr for analysis: ir ($CHCl_3$) 5.91 (ester C=O) and 7.92 μ (ether).

Anal. Calcd for $C_{18}N_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.32; H, 6.73; N, 8.87.

Fischer Cyclization of 19. A. Dilute Sulfuric Acid.—This reaction was run by the Pausacker procedure[13a] starting with 99 g (0.453 mol) of cyclohexanone 2-methoxyphenylhydrazone. The ether-soluble portion gave 59.5 g (65.3%) of an orange oil, which was distilled to give 34.3 (38%), bp 138–155° (0.4 mm). A second distillation gave an analytical sample of **20**, bp 140–143° (0.3 mm) [lit.[13a] bp 205–215° (15 mm)].

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.48; H, 7.38; H, 6.68.

The ether-insoluble fraction was extracted with hot benzene which gave 8.0 g (9.6%) of solid, mp 148–152°. Several recrystallizations from benzene–hexane gave an off-white solid, mp 152–155°.

Anal. Calcd for $C_{25}H_{28}N_2O$: C, 81.04; H, 7.07; N, 7.56. Found: C, 80.69; H, 7.64; N, 7.55.

Recrystallization of a sample from ethanol to constant melting point gave a solid, mp 235–237°.

Anal. Found: C, 80.98; 80.79; H, 7.27, 7.07; N, 7.37, 7.50.

The solution ir spectra of the two compounds were superimposable: ir ($CHCl_3$) 2.8, 3.25, 3.32, 3.43, 6.13, 6.23, 6.28, 6.69, 7.8 μ; uv (EtOH) 240, 292 mμ (ϵ 49,300, 12,500); mass spectrum m/e 370; nmr δ 1.11–3.30 (m, with large peaks at 1.61, 1.86, and 2.68), 3.93 (s, OCH_3), 6.58–7.47 (m, 6–7), and 8.12 (broad s, NH); tlc [silica gel, benzene–hexane (9:1)], single spot, R_f 0.75.

On standing either as a solid or in solution, this compound began to show a second tlc spot at the origin; however, neither the melting point nor the infrared spectrum is affected.

B. Ethanolic Hydrogen Chloride.—A solution of 35.0 g (0.16 mol) of 19 in 600 ml of saturated ethanolic hydrogen chloride was heated and stirred at 55° for 50 min. The suspension was cooled and poured into water. The resulting semisolid was collected, dried, and triturated with ether. The ether was used to extract the filtrate from which the solid was obtained. The ether layer was dried (Na_2SO_4) and concentrated to dryness. The residual oil was taken up in benzene and poured over a dry packed column of alumina. There was obtained 2.9 g (9.2%) of oil, the ir and tlc of which were identical with those of authentic **20**. The compound was further identified as the picrate, mp 145–146° dec, undepressed on admixture with authentic picrate (lit.[15] mp 145–146° dec).

The ether-triturated solid (15.5 g) was crystallized from ethanol to yield in 4 crops 9.5 g (28.4%) of solid, mp 195–197° dec. A sample was recrystallized from ethyl acetate–ethanol to a constant melting point of 195–197° dec and dried at 27° under vacuum for 20 hr for analysis: ir ($CHCl_3$) 2.8, 3.01, 3.32, 3.45, 4.11 (broad), 5.02, 6.08, 6.16, 6.67, 7.71 μ; uv (EtOH) 240, 292 mμ (ϵ 35,400, 10,300); nmr (DMSO-*d*) δ 1.19–3.69 (m with large peaks at 1.81 and 2.66), 4.07 (s, OCH_3), 4.38 (large s, water from sample and/or DMSO), and 6.56–7.55 (m, aromatic); tlc [silica gel, benzene–hexane (9:1)], single spot, R_f 0.00.

Anal. Calcd for $C_{25}H_{29}ClN_2O_2$: C, 70.65; H, 6.89; N, 6.59; Cl, 8.34. Found: C, 70.74, 70.83; H, 7.10, 6.87; N, 6.47, 6.51; Cl, 8.31, 8.27.

This substance is insoluble in hot water, but dissolves readily in cold ethanol. It gives a positive silver nitrate test only on heating. After standing for a short time the solution begins to show a second spot at R_f 0.75 upon respotting.

Interconversion of B and A. A.—To a solution of 0.3 g of compound B in methanol was added methanolic potassium hydroxide. The yellow color disappeared. Removal of the solvent left 0.26 g of solid, mp 150–153°. Recrystallization from ethanol raised the melting point to 235–237°. This compound is identical with compound A with respect to melting point, mixture melting point, and ir.

B.—Compound A, 200 mg, mp 235–237°, was dissolved in 2 ml of ethanolic hydrogen chloride. The solution was concentrated at atmospheric pressure. Trituration of the residue with ethyl acetate–hexane gave a solid which was then recrystallized from ethanol–ethyl acetate to give a solid, mp 195–197° dec. This solid was identical with compound B with respect to melting point, mixture melting point, and ir.

Registry No.—**1** (*syn* isomer), 20538-15-2; **1** (*anti* isomer), 20538-16-3; **2**, 20538-12-9; ethyl pyruvate 2-benzyloxyphenylhydrazone (*syn* isomer), 20538-14-1; ethyl pyruvate 2-benzyloxyphenylhydrazone (*anti* isomer), 20538-13-0.

Acknowledgment.—The authors wish to express their appreciation to Dr. John Daly of the National Institutes of Health for performing some of the nmr and mass spectral measurements.

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Cyclization of Basic Amide Hydrochlorides. A New Synthesis of Substituted Lactams

RAYMOND E. STENSETH,[1a,b] AND FREDERICK F. BLICKE[1c]

College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48104

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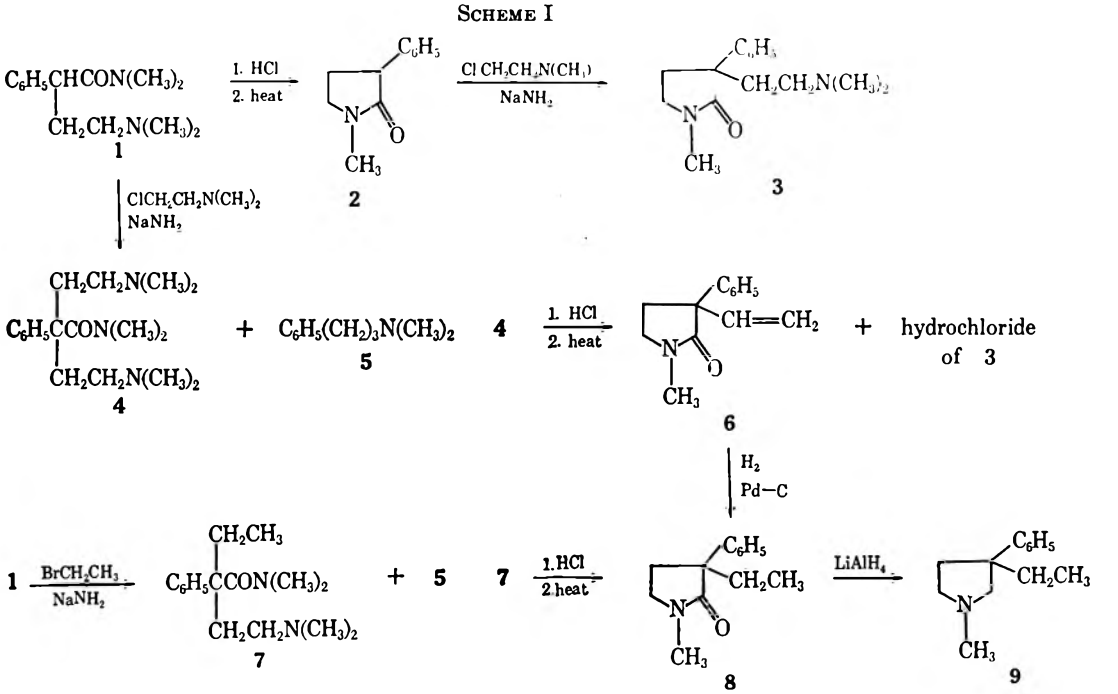
Hydrochlorides of certain basic amides were cyclized by heat to form a 2-pyrrolidinone or 2-piperidone in high yields. N,N-Dimethyl-4-dimethylamino-2-phenylbutyramide (1) hydrochloride, pyrolyzed at 280–285°, gave 1-methyl-3-phenyl-2-pyrrolidinone (2, 86%). The 3-ethyl and 3-phenyl derivatives of 2 and 1-methyl-3-phenyl-2-piperidone were similarly prepared. N,N-Dimethyl-4-dimethylamino-2-(2-dimethylaminoethyl)-2-phenylbutyramide dihydrochloride yielded a mixture of the 3-(2-dimethylaminoethyl) and 3-vinyl derivatives of 2. Compounds 1 and 2 were converted into Ivanov-like reagents which, by reaction with formaldehyde, formed the 2- and 3-hydroxymethyl derivatives, respectively.

Discovery in this laboratory that Ivanov-like reagents can be prepared from suitably substituted β-lactams[2] was extended to the γ-lactam series. A suitable lactam for this purpose is 1-methyl-3-phenyl-2-pyrrolidinone[3,4] (2). An attempt to prepare 2 by treating 4-dimethylamino-2-phenylbutyric acid[5] with phosphorus trichloride to form the acid chloride as an intermediate and then heating the reaction mixture yielded only a gummy product, although other 2-pyrrolidinones have been prepared in this manner.[6-10]

The desired pyrrolidinone was prepared instead from the hydrochloride of the N,N-dimethylamide of the above acid. Thus, 2 was synthesized in 86% yield by heating N,N-dimethyl-4-dimethylamino-2-phenylbutyramide (1) hydrochloride for a short time at 280–285° (see Scheme I). Trimethylamine hydrochloride, which also formed, partially decomposed liberating trimethylamine.

Cyclization of other basic amide hydrochlorides is summarized in Table I. Pyrolysis of **4a** yielded a mixture of 3-(2-dimethylaminoethyl)-1-methyl-3-phenyl-2-pyrrolidinone[9] (3) hydrochloride and 1-methyl-3-phenyl-3-vinyl-2-pyrrolidinone (6); 3 was also prepared from 2. The reaction was extended to the piperidone series by cyclization of **15a** to give 1-methyl-3-phenyl-2-piperidone (17). Other reactions are shown in Scheme I.

SCHEME I



N,N-Dimethyl-3-phenylpropylamine (5) was formed in substantial yield owing to elimination of the amide group from 1 when 4 and 7 were prepared. A similar cleavage has been reported during the second alkylation of the 2 position of related substituted phenylacetamides using sodium amide.[11]

Reaction of formaldehyde with Ivanov-like reagents[12] prepared from 1 and 2 gave the corresponding 2- and 3-hydroxymethyl derivatives (10 and 12, repectively,

(1) (a) Abstracted in part from the Ph.D. dissertation of R. E. S., Lilly Endowment, Inc., Fellow, University of Michigan, 1961. (b) To whom correspondence should be addressed: Organic Chemicals Division, Monsanto Co., 1700 S. Second Street, St. Louis, Mo. 63177. (c) Deceased.

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(7) D. J. Dupré, J Elks, B. A. Hems, K. N. Speyer, and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

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(9) R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Amer. Chem. Soc.*, **71**, 2821 (1949).

(10) See also W. Wilson, *J. Chem. Soc.*, 3524 (1952), and F. F. Blicke and E.-P. Tsao, *J. Amer. Chem. Soc.*, **75**, 4334 (1953).

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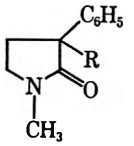
(12) Hydrolysis of the reagents with HCl regenerated **1** and **2** in 92% and 87% yield, respectively.

TABLE I

SUBSTITUTED 1-METHYL-3-PHENYL-2-PYRROLIDINONES[a]

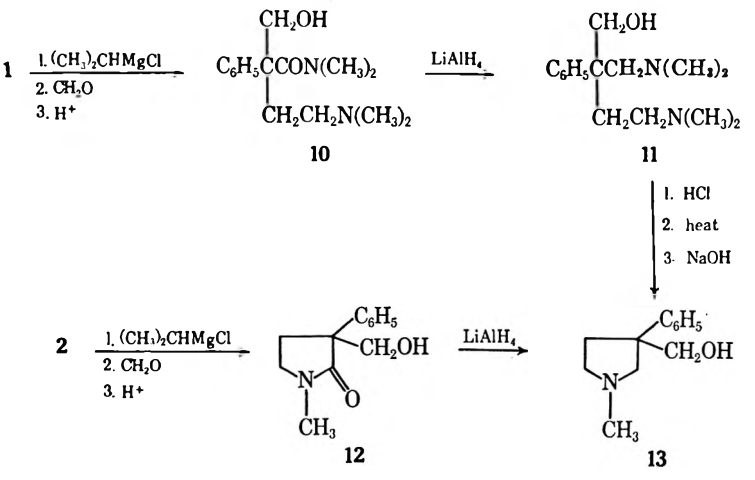


Product	R	Base or salt	Compound cyclized	Bath temp, °C	Yield, %	Bp (mm), °C	Mp, °C
2	H		1a	280–285	86	120–124 (0.4)	60–61[b]
3	$CH_2CH_2N(CH_3)_2$	Base	4a	280–285	38	137–141[c] (0.6)	68–69[d]
3a	$CH_2CH_2N(CH_3)_2$	Hydrochloride					191–192
3b	$CH_2CH_2N(CH_3)_2$	Acid oxalate					161–162
6	$CH{=}CH_2$		4a	280–285	36	110–113[e] (0.2)	
8	CH_2CH_3		7a	265–270	93	106–108[e,f] (0.15)	
16	C_6H_5		14a	250	88		144–145[g]

		Analyses, %					
		Carbon		Hydrogen		Nitrogen	
Product	Formula	Calcd	Found	Calcd	Found	Calcd	Found
2	$C_{11}H_{13}NO$	75.40	75.42	7.48	7.41	7.99	8.24
3	$C_{15}H_{22}N_2O$	73.13	72.86	9.00	8.95	11.37	11.43
3a	$C_{15}H_{23}ClN_2O$[h]	63.70	63.49	8.20	8.29	9.91	10.13
3b	$C_{17}H_{24}N_2O_6$	60.70	60.74	7.19	7.19	8.33	8.49
6	$C_{13}H_{15}NO$	77.58	77.43	7.51	7.83	6.96	6.96
8	$C_{13}H_{17}NO$	76.81	76.82	8.43	8.63	6.89	6.97

[a] All of the salts were prepared in ether. Compound 2 was recrystallized from ether; 3 from petroleum ether (bp 30–40°); 3a from acetone–absolute ethanol; 3b from isopropyl alcohol; 16 from benzene–cyclohexane. [b] Lit.[3] mp 58–59°; lit.[4] mp 60–61°. [c] Crystalline 3 was obtained by being converted to 3a (27% yield from 4a), liberating 3, and redistilling: bp 128–130° (0.4 mm); 27% yield of 3a from 4a; 3, bp 123–126° (0.2 mm). [d] Lit.[5] bp 137–138° (0.25 mm), mp 66.5–68°, ir (Nujol) 1685 cm^{-1} (C=O). The ir spectra of 3 prepared from 4a and from 2 (Table II) were identical. [e] Ir (neat) 1685 cm^{-1} (C=O) and, for 6, ir 918 and 1000 (C=C bend) and 1635 cm^{-1} (C=C stretch). [f] F. J. Marshall [*J. Org. Chem.*, 23, 503 (1958)] reported bp 130–132° (0.75 mm). [g] Lit.[7] mp 146.5–147°. The mixture melting point with an authentic sample[7] (mp 144–145°) was 144–145°. [h] Calcd: Cl, 12.54. Found: Cl, 12.64.

SCHEME II



Scheme II). The 2-(1-hydroxypropyl) derivative (**18**) of **1** and the 3-(1-hydroxycyclohexyl) derivative (**19**) of **2** were similarly prepared. Other reactions are shown in Scheme II.

Experimental Section

Melting points are corrected and boiling points uncorrected.

Basic Amides (Table II).—The general procedure is illustrated in the case of **1**; modifications for **3**, **4**, **7**, and **14** are given below.

N,N-Dimethyl-4-dimethylamino-2-phenylbutyramide (1).—N,N-Dimethylphenylacetamide (163.2 g, 1.0 mol) in dry toluene was added dropwise to a stirred, refluxing suspension of 58.5 g (1.5 mol) of sodium amide in toluene and the mixture was refluxed for 4 hr. The temperature was lowered slightly and 161.4 g (1.5 mol) of 2-dimethylaminoethyl chloride[13] in toluene was added dropwise. The mixture was refluxed for 6 hr and cooled, and water was added. The toluene phase and a toluene extract of the aqueous phase were extracted with HCl. Crude **1** was liberated with NaOH, extracted with ether, dried ($MgSO_4$), and distilled.

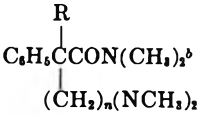
For **3**, **4**, **7**, and **14**, the mole ratio of sodium amide to alkylating agent to organic amide was 1.2:1.2:1. For **14**, the organic amide was added as a suspension in hot toluene to the sodium amide suspension; ether removal gave crude **14** as a solid.

The crude oils of **4** and **7** yielded **5**, bp 35–36° (0.2 mm) (24%)

(13) Liberated from the hydrochloride just before use by R. R. Burtner's method [*J. Amer. Chem. Soc.*, 71, 2578 (1949)] and the toluene solution was kept ice cold to minimize cyclization.

TABLE II

BASIC AMIDES[a]



Compd	n	R	Base or salt	Yield, %	Bp (mm), °C	Mp, °C
1	2	H	Base	84	109–115 (0.3)	
1a	2	H	Hydrochloride			159–160
1b	2	H	Acid oxalate			155–156
4	2	$CH_2CH_2N(CH_3)_2$	Base	39	154–155 (1)	64–66
4a	2	$CH_2CH_2N(CH_3)_2$	Dihydrochloride			242–243
7	2	CH_2CH_3	Base	41	106–109 (0.2)	
7a	2	CH_2CH_3	Hydrochloride			209–210
14	2	C_6H_5	Base	44		95–97[c]
14a	2	C_6H_5	Hydrochloride			226–228[c]
15	3	H	Base	89	132–135 (0.6)	
15a	3	H	Hydrochloride			134–135
3[b]	Prepared from 2		Base	70	133–135[d] (0.5)	68–69[e]
3a			Hydrochloride			192–193
3b			Acid oxalate			161–162

		Analyses, %							
		Carbon		Hydrogen		Nitrogen		Chlorine	
Compd	Formula	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
1	$C_{14}H_{22}N_2O$	71.75	71.65	9.46	9.36	11.96	11.90		
1a	$C_{14}H_{23}ClN_2O$	62.09	62.07	8.56	8.47	10.35	10.55	13.09	13.22
1b	$C_{16}H_{24}N_2O_5$	59.24	59.35	7.46	7.49	8.64	8.81		
4	$C_{18}H_{31}N_3O$	70.78	70.76	10.23	10.10	13.76	13.99		
4a	$C_{18}H_{33}Cl_2N_3O$	57.13	57.13	8.79	8.69	11.11	11.17	18.74	18.64
7	$C_{16}H_{26}N_2O$	73.24	73.08	9.99	9.93	10.68	10.77		
7a	$C_{16}H_{27}ClN_2O$	64.30	63.98	9.11	8.91	9.38	9.52	11.86	11.99
15	$C_{15}H_{24}N_2O$	72.54	72.36	9.74	9.59	11.28	11.00		
15a	$C_{15}H_{25}ClN_2O$	63.25	63.27	8.85	8.87	9.84	10.04	12.45	12.50

[a] All of the salts were prepared in ether. Compounds **1a** and **1b** were recrystallized from absolute ethanol; **4a** from absolute ethanol–ether; **7a**, **14a**, and **3b** from isopropyl alcohol; **14** from cyclohexane; **15a** from acetone; **3** from petroleum ether (bp 30–40°); **3a** from acetone–absolute ethanol. Compound **4** was triturated with petroleum ether (bp 30–40°). [b] Compound **3** does not conform to the general formula. [c] R. B. Moffett and B. D. Aspergren [*J. Amer. Chem. Soc.*, **79**, 4462 (1957)] reported mp 97–99°, hydrochloride mp 228–230°. [d] Crystalline **3** was obtained by being converted to **3a** (62% yield from **2**), liberating **3**, and redistilling: bp 128–130° (0.4 mm). [e] Lit.[9] bp 137–138° (0.25 mm), mp 66.5–68°. Ir (Nujol) 1685 cm^{-1} (C=O); the ir spectra of **3** prepared from **2** and from **4a** (Table I) were identical.

and bp 42° (0.3 mm) (17%), respectively [lit.[14] bp 117–118° (26 mm)]. The positive identification of **5** was established by mixture melting points of picrates,[15] hydrochlorides,[14] acid oxalates,[15] and methiodides,[14] using an authentic sample of **5**.[14]

Substituted 1-Methyl-3-phenyl-2-pyrrolidinones (Table I).—The general procedure is illustrated in the case of **2**; modifications for **3**, **6**, and **16** are given below.

1-Methyl-3-phenyl-2-pyrrolidinone (2).—The salt **1a** (13.5 g, 0.05 mol) was heated at 280–285° under a stream of dry N_2 connected to an ether scrubber. When gas evolution had almost ceased (about 20 min), **2** was extracted with anhydrous ether, leaving a residue of trimethylamine hydrochloride. The extract was dried ($MgSO_4$), concentrated, and distilled.

Picric acid in ether was added to the trimethylamine solution in the scrubber to give 1.1 g of the picrate, mp 215–216° (from absolute ethanol) (lit.[16] mp 216°).

Compounds **3** and **6** were separated by adding water to the reaction mixture and extracting crude **6** with ether; **3** was liberated from the aqueous phase with NaOH and extracted with ether. Mixture melting points of **3**, **3a**, and **3b**, Table I, with their counterparts from Table II verified the structure of **3**. Compound **6** decolorized instantly solutions of Br_2 and $KMnO_4$.

(14) M. Tiffeneau and K. Fuhrer, *Bull. Soc. Chim. Fr.*, (4) **15**, 162 (1914).

(15) P. M. G. Bavin, C. R. Ganellin, J. M. Loynes, P. D. Miles, and H. F. Ridley, *J. Med. Chem.*, **9** (5), 790 (1966).

(16) M. Delépine, *Ann. Chim.* (Paris), (7) **8**, 439 (1896).

Compound **16** was extracted with benzene after water was added to the reaction mass.

1-Methyl-3-phenyl-2-piperidone (17).—This compound was prepared from **15a** at 285–290° by the pyrrolidinone general procedure: 79% yield; bp 120–123° (0.3 mm).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.83; H, 7.94; N, 7.18.

3-Ethyl-1-methyl-3-phenyl-2-pyrrolidinone (8) (Prepared from 6).—A mixture of 6.0 g (0.03 mol) of **6**, 0.06 g of 5% palladium on carbon, and absolute ethanol was hydrogenated under an initial pressure of 50 psi for 2 hr. Filtration and distillation of the filtrate gave 5.9 g (97%) of **8**: bp 108–111° (0.4 mm); ir (neat) 1685 cm^{-1} (C=O). The ir spectrum was identical with that of **8** prepared from **7a**.

3-Ethyl-1-methyl-3-phenylpyrrolidine (9). A.—Compound **8** (8.1 g, 0.04 mol, prepared from **7a**) in ether was reduced with 2.3 g (0.06 mol) of $LiAlH_4$ to give 7.5 g of crude **9** (not distilled because of foaming).

The hydrochloride was prepared in ether: mp 164–165° (from acetone).

Anal. Calcd for $C_{13}H_{20}ClN$: C, 69.16; H, 8.93; N, 6.20; Cl, 15.71. Found: C, 69.29; H, 8.99; N, 6.30; Cl, 15.89.

The acid oxalate was prepared in ether: mp 132–133° (from acetone).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64 84; H, 7.72; N, 5.17.

B.—Compound **9** was similarly prepared from **8** prepared from

6. The hydrochloride melted at 164–165°, mmp 164–165°. The acid oxalate melted at 132–133°, mmp 132–133°.

Compounds Obtained from Ivanov-Like Reactions (Table III).—The general procedure is illustrated in the case of **10**; modifications for **12**, **18**, and **19** are given below.

TABLE III

COMPOUNDS OBTAINED FROM IVANOV-LIKE REACTIONS[a]

	Base or salt	Yield, %	Mp, °C
	Basic Amides		
10	Base	61	121–122
10a	Hydrochloride		180–181
10b	Acid oxalate		162–163
18	Base	84[b]	
18a	Acid oxalate	64	200–201
	Pyrrolidinones		
12		15	103–104
12a	*p*-Nitrobenzoate		172–173
19		12	133–134

		Analyses, %					
		Carbon		Hydrogen		Nitrogen	
Compd	Formula	Calcd	Found	Calcd	Found	Calcd	Found
10	$C_{16}H_{24}N_2O_2$	68.15	68.24	9.15	9.13	10.60	10.72
10a	$C_{16}H_{25}ClN_2O_2$[c]	59.88	59.77	8.38	8.40	9.31	9.39
10b	$C_{17}H_{16}N_2O_6$	57.61	57.69	7.39	7.38	7.91	8.16
18a	$C_{16}H_{20}N_2O_6$	59.67	59.64	7.91	7.90	7.33	7.56
12	$C_{12}H_{15}NO_2$	70.21	70.36	7.37	7.44	6.83	6.91
12a	$C_{19}H_{18}N_2O_5$	64.40	64.44	5.12	5.32	7.91	7.70
19	$C_{17}H_{23}NO_2$	74.69	74.85	8.48	8.59	5.12	5.17

[a] The salts **10a** and **10b** were prepared in ether–absolute ethanol and **18a** in ether. Compounds **10**, **10b**, **18a**, and **12a** were recrystallized from absolute ethanol; **10a** from absolute ethanol–ether; **12** and **19** from benzene–petroleum ether (bp 60–75°). [b] Crude yield. [c] Calcd: Cl, 11.79. Found: Cl, 11.78.

N,N-Dimethyl-4-dimethylamino-2-hydroxymethyl-2-phenylbutyramide (10).—Compound **1** (23.4 g, 0.1 mol) in anhydrous ether was added dropwise to a stirred solution of isopropylmagnesium chloride prepared from 11 ml (0.12 mol) of isopropyl chloride, 2.7 g (0.11 g-atom) of magnesium, 0.5 ml of ethyl bromide, and ether. The mixture was refluxed for 2 hr. Formaldehyde (approximately 0.11 mol), prepared by depolymerization[17] at 200° of 3.5 g of paraformaldehyde (dried over P_2O_5), was swept by dry N_2 into the cooled mixture over a 1-hr period, followed by an additional 10 hr at room temperature. Water and HCl were added to extract **10**, which was liberated with NaOH, extracted with benzene, and dried ($MgSO_4$). Solvent removal gave crude **10**, which was triturated with ether.

For **18**, propionaldehyde in ether was added to the Ivanov-like reagent and the mixture was refluxed for 3 hr.

When preparing **12**, a black oil precipitated midway through addition of **2**. Benzene addition failed to dissolve it. After hydrolysis with HCl, the aqueous layer was extracted with ether. This extract and the ether–benzene layer were dried ($MgSO_4$) and concentrated and the residue was refrigerated in ether–petroleum ether (bp 60–75°) to yield **12**; **2** was recovered (58%) from the mother liquor.

For **19**, **2** was added in benzene to the Grignard reagent. A black oil separated during addition of cyclohexanone in benzene. The mixture was stirred for 5 hr and treated as given above for **12**. The residue was triturated with ether–petroleum ether (bp 30–40°) to give crude **19**; **2** was recovered (53%) from the mother liquor.

4-Dimethylamino-2-(dimethylaminomethyl)-2-phenyl-1-butanol (11) Dihydrochloride.—Compound **10** (26.4 g, 0.1 mol), in a modified Soxhlet extractor,[18] was reduced with 5.7 g (0.15 mol) of $LiAlH_4$ in ether to give 24 g (96%) of crude **11**.

The dihydrochloride was prepared in ether: mp 211–212° (from absolute ethanol); 90% yield of **11** based on the salt.

Anal. Calcd for $C_{15}H_{28}Cl_2N_2O$: C, 55.72; H, 8.73; N, 8.66; Cl, 21.93. Found: C, 55.56; H, 8.53; N, 8.47; Cl, 21.67.

3-Hydroxymethyl-1-methyl-3-phenylpyrrolidine (13). A. Prepared from 11 Dihydrochloride.—The cyclization procedure was used except that after treatment (290–295°) water was added and the base was liberated with NaOH, extracted with ether, and distilled to give **13** (67%): bp 110–114° (0.6 mm); mp 59–60° (from 30–40° petroleum ether).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.19; H, 8.98; N, 7.40.

The acid oxalate was prepared in ether: mp 112–113° (from absolute ethanol).

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.97; H, 6.95; N, 5.09.

B. Prepared from 12.—Compound **12** (0.95 g, 0.0046 mol) in ether was reduced with 0.26 g (0.0069 mol) of $LiAlH_4$ to give **13** in pure form: mp and mmp 59–60°. The acid oxalate was prepared in ether and recrystallized from absolute ethanol–ether: mp and mmp 112–113°.

Registry No.—**1**, 20538-19-6; **1a**, 20538-20-9; **1b**, 20555-20-8; **3**, 20538-18-5; **3a**, 20555-21-9; **3b**, 20538-27-6; **4**, 20538-43-6; **4a**, 20555-26-4; **6**, 20538-28-7; **7**, 20538-29-8; **7a**, 20555-22-0; **8**, 20555-23-1; **9** (HCl), 20538-30-1; **9** (oxalate), 20538-31-2; **10**, 20538-32-3; **10a**, 20555-24-2; **10b**, 20555-25-3; **11** (2HCl), 20538-33-4; **12**, 20538-34-5; **12a**, 20538-44-7; **13**, 20538-35-6; **13** (oxalate), 20538-36-7; **15**, 20538-37-8; **15a**, 20538-38-9; **16**, 20538-39-0; **17**, 20538-40-3; **18a**, 20538-41-4; **19**, 20538-42-5.

(17) See F. F. Blicke, H. Raffelson, and B. Barna, *J. Amer. Chem. Soc.*, **74**, 253 (1952).

(18) No siphon tube. Liquid from the condenser dropped directly into the reaction mixture.

Ethylene Thionocarbonate and 1,3-Oxathiolane-2-thione

F. N. JONES AND S. ANDREADES

Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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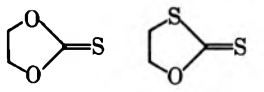
Syntheses and reactions of the title compounds are reported. These compounds are isomerized to thiol- and dithiolcarbonates by halide ions. Alkylation with alkyl halides gives unstable intermediates which rearrange to β-haloethyl thiol- and dithiolcarbonates. Acids induce polymerization to polythiol and polydithiolcarbonates. Both 1 and 2 give ethylene when treated with triphenylphosphine. Nmr and ir spectral comparisons of the six possible ethylene carbonates with sulfur substituted for oxygen are tabulated.

Corey and Winter discovered that cyclic 1,2-thionocarbonates and 1,2-trithiocarbonates are converted into olefins by *cis* elimination in high yields when treated with tertiary phosphines or phosphites.[1,2] This new olefin synthesis is broadly useful for stereospecific syntheses of olefins and provides the first synthesis of the strained *trans*-cycloheptene.[2] Cyclic 1,3-trithiocarbonates, however, are converted into phosphorus ylides by sulfur–phosphite exchange,[3] and intermediate ylides have been implicated in the reaction of 1,2-trithiocarbonates with phosphites.[3]

Previous work on cyclic 1,2-thionocarbonates has centered on substituted cases and has been concerned primarily with their conversion into olefins. The parent ethylene thionocarbonate (1) has not been described. Synthesis of the related compound 1,3-oxathiolane-2-thione (2) has been reported,[4] but we have been unable



1 2

to repeat this synthesis. Earler reports of 2 are clearly erroneous. In this paper, we describe satisfactory syntheses of 1 and 2 and studies of their chemistry.

Results

Compound 1 was synthesized directly from thiophosgene and ethylene glycol in 33% yield. The most successful technique was slow addition of the glycol in tetrahydrofuran (THF) to a boiling mixture of thiophosgene, methylene chloride, and potassium carbonate (eq 1).

$$HOCH_2CH_2OH + Cl_2C{=}S \xrightarrow[CH_2Cl_2\text{–THF}]{K_2CO_3;\ 45^\circ} 1 \qquad (1)$$

Compound 2 was synthesized indirectly from a lead salt of 2-mercaptoethanol and thiophosgene in 46% yield (eq 2). Other heavy metal salts of 2-mercaptoethanol gave lower yields.

$$HOCH_2CH_2SH \xrightarrow{Pb(OAc)_2} (HOCH_2CH_2S)Pb(OAc) \xrightarrow[CH_2Cl_2]{Cl_2CS} 2 \qquad (2)$$

Compound 1 is a colorless solid, mp 55–55.5°; compound 2 is a pale yellow oil, mp *ca.* −20°. Both 1 and 2 are thermally unstable, decomposing appreciably at 100°, and both are reactive toward acids, bases, and moisture. Synthesis of 1 and 2 makes available for characterization the six possible ethylene carbonates in which S is systematically substituted for O. Physical and spectral data for these six compounds are assembled in Table I. These data establish the structures of 1 and 2.

The CH_2O hydrogens in ethylene carbonate and 3 exhibit decreased nmr shielding in the presence of the thiocarbonyl function in 1 and 2, respectively. In both cases the CH_2O hydrogens are more shielded than the CH_2O hydrogens in 1,3-dioxolanes, whose peaks fall at *ca.* τ 6.[5] The presence of two sulfur atoms in 2 results in a paramagnetic shift for the CH_2O relative to 1. Similarly, the CH_2S protons in ethylene trithiocarbonate and 2 show corresponding downfield shifts compared with carbonyl compounds 4 and 3, respectively. Finally, two sulfurs in the ring in the trithiocarbonate and 4 result in a downfield shift for the CH_2S protons relative to 2 and 3, respectively.

The C=S stretching frequencies in 1, 2, and ethylene trithiocarbonate (1303, 1368, 1181, 1234, and 1069) are consistent for these structures[6] when account is taken of the anticipated shift to higher frequencies due to the five-membered ring. Spectra of related heterocycles, including ethylene dithiol- and trithiocarbonates, have been analyzed.[7]

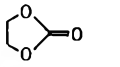
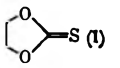
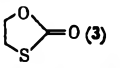
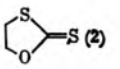
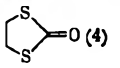
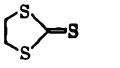
Reactions of 1 and 2 are outlined in Scheme I. Compounds 1 and 2 are readily isomerized to 3 and 4, respectively, by halide ions. We postulate that the reaction involves nucleophilic displacement to give intermediates 3′ and 4′ (not detected) followed by ring closure. Bond energy data[8] indicate that isomerization of thionocarbonates to the corresponding thiolcarbonates should be exothermic by about 24 kcal/mol. Other examples which illustrate the instability of thionocarbonates relative to thiolcarbonates are the Schönberg rearrangement of diarylthionocarbonates[9] and the well-known tendency of monothio acids to exist almost exclusively in the thiol form.

The ease with which 1 and 2 isomerize indicates that earlier workers,[4,10] who claimed to have prepared 2, had

(1) E. J. Corey and R. E. A. Winter, *J. Amer. Chem. Soc.*, **85** 2677 (1963).
(2) E. J. Corey, F. A. Carey, and R. E. A. Winter, *ibid.*, **87**, 934 (1965).
(3) E. J. Corey and G. Markl, *Tetrahedron Lett.*, No. 33, 3201 (1967); R. Hull and R. Farrand, *Chem. Commun.*, 164 (1967)
(4) V. S. Etlis, *J. Org. Chem. USSR*, **34**, 3032 (1964).
(5) E. Caspi, T. A. Wittstruck, and D. M. Piatek, *J. Org. Chem.*, **27**, 3183 (1962); E. Caspi, H. Zajac, and T. A. Wittstruck, *ibid.*, **29**, 640 (1964).
(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958, p 356; Jones, Kynaston, and Hales, *J. Chem. Soc.*, 614 (1957).
(7) R. Mecke, R. Mecke, and A. Luttringhaus, *Chem. Ber.*, **90**, 975 (1957).
(8) E. S. Kooyman in "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience Publishers, New York, N. Y., 1967, Chapter 1.
(9) A. Schönberg and L. Vargha, *Chem. Ber.*, **63**, 178 (1930); A. Schönberg, L. Vargha, and W. Paul, *Ann.*, **483**, 107 (1930); H. R. Al-Kazimi, D. S. Tarbell, and D. Plant, *J. Amer. Chem. Soc.*, **77**, 2479 (1955); D. H. Powers and D. S. Tarbell, *ibid.*, **78**, 70 (1956).
(10) A. Husemann, *Ann.*, **126**, 268 (1863).

TABLE I

PROPERTIES OF ETHYLENE CARBONATE AND THIOCARBONATES

Compd	Registry no.	Color	Mp, °C	Chemical shift (τ), ppm[a]	Ir absorption,[b] cm⁻¹				
	96-49-1	None	38.5–39[c]	5.45	1076	1153	1779	1808	
	20628-59-5	None	55–55.5	5.22	955	1013	1151	1303	1368
	3326-89-4	None		A_2B_2[d] 6.41, 5.47	1037	1074	1739		
	20628-60-8	Pale yellow	*Ca.* −20	A_2B_2[d] 6.27, 5.02	924	1003	1057	1181	1231
	2080-58-2	None	35[e]	6.28	827	885	1637	1672	
	822-38-8	Yellow	40–41[f]	5.99	832	880	1074		

[a] Measured at 60 MHz in $CDCl_3$. [b] Strongest peaks only; $CHCl_3$ solutions. [c] J. Nemirowsky, *J. Prakt. Chem.*, [2] **28**, 493 (1883). [d] Pair of triplets with fine splitting; J = 7 Hz. [e] See ref 22. [f] A. Miolati, *Ann. Chem.*, **262**, 61 (1891).

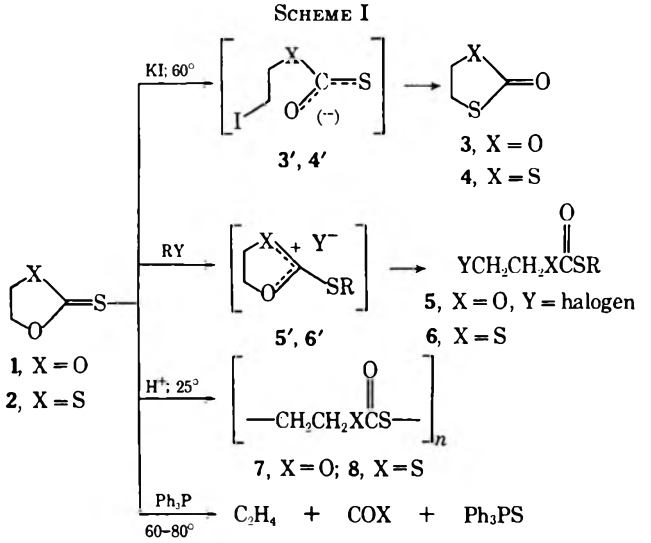
TABLE II

DATA FOR COMPOUNDS $YCH_2CH_2X\overset{O}{\overset{\|}{C}}SR$

Compd	R	X	Y	Time, hr	Temp, °C	Yield, %	Bp (mm) or mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% other Element	% other Calcd	% other Found	C=O peak, cm⁻¹ ±3
5a	CH_3	O	I	72[a]	25	72	93 (5)	$C_4H_7IO_2S$	19.52	19.60	2.87	2.84	S	13.03	13.22	1715
5b	$C_6H_5CH_2$	O	Br	0.5[b]	200	98	Oil	$C_{10}H_{11}BrO_2S$	43.65	43.94	4.03	3.98	Br	29.04	28.61	1709
5c	$C_6H_5CH_2$	O	I	18[a]	25	40	Oil[c]	$C_{10}H_{11}IO_2S$	37.29	37.14	3.44	3.50	S	9.95	10.23	1712
5d	$4\text{-}O_2NC_6H_4CH_2$	O	Br	72[a]	82	62	81–83.5[d]	$C_{10}H_{10}BrNO_4S$	37.51	37.24	3.15	3.05	Br	24.92	25.11	1709
5e	$2,4\text{-}Cl_2C_6H_3CH_2$	O	Cl	8[a]	150	11	29–31[f]	$C_{10}H_8Cl_2O_2S$	40.09	39.91	3.03	3.05	Cl	35.50	35.09	1712
5f	$(C_6H_5)_2CH$	O	Cl	16[b]	120	..	Oil	$C_{16}H_{13}ClO_2S$	62.64	62.55	4.93	4.84	S	10.45	10.74	1715
5g	$(C_6H_5)_2C$	O	Cl	140[a]	25	44	119–121.5[g]	$C_{22}H_{19}ClO_2S$	69.01	69.31	5.00	5.09	S	8.37	8.35	1724
5h	$ClH_2C{=}CHCH_2$	O	Br	5[h]	70	26	96 (5)	$C_6H_9BrO_2S$	32.01	32.18	4.03	3.97	Br	35.50	35.50	1712
5i	$HOOCCH_2$	O	I	18[a]	25	34	109–110.5[f]	$C_3H_7IO_4S$	20.70	20.92	2.43	2.45	I	43.75	42.91	1706
5j	$HC{\equiv}CCH_2$	O	Cl	18[i]	125	67	~120 (0.0001)	$C_6H_6ClNO_2S$	33.43	33.36	3.37	3.33	Cl	19.74	19.61	1727
6a	CH_3	S	I	14[a]	82	90	90–95 (1)	$C_4H_7IOS_2$	18.33	18.75	2.69	2.73	S	24.46	24.69	1650
6b	$4\text{-}O_2NC_6H_4CH_2$	S	Br	18[a]	82	43	66–67[f]	$C_{10}H_{10}BrNO_3S_2$	35.72	35.64	3.00	3.22	S	19.07	19.12	1645

[a] Reaction solvent was acetonitrile. [b] No solvent; equimolar amounts of reagents were used. [c] Product was flash distilled at 0.0001 mm. [d] Recrystallized from pentane–methylene chloride. [e] A steel pressure vessel was used. [f] Recrystallized from hexane–methylene chloride. [g] Recrystallized from hexane. [h] Compound **1** was added to refluxing, excess allyl bromide during 3 hr. [i] The solvent was excess chloroacetonitrile at reflux.

SCHEME I



actually obtained **4**. Attempted synthesis of **2** from 2-mercaptoethanol and thiophosgene in the presence of aqueous NaOH as described by Etlis[4] gave **4** but not **2**. Compound **2** is rapidly hydrolyzed by dilute aqueous NaOH.

The ring-opening alkylation of **1** and **2** was used to synthesize twelve unsymmetrical β-haloethyl thiolcarbonates (**5a–j**) and dithiolcarbonates (**6a–b**), generally in good yield. The alkyl halides used, conditions, and yields are specified in Table II. The only apparent limitation in scope is that the alkyl halide must be of reactivity comparable with or greater than that of the product. Unreactive alkyl halides such as *t*-butyl bromide give polymers **7** or **8**, even when used in excess. The ring-opening alkylation is analogous to the previously observed ring-opening alkylation of 1,3-oxazolidine-2-thione with methyl iodide.[11]

The ring-opening reaction presumably involves intermediate salts, such as **5'** and **6'**, analogous to the 1,3-dioxolenium salts[12] or to the formation of intermediate alkylthiuronium salts from thiourea and alkyl halides.[13]

(11) T. Mukaiyama, I. Kuwajima, and K. Mixui, *J. Org. Chem.*, **31**, 32 (1966).

(12) H. E. Zaugg and R. J. Michals, *Tetrahedron*, **18**, 893 (1962).

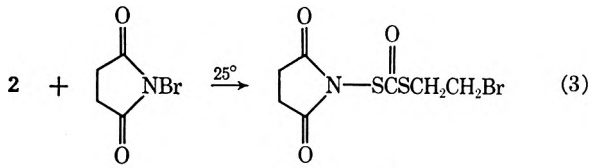
(13) F. G. Bordwell, "Organic Chemistry," The Macmillan Co., Inc., New York, N. Y., 1963, p 210.

Ring-opening polymerizations of 1 and 2 to polymers 7 and 8, respectively, were effected by treatment with anhydrous acids at 25°. Trifluoroacetic acid appears to form a 1:1 complex with 1 which polymerizes when the acid is volatilized. Polymers 7 and 8 were unstable above 200°. Analogous ring-opening polymerizations of 1,3-oxazolidine-2-thiones are known.[11]

Treatment of 1 with triphenylphosphine at 60° caused rapid evolution of CO_2 and ethylene, as expected from previous work.[1,2] The yield of ethylene was only 10%. Similar treatment of 2 gave COS and ethylene in 42% yield; this is the first example of a Corey–Winter reaction of a dithiocarbonate.

Heating compound 1 at 140° caused decomposition to mixtures of isomer 3, polymer 7, and other substances. Heating 2 at 120° gave a similar mixture.

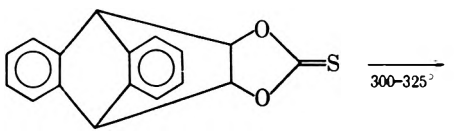
Treatment of 2 with N-bromosuccinimide (NBS) gave a 1:1 adduct tentatively assigned structure 9 (eq 3) on the basis of spectroscopic data. Formation of N–S bonds in reactions of NBS have been noted.[14]



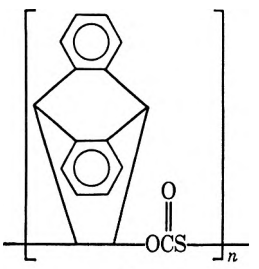
(3)

9

Anthracene-substituted derivative 10 was synthesized by heating 9,10-dihydro-9,10-ethanoanthracene-11,12-diol[15] with N,N′-thiocarbonyldiimidazole.[16,17] When heated at 325°, compound 10 gave polymer 11 (eq 4).



10



(4)

11

Experimental Section[18]

Ethylene Thionocarbonate (1).—In a 1-l. 4-neck flask was placed a mixture of 550 ml of methylene chloride, 120 g of anhydrous potassium carbonate, and 50 ml (74 g, 0.65 mol) of thiophosgene. The orange mixture was stirred mechanically and heated at reflux as a solution of 40 g (0.65 mol) of dry, redistilled ethylene glycol in 125 ml of tetrahydrofuran was added dropwise during 2 hr. Refluxing was continued for 16 hr. The mixture was filtered; the liquid was concentrated to give 58 g of partly crystalline residue. (*Caution:* The temperature must be kept at 25° or below during the late stages of solvent removal. The concentrated residue contains by-products which can undergo violent exothermic decomposition.)

The residue was recrystallized by dissolving in 300 ml of methanol, filtering, and cooling to −78° to give 28 g of solid, mp 48–52°, containing orange impurities and polymer. This solid was sublimed at a pressure of 0.05 μ using a controlled oil bath temperature of 58–62° to give 23.5 g of sublimate. Recrystallization from 300 ml of methanol gave 22.7 g (33%) of 1 as colorless needles, mp 54.5–55.5°. Compound 1 should be stored under dry, dark, cold conditions.

Anal. Calcd for $C_3H_4O_2S$: C, 34.60; H, 3.87; S, 30.71. Found: C, 34.63; H, 3.85; S, 30.73.

The ultraviolet spectrum of 1 in ethanol had λ_{max} 304 (ε 28) and 235 mμ (ε 14,100). Winter reports that *trans*-4,5-dimethylethylenethionocarbonate has λ_{max} 302 (ε 33) and 236 mμ (ε 16,100).[19] The strongest peaks in the mass spectrum were at *m/e* (rel intensity) 60 (1.00), 104 (molecular ion, 0.87), 29 (0.82), 45 (0.81), 32 (0.65), 59 (0.59), and 43 (0.48).

1,3-Oxathiolane-2-thione (2).—Lead(II) mono(β-hydroxyethylmercaptide)monoacetate was prepared by stirring a mixture of 500 g (1.3 mol) of lead(II) acetate trihydrate, 150 g (1.9 mol) of 2-mercaptoethanol, and 300 ml of ethanol overnight in the dark. Powerful stirring is required, particularly during addition of the lead acetate. The cream-colored product was collected and washed three times with ethanol, three times with tetrahydrofuran, and twice with methylene chloride. The product was dried by prolonged pumping at 0.5 mm. The yield was 400 g (87%) of finely divided solid, mp 180–190° dec (lit.[20] mp 173–176° dec).

A 1-l. 3-neck flask containing 172 g (0.50 mol) of the above lead compound and 600 ml of methylene chloride was surrounded by a large bath of water at about 15°. The slurry was stirred as 35 ml (52 g, 0.45 mol) of thiophosgene was added by means of pipets. The mixture was stirred for 20 hr with minimum exposure to light. During the first 5 hr, the temperature was maintained at 18–25° by occasional addition of ice to the water bath to keep it at 10–15°. Later, the bath and the reaction flask were allowed to warm to ambient temperature. The mixture was filtered. The liquid was concentrated on a rotary evaporator, keeping the temperature below 25°, to give 55 g of pale yellow oil. The oil was chromatographed on a 9.5-cm column of 1 kg of neutral silica gel (Woelm activity I) using methylene chloride to elute the product. Most by-products, including substantial amounts of $(HOCH_2CH_2S)CS$, were not eluted. The yellow-orange eluent was collected in fractions. Concentration of the earlier fractions gave 25 g (46%) of product 2, containing a few per cent isomer 4. Distillation using a high-vacuum Vigreux apparatus gave 18 g of pale yellow liquid, bp 56–62° (0.08–0.1 μ). All fractions contained about 5% isomer 4. The product should be stored under cold, dry, dark conditions. Further purification by zone refining did not remove isomer 4.

Anal. Calcd for $C_3H_4OS_2$: C, 29.98; H, 3.35; S, 53.35. Found: C, 30.00; H, 3.50; S, 53.44.

Isomerization Reactions.—A mixture of 0.52 g (5 mmol) of compound 1, 3 g of KI, and 20 ml of acetonitrile was stirred and heated at 60° for 68 hr. Removal of solvent and salts gave 0.4 g of essentially pure ethylene thiolcarbonate (3), identical with a sample prepared as described.[21] (See Table I for nmr and ir spectra.)

Similar treatment of compound 2 caused essentially complete isomerization to ethylene dithiocarbonate (4) identical with a sample, mp 30–30.5° (lit.[22] mp 35°), prepared as described.[22]

Reactions with Alkyl Halides.—These reactions were performed in acetonitrile solution or using the neat alkyl halide as solvent. The products were isolated by distillation, recrystallization, or volatilization of starting materials, as appropriate. The data for individual reactions and the properties of the products are collected in Table II. The ir spectra of thiocarbonates 5a–j showed C=O peaks in the range 1706–1727 cm^{-1}; the corresponding peaks in the spectra of dithiolcarbonates were at 1645–1650 cm^{-1}. Similar frequencies were noted in the spectra of cyclic carbonates 3 and 4 (see Table I). The nmr spectra of these products were consistent with the assigned structures. Typically, the β-haloethyl groups in 5a–j give rise to 6-line A_2B_2 patterns,

(14) D. S. Tuleen and D. N. Buchanan, *J. Org. Chem.*, **32**, 465 (1967).
(15) T. L. Patton, U. S. Patent 2,857,434 (1958).
(16) H. A. Staab and G. Walther, *Ann.*, **657**, 98 (1962).
(17) T. J. Pullokat and G. Urry, *Tetrahedron Lett.*, 1953 (1967).
(18) Melting and boiling points are uncorrected. Infrared spectra were recorded linearly in wavelength on a Perkin-Elmer 21 spectrophotometer. Nmr spectra were produced at 60 MHz using Varian A-60 and A-56-60 devices; the solvent was deuteriochloroform doped with Me_4Si except where noted.
(19) R. E. A. Winter, Ph.D. Dissertation, Harvard University, Cambridge, Mass., 1964, p 64.
(20) A. Schoberl and G. Wiebler, *Ann.*, **595**, 101 (1955).
(21) D. D. Reynolds, *J. Amer. Chem. Soc.*, **79**, 4951 (1957).
(22) C. G. Overberger and P. V. Bonsignore *ibid.*, **80**, 5427 (1958).

J = 6–8 Hz. For example, the nmr spectrum of **5a** had peaks at τ 7.65 (s, 3, SCH_3), 6.68 (t, 2, J = 7 Hz, OCH_2), and 5.53 (t, 2, J = 7 Hz, ICH_2). The nmr spectrum of compound **6a** had peaks at τ 7.55 (s, 3, SCH_3) and 6.60 (m, 4, ICH_2CH_2S).

Reaction of 1 with *t*-Butyl Bromide.—A solution of 1.04 g (10 mmol) of compound **1** in 25 ml of *t*-butyl bromide was heated at 78° overnight. Polymeric material began to separate within a few minutes. The solid was filtered and dried. The yield was 0.80 g of white polymer, substantially identical with polymer **7** (see below). The soluble fraction appeared to contain telomers.

Ring-Opening Polymerizations.—A solution of 2.08 g (0.020 mol) of **1**, 4.5 g (6.040 mol) of trifluoroacetic acid, and 30 ml of methylene chloride was kept for 3 days at 25°. The solvent was removed under high vacuum to give 2.1 g of white polymer **7**: mp 128°, η_{inh} 0.08 (0.1% in dimethylformamide); ir 1715 cm^{-1} (C=O). The polymer was a crystalline substance which could be drawn into fibers. Thermogravimetric analysis (TGA) showed decomposition at 200–250°.

Anal. Calcd for $(C_3H_4O_2S)_x$: C, 34.60; H, 3.87; S, 30.71. Found: C, 34.54; H, 3.88; S, 30.27.

This polymer was insoluble in chloroform, but readily dissolved when 1 equiv of trifluoroacetic acid was added: nmr ($CDCl_3$) τ −0.93 (br), 5.50 (t, J = 6 Hz), and 6.78 (t, J = 6 Hz). A solution having an identical nmr spectrum was formed from monomeric **1** and trifluoroacetic acid. Formation from **1** of the species which gives the pair of triplets was 93% complete in about 10 min.

A solution of 1.2 g of **2** in 2.4 g of trifluoroacetic acid was kept overnight to give a precipitate of white polymer **8**: mp 191–194° dec; ir (KBr) 1655 (C=O).

Anal. Calcd for $(C_3H_4OS_2)_x$: C, 29.98; H, 3.35; S, 53.35. Found: C, 30.12; H, 3.45; S, 52.29.

Reaction with Triphenylphosphine.—A mixture of 1.04 g (10 mmol) of **1** and 10 g of triphenylphosphine was heated to 80° in an evacuated flask with a manometer. As soon as the solids melted (about 60°), 11.7 mmol of gas evolved. Mass spectroscopic and infrared analysis showed this to consist mainly of CO_2 and C_2H_4 in a 92:8 ratio.

Similar treatment of **2** gave 0.012 mol of gas. Mass spectroscopic and infrared analysis showed carbonyl sulfide and ethylene in a 65:35 ratio, a 42% conversion to ethylene.

S-(β-Bromoethyl)-S-(N-succinimido)dithiocarbonate (9).—A solution of 6.0 g (0.045 mol) of **2** (90% pure) and 8.0 g (0.045 mol) of N-bromosuccinimide in 70 ml of methylene chloride was stirred at 0° for 3 hr and then at ambient temperature overnight. The solution was filtered and concentrated to give 13.2 g of solid. Two recrystallizations from a mixture of carbon tetrachloride, methylene chloride, and pentane gave 4.4 g (34%) of colorless solid, mp 111–113°. Further recrystallization gave a sample which melted at 117.5–118.5°; nmr τ 6.52 (s, 4) and 7.03 (s, 4); ir (KBr) 1650 and 1730 cm^{-1}.

Anal. Calcd for $C_7H_8BrNO_3S_2$: C, 28.19; H, 2.70; Br, 26.80; N, 4.70; S, 21.50. Found: C, 28.16; H, 3.31; Br, 27.36; N, 5.07; S, 21.77.

Treatment of a solution of **2** in carbon tetrachloride with NBS gave the same product.

"Anthracene–Vinylene Thionocarbonate Adduct" (10).—The adduct of anthracene with vinylene carbonate was prepared as described.[23] Hydrolysis to 9,10-dihydro-9,10-ethanoanthracene-11,12-diol, mp 204–206°, was done by Patton's procedure.[15]

A mixture of 32.0 g (0.134 mol) of the above diol, 23.9 g (0.134 mol) of N,N′-thiocarbonyldiimidazole,[16,17] and 400 ml of toluene was heated at reflux under nitrogen for 18 hr. The solution was washed with water while warm. Cooling to 0° gave crystals which were collected, dried, and recrystallized from toluene (Darco) to give 34 g (91%) of product **10**: mp 228–230°; nmr (acetone-d_6–TMS) τ 4.65 (t, 2, J = 2 Hz), 5.06 (t, 2, J = 2 Hz), and aromatic (m, 8).

Anal. Calcd for $C_{17}H_{12}O_2S$: C, 72.83; H, 4.32; S, 11.43. Found: C, 72.83; H, 4.37; S, 11.51.

Polymerization of 10.—Solid **10** (1.0 g) was placed in a sublimer containing N_2 at 400 mm. The sublimer was partly immersed for 5 min in a fluidized-bed sand bath heated at 315–325°. Partial sublimation of starting material (0.3 g) occurred. The remainder (0.69 g) was molten polymer which solidified when cooled: ir 1690 (C=O) and 1275 cm^{-1}; TGA decomposition at 350–375°.

Anal. Calcd for $(C_{17}H_{12}O_2S)_x$: C, 72.83; H, 4.32. Found: C, 72.91; H, 4.43; η_{inh} = 0.31 (0.1% in toluene at 25°).

Registry No.—**5a**, 20628-63-1; **5b**, 20628-64-2; **5c**, 20628-65-3; **5d**, 20628-66-4; **5e**, 20628-67-5; **5f**, 20628-68-6; **5g**, 20628-69-7; **5h**, 20628-70-0; **5i**, 20628-71-1; **5j**, 20628-72-2; **6a**, 20628-73-3; **6b**, 20628-74-4; **9**, 20628-75-5; **10**, 20628-76-6; 9,10-dihydro-9,10-ethanoanthracene-11,12-diol, 20678-93-7.

(23) N. D. Field, *J. Am. Chem. Soc.*, **83**, 3504 (1961).

Hydroboration of Terpenes. V. Isomerization of (+)-Sabinene to (−)-α-Thujene. Hydroboration of (+)-Sabinene and (+)-α-Thujene with Configurational Assignments for the Thujanols

SHRINIVAS P. ACHARYA,[1a,b] HERBERT C. BROWN,[1b] AKIRA SUZUKI,[1c,d] SEICHI NOZAWA,[1d] AND MITSUOMI ITOH[1d]

Richard B. Wetherill Laboratory of Purdue University, Lafayette, Indiana 47907, and Department of Chemical Process Engineering, Hokkaido University, Sapporo, Japan

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A revised nomenclature for various configurational thujanols is proposed. (+)-Sabinene readily isomerizes to an equilibrium mixture of 91% (−)-α-thujene (2) and 9% (+)-sabinene (1) under the influence of potassium *t*-butoxide in dimethyl sulfoxide, and this provides an improved synthetic route to (−)-α-thujene. Catalytic hydrogenation of (+)-α-thujene over platinum preferentially takes place away from the side of the cyclopropane ring to give chiefly (−)-*trans*-thujane (4) whereas catalytic hydrogenation of (+)-sabinene (1) takes place preferentially from the opposite side to give chiefly (−)-*cis*-thujane. Hydroboration of (+)-α-thujene takes place exclusively from the same direction as hydrogenation, *i.e.*, the side away from the cyclopropane ring. Hydroboration of sabinene also takes place from the side away from the cyclopropane ring, from the direction which is opposite to that taken in hydrogenation. The organoborane formed preferentially in the hydroboration of sabinene appears to be the thermodynamically more stable isomer, since it did not epimerize under isomerization conditions. A similar thermodynamic stability favoring the isomer with the mobile substituent (10-C) located on the side toward the cyclopropane ring is present in 10-thujaldehydes and 3-thujones. This unusual stability of the epimers which contain the substituents *cis* to the cyclopropane ring is interpreted in terms of a preferred existence of thujane derivatives in a boat conformation, rather than in the more usual planar or chair forms. The nmr spectra are subjected to a detailed analysis and provide support for these conformational assignments.

In our previous studies of the hydroboration of terpenes, *viz.*, α-pinene,[2] β-pinene,[2] 2-carene,[3] and 3-carenes,[4] only one side of the double bond was relatively free for reactions involving large steric requirements. Such steric effects controlled the direction taken by these reactions. The molecular models of α-thujene (2) and sabinene (1) indicate that both sides of the double bond are relatively accessible. However, a new feature is present in these systems. The double bond of both of these structures is in a position to conjugate with the cyclopropane ring. However, this ring is unsymmetrically situated with respect to the π electrons, so that the possibility exists that differences in such conjugation from the two sides may greatly affect the direction taken by the individual reactions. In order to explore this possibility a study was undertaken of the hydrogenation and hydroboration of thujene and sabinene. In the course of this work a new simple isomerization of the readily available sabinene to the relatively rare α-thujene was developed.

Nomenclature.—Previous investigations of the stereochemistry of the four naturally occurring thujyl alcohols and the corresponding thujones have been reviewed and the steric relationship between these compounds and the other members of the thujane group have been proposed and corrected by Norin[5,6] based on their chemical and spectroscopic properties. However, he retained the names assigned on the basis of the original erroneous structures. These new assignments have been further confirmed by other workers.[7-10] As in the case of stereoisomeric menthols, carvomenthols, caranols, and pinocampheols, the prefixes neo, iso, and neoiso have been applied to distinguish the different thujanols. However, considerable confusion has arisen in the application of these prefixes. For example, iso is used to indicate that methyl and cyclopropane are *cis* to each other in all thujyl alcohols and thujones,[5,6] but *cis* is also used to indicate that the methyl and isopropyl groups are *cis* to each other in the parent hydrocarbons.[9] Similarly neo is used to indicate that methyl and hydroxyl groups are *cis* to each other[5,6] in the "iso" series and *trans* to each other in the "normal" series.[5,6] It appears highly desirable to minimize the possibilities for such confusion by achieving uniformity between the thujyl derivatives and the related menthol, carvomenthol, pinocampheol, and caranol series. It is therefore proposed that iso or *cis* be used to indicate that methyl and isopropyl are *cis* to each other and that neo be used to indicate that methyl and hydroxyl are *cis* to each other, in accordance with the recommendation of Schroeter and Eliel[11] for the carvomenthol and related terpenes. This revision has been reviewed by Norin and Klein and has been approved by them.[12] To rule out any possible misunderstandings we have added the properties and the optical rotations of all four alcohols in Figure 1.

Results

Isomerization of (+)-Sabinene (1).—Savin oil contains (+)-sabinene of high optical purity in the hydrocarbon fraction and sabina acetate also of high optical purity, in the ester fraction. Consequently, (+)-sabinene is readily available in a state of high

(1) (a) Postdoctoral Research Associate, 1966–1968, on Grant GM-10937 of the National Institutes of Health. (b) Department of Chemistry, Purdue University, Lafayette, Ind. (c) Postdoctoral Research Associate, 1963–1965, on Contract No. 12-14-100-7152(72) supported by the Southern Utilization Research and Development Division of the U. S. Department of Agriculture. (d) Department of Chemical Process Engineering, Hokkaido University, Sapporo, Japan.

(2) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964).

(3) S. P. Acharya and H. C. Brown, *ibid.*, **89**, 1925 (1967).

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(5) T. Norin, *Acta Chem. Scand.*, **16**, 640 (1962).

(6) M. S. Bergquist and T. Norin, *Arkiv Kemi*, **22**, 137 (1964).

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(10) M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967).

(11) S. H. Schroeter and E. L. Eliel, *J. Org. Chem.*, **30**, 1 (1965).

(12) Private communications from T. Norin and E. Klein.

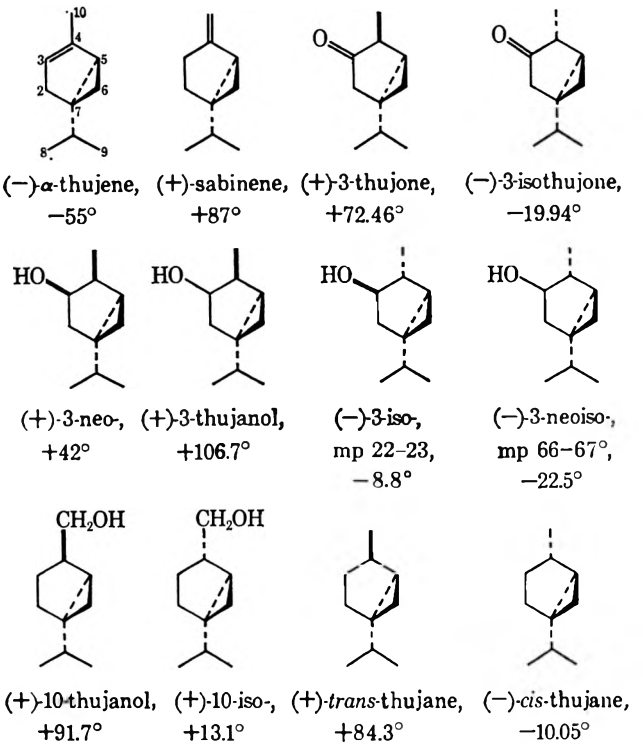


Figure 1.—Corrected nomenclature for thujane derivatives and rotations ([α]D).

purity and its stability permits it to be stored for a considerable length of time. The situation is less favorable for α-thujene. It can be obtained by a Birch reduction of sabina acetate.[9] This gives the desired hydrocarbon predominantly with a ratio of sabinene to thujene of 15:85. Another but less satisfactory approach to α-thujene is the thermal decomposition of the thujyl xanthates[13] which gives α- and β-thujene in a ratio 30:70. A further difficulty is the fact that optically active α-thujene is difficult to store, since it undergoes racemization on standing[14] possibly through the same vinylcyclopropane mechanism postulated by Doering and Lambert[13] for the racemization at higher temperature. Consequently, it would be highly desirable to have a simple synthesis of optically active α-thujene available so that it could be prepared as needed.

Previously, we had observed that potassium *t*-butoxide in dimethyl sulfoxide provides a favorable simple route for the conversion of 3-carene into 2-carene.[3] We tested this procedure on (+)-sabinene and realized a rapid conversion into (−)-α-thujene of high optical activity. This procedure now makes (−)-α-thujene easily obtainable from the readily available (+)-sabinene (Figure 2).

Isomerization of (+)-sabinene by this procedure at 90° for 1.5 hr yielded an equilibrium mixture of 91% (−)-α-thujene and 9% (+)-sabinene. These are readily separated by column chromatography of a petroleum ether solution through a silicic acid–silver nitrate column, yielding pure (−)-α-thujene, $[\alpha]^{25}D$ −55°.

Ethylenediaminolithium, previously used for the isomerization of 3-carene to 2-carene,[15] was also applied

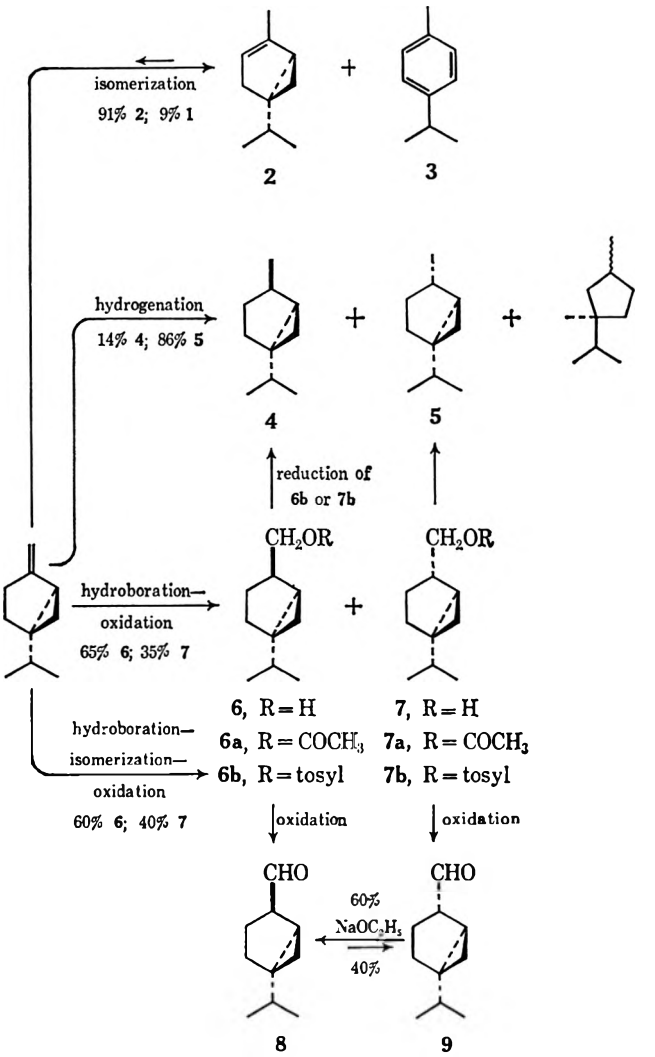


Figure 2.—Reactions of (+)-sabinene (1).

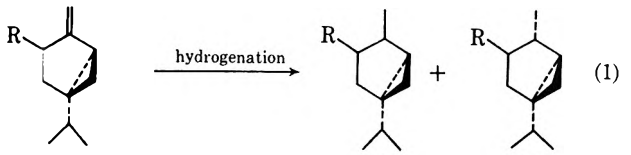
to (+)-sabinene. Although essentially the same mixture of (+)-sabinene and (−)-α-thujene was realized, the product also contained considerable amounts of *p*-cymene (3). Consequently, we believe the potassium *t*-butoxide in dimethyl sulfoxide procedure is preferable.

An interesting feature is the presence of approximately 9% of sabinene at equilibrium. Both methylenecyclohexane and methylenecyclopentane isomerize almost completely to the endocyclic olefin at equilibrium.[16] A possible explanation is that a double bond in the bicyclic thujyl system is more strained than a similar double bond in the cyclopentane system, so that there exists a greater tendency in the thujyl system to move the double bond out to the exocyclic position. Such strain appears to be responsible for the presence of 92% of methylenenorbornane in an equilibrium mixture of that bicyclic olefin.[17] However, there is also the possibility that the better opportunity for conjugative interaction of the π electrons of the exocyclic double bonds of (+)-subinene with cyclopropane ring contributes to the enhanced stability of this exocyclic derivative.

Hydrogenation of (+)-Sabinene (1) and (+)-α-

(13) W. E. Doering and J. B. Lambert, *Tetrahedron*, **19**, 1989 (1963).
(14) J. L. Simonsen, "The Terpenes," Vol. 2, Oxford University Press, Cambridge, 1949, p 12; Vol. 3, 1952, p 533.
(15) G. Ohloff, K. H. Schulte-Elte, and W. Giersch, *Helv. Chim. Acta*, **48**, 1665 (1965).
(16) J. Herling, J. Shabtai, and E. Gil-Av, *J. Amer. Chem. Soc.*, **87**, 4107 (1965).
(17) S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Nasland, *ibid.*, **89**, 6897 (1967); P. von R. Schleyer, S. Bank, W. F. Watts, and A. Schriesheim, private communication.

Thujene (2).—It has been reported that the catalytic hydrogenation of the alkenylcyclopropane system[5] in thujopsene, sabinene, thujene, sabinol, and sabina acetate on palladium gives the dihydro compounds under controlled conditions but, the products are always those obtained through a 1,4 addition of the hydrogen with the opening of the cyclopropane ring. However, simple addition of hydrogen to the double bond in sabinene[18] and thujene[19] has been achieved with platinum as the catalyst. Unfortunately, the stereochemistry of these products was not specified. Norin[5] reported that the hydrogenation of sabinol over supported platinum takes place predominantly from the cyclopropane side, whereas that of sabina acetate proceeds away from the cyclopropane ring as shown in eq 1.



We observed that hydrogenation of (+)-α-thujene over platinum at room temperature yielded considerable amounts of a tetrahydro derivative with the opening of the cyclopropane ring. However, hydrogenation at −20° avoided this side reaction and gave essentially pure dihydro derivative. The product was 85% (−)-*trans*-thujane (**4**), with minor amounts, 15%, of (+)-*cis*-thujane (**5**) (Figure 3). Thus the addition of hydrogen took place preferentially from the side away from the cyclopropane ring. On the other hand, (+)-sabinene underwent hydrogenation, under identical conditions from the cyclopropane side, to give 14% (+)-*trans*-thujane and 86% (−)-*cis*-thujane.

Hydroboration of (+)-α-Thujene.—(+)-α-Thujene readily undergoes hydroboration (Figure 3) to form the corresponding organoborane, converted by the usual hydrogen peroxide oxidation[20] into (−)-3-thujyl alcohol (**10**), n^{18}D 1.4603, [α]D −46.7,[21] compared with the product from (−)-α-thujene,[9] n^{20}D 1.4602, [α]^{20}D +114°. The structure of the product was confirmed by comparison with an authentic sample.[22] Isothujyl alcohol was not detected. This confirms that hydroboration of α-thujene essentially proceeds from the side away from the cyclopropane ring, in agreement with the indicated high sensitivity of the hydroboration reaction to steric requirements. Reduction of the tosylate of the thujyl alcohol with lithium aluminum hydride in ether gave pure (−)-*trans*-thujane (**4**), n^{20}D 1.4384, [α]$^{28.5}$D −37.3, whereas that obtained from the hydrogenation of same (+)-α-thujene had n^{20}D 1.4376, [α]^{28}D −29.3, the lower rotation corresponding to the presence of 15% (+)-*cis*-thujane. The oxidation of the alcohol by the ether–chromic acid procedure[23] gave pure (−)-thujone (**11**), n^{23}D 1.4538 and [α] −27.8°, which on epimerization with sodium ethoxide in ethanol at room temperature provided an equilibrium mixture, containing 68% (−)-thujone (**11**) and 32% (+)-isothujone (**12**), in satisfactory agreement with the 65:35 ratio reported earlier.[24] This indicates that in thujone the *cis* relationship between the 10-methyl group and the cyclopropane ring is thermodynamically more stable than the *trans* one, a case analogous to 4-isocaranone,[4] but differing from isopinocamphone[2] and 2-isocaranone.[3]

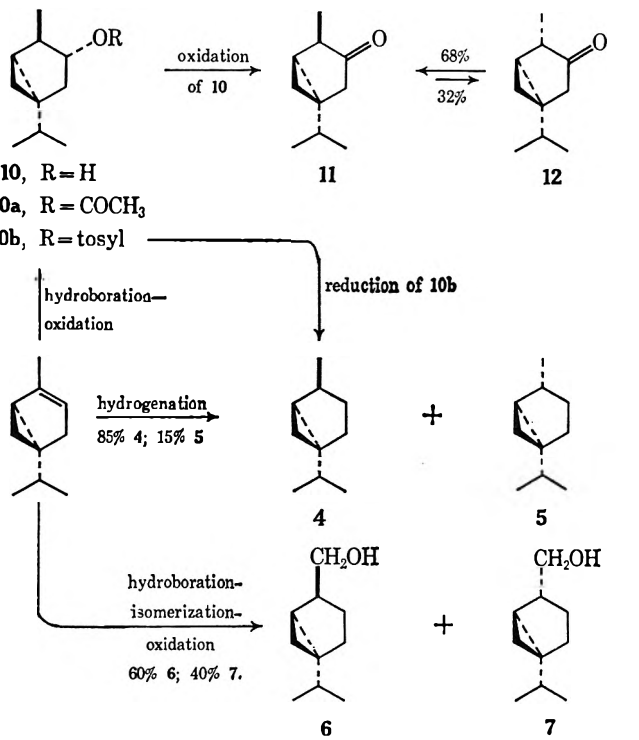


Figure 3.—Reactions of (+)-thujene.

Hydroboration of (+)-Sabinene.—Ohloff[9] hydroborated (+)-sabinene (**1**) and protonolyzed the organoborane with propionic acid for 2 hr and showed that hydroboration preferentially takes place away from the cyclopropane side to give 35% *cis*- and 65% *trans*-thujanes. Heating the organoborane for 2.5 hr at reflux in diglyme failed to epimerize the organoborane, contrary to the experience in the related pinane series.[2] In the later case, the organoborane from β-pinene undergoes protonolysis to give 98% *cis*- and 2% *trans*-pinane, but the isomerized organoborane gives the opposite, 2% *cis* and 98% *trans*.

This marked difference in the behavior of the organoboranes from β-pinene and sabinene in the isomerization reaction prompted us to examine this reaction in more detail. In order to avoid the possibility that the protonolysis reaction might be the cause of the apparent anomalous behavior of the organoborane in the isomerization reaction, we decided to proceed through oxidation to the alcohol (**6**, **7**), conversion into the tosylate (**6B**, **7B**) and reduction

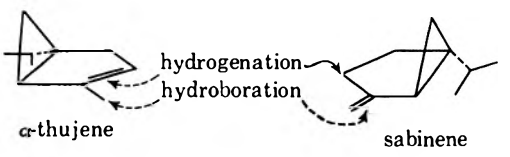
(18) N. Kizhner, *J. Russ. Phys. Chem. Soc.*, **43**, 1157 (1911).
(19) F. Richter, W. Wolff, and W. Presting, *Ber.*, **64**, 871 (1931).
(20) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).
(21) The lower rotation of our product is a consequence of our original use of (+)-α-thujene from natural sources, kindly supplied by Dr. E. Klein of Dragoco. This was a material of relatively low optical purity, [α]D +14.4°, compared with the material used by Ohloff, −49.5°, and that realized in our isomerization procedure, −55.0°. The new synthesis was developed only in the latter stages of this study, after we had exhausted our stock and could no longer obtain the natural material. All rotations reported in this paper for derivatives prepared from (+)-α-thujene were realized with the above material from natural sources.
(22) We are thankful to Dr. T. Norin of Kungl Tekniska Högskolon, Stockholm, Sweden, for a generous gift of the authentic thujyl alcohol and thujone.
(23) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).
(24) A. G. Short and J. Read, *J. Chem. Soc.*, 2016 (1938).

with lithium aluminum hydride to the hydrocarbons (**4**, **5**) (Figure 2). As described earlier, an authentic sample of pure *trans*-thujane was available by the hydroboration–oxidation of thujene followed by the reduction of the tosylate of the alcohol thus produced. A mixture of *trans*- and *cis*-thujane was available from the hydrogenation of (+)-α-thujene, and (+)-sabinene. Consequently, it was possible to relate the alcohols from the hydroboration–oxidation of both thujene and sabinene by relating them to *cis*- and *trans*-thujanes.

Hydroboration of sabinene (Figure 2) proceeds to the trialkylborane stage. Oxidation by alkaline hydrogen peroxide gives two alcohols, **A** (**7**) and **B** (**6**), in the ratio 35:65, and hydroboration with disiamylborane (which usually is more sensitive to steric requirements), followed by oxidation gives the same alcohols in essentially the same ratio, 32:68. The corresponding acetates were separated by preparative glpc and were converted into the hydrocarbons. Hydrocarbon **5** from alcohol **A** had n^{20}D 1.4390, $[\alpha]^{25}$D −10.5, and was identical with *cis*-thujane by nmr and glpc. Hydrocarbon **4** from alcohol **B** had n^{20}D 1.4367, $[\alpha]^{25}$D +84.3, and corresponded by nmr and glpc with the *trans* component of the thujane mixtures obtained in the hydrogenation of thujene and sabinene. Therefore alcohol **A** must be the *cis* derivative and **B** must be the *trans* derivative. Hydroboration–isomerization–oxidation of both thujene and sabinene yields these two alcohols in the ratio of 41% *cis*/59% *trans*. It is also of interest that the corresponding aldehydes epimerize to give 40% *cis*/60% *trans*. Therefore we confirm Ohloff in that the isomerization procedure fails to epimerize the initially formed organoborane in the manner observed for β-pinene.

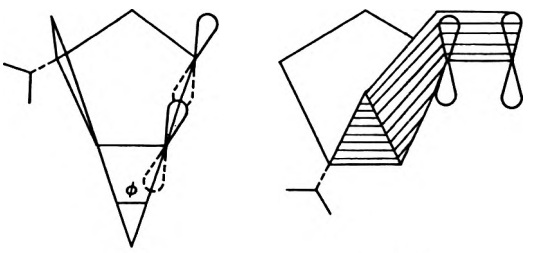
Discussion

In practically all systems previously examined, both hydrogenation and hydroboration takes place preferentially from the same direction, the least hindered side of the double bond. The same behavior is observed for α-thujene, with both hydroboration and hydrogenation taking place preferentially from the side away from the cyclopropane ring. In the case of sabinene we have a special feature appearing—hydroboration and hydrogenation take place from the opposite sides. We believe that in this case the hydroboration reaction is normal and takes place from the less hindered side of the double bond. An examination of the molecular models provides support for the position that the side away from the cyclopropane ring is indeed the less sterically encumbered of the two sides. It follows that the hydrogenation of sabinene may be anomalous and it is of interest to consider possible explanations.



Hydrogenation on platinum catalysts is believed to proceed through the prior formation of a complex involving association of the π electrons of the double bond with the metal surface. Hydrogen associated with the metal surface then combines with the double bond from the same direction.[25]

It is generally accepted that the cyclopropane ring is rich in π character, approaching the π behavior of a double bond. Moreover, it is believed that the π-electron density[26] is at a maximum in the plane of the cyclopropane ring. In α-thujene the angle made by the cyclopropane ring with the π electrons of the double bond is unfavorable for conjugation (**2A**), whereas the possibilities for conjugation are much more favorable in sabinene (**1A**). It is our suggestion that such conjugation causes the sabinene molecule to associate with the platinum catalyst from the cyclopropane side in order to give this conjugated system maximum opportunity to interact with the platinum surface. This overcomes the usual steric preferences. In hydroboration, where such conjugation is unimportant, the reaction is controlled primarily by the ease of steric approach.



2A

electronic system making an angle ϕ in thujene

1A

maximum overlap in electronic system is possible from β-side in sabinene.

Anomolous Behavior of the 10-Thujyl Derivatives.—The equilibration of 3-thujone, the hydroboration–isomerization of thujene and sabinene, and the equilibration of 10-thujylaldehydes, all indicate that the thujyl system is more stable with the group in the 10 position situated *cis*, rather then *trans*, with respect to the cyclopropane ring. In the pinane case, however, it is the corresponding *trans* compounds[2] that are more stable. This unusual behavior could be explained if the assumption is made that the above thujyl derivatives prefer to exist in the boat form, thereby forcing the 10-methyl into equatorial conformation. In the usual chair form the 10-methyl group occupies the quasiaxial position. Support for this proposal is provided by a detailed study of the nmr spectra.

Spectroscopic Evidence.—Norin[6] postulated boat conformations for all thujane derivatives that he studied. This postulation now seems to be universal for all derivatives of the bicyclo[3.1.0]heptane series[27,28] and is now successfully extended to the 10-thujyl derivatives.

Proton H_D in 10-isothujanol (**7B**) appears as quartet with a coupling constant of 7 cps. On the other hand, the same proton in **6B** appears as a broad multiplet spread over 40 cps (Figures 4 and 5). If 10-isothujanol (**7B**) exists in a boat form, then no coupling

(25) M. Freifelder, *Ann. N. Y. Acad. Sci.*, **145** (1), 5 (1967).
(26) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, **21**, 163 (1965).
(27) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965).
(28) W. G. Dauben and W. T. Wipke, *ibid.*, **32** 2977 (1967).

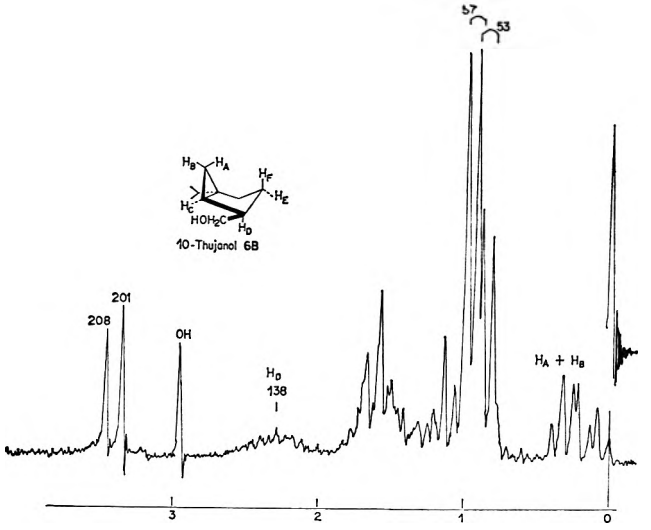
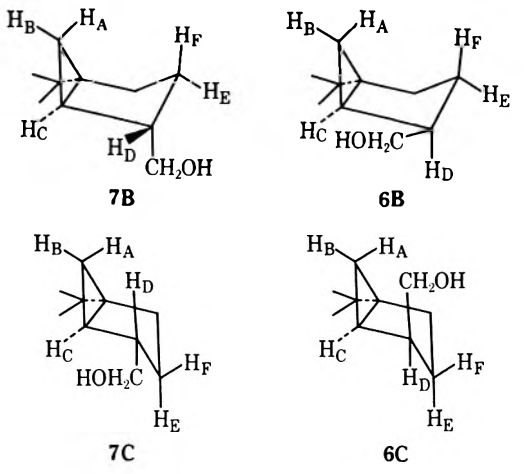


Figure 4.—Nmr spectrum of 10-thujanol (**6B**).

between H_D and H_C would be expected because the dihedral angle between these protons is 90°. Similarly,



the dihedral angle between H_D and H_E protons is 90° and again no coupling between these two protons should be observed. Proton H_D can couple only with proton H_F, for the dihedral angle between these protons is 20°, and with protons of CH_2OH groups, with the result that the signal for H_D proton is a relatively narrow peak (half band width 24 cps). Similarly, in boat form of **6B**, proton H_D can couple with H_C (dihedral angle 20°), H_E (dihedral angle 20°), H_F (dihedral angle 110°), and the protons of CH_2OH group. Therefore the signal for this proton should be broad and it actually appears as a broad peak spread out over 40 cps.

The signal for H_D in **7B** (120 cps) is shifted upfield because it faces cyclopropane and the diamagnetic anisotropic effects of cyclopropane are operative. The corresponding signal in **6B** (138 cps) is shifted downfield because of the paramagnetic effects of the cyclopropane. Contrary to these observations, the signal for the carbinyl protons of CH_2OH is shifted upfield for **7B** (197.5 cps) and downfield for **6B** (204.5 cps). This may be due to the equatorial relationship of the CH_2OH group to both cyclopropane and cyclopentane in **6B** and to the axial relationship to the cyclopentane moiety in **7B**. The anisotropic effects of cyclopropane

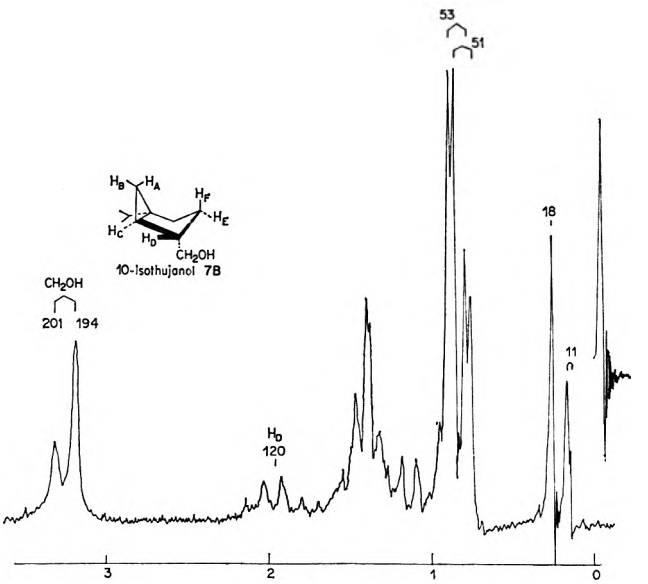


Figure 5.—Nmr spectrum of 10-isothujanol (**7B**).

are operative only to H_D protons because of the proximity and not to the more distant carbinyl protons.

On the other hand, if 10-isothujanol (**7C**) and 10-thujanol (**6C**) are in the chair forms, the signal for H_D should be broader in **7C** than in **6C** and the chemical shift for the carbinyl protons of CH_2OH should be shifted upfield because now they face the cyclopropane ring and downfield in **7C** because they would be in an equatorial relationship to the cyclopropane and cyclopentane moieties. Since none of these characteristics is seen in the spectra, the 10-thujanol derivatives must exist in the boat form.

The stability of the boat form of thujane derivatives can be understood by considering the various nonbonded interactions. H_A will have two nonbonded interactions between 2-β-H and 4-β-CH_2OH or 4-β-H in **6C** and **7C**, instead of one in the boat form between H_A and H_F in **6B** and **7B**. In the boat form, 10-CH_3 or 10-CH_2OR will be in the equatorial conformation in **6B** and this is the reason why *cis* isomers (*cis* with respect to cyclopropane) are thermodynamically more stable than *trans*.

A similar pattern of nmr spectra is observed with all of the 10-thujanol derivatives, including the parent hydrocarbons. These results are summarized in Table I. Recently a detailed analysis was made of the nmr spectra of *cis*- and *trans*-thujanes.[29]

Experimental Section

Materials.—(+)-α-Thujene was a sample generously supplied by the Dragoco Co. This contained 15% α-pinene, but was used as such. This was also purified by using the Varian Autoprep from 85 to 96% purity and had $[\alpha]^{19}D$ + 14.4° (lit. + 37.7°,[14] −49.3°[9]), $n^{20}D$ 1.4568 (lit. 1.4502,[12] 1.4511[9]). The infrared spectra completely superimposed the published spectra (Sadtler ir spectra, no. 1089). (+)-Sabinene was a sample kindly made available by the International Flavors and Fragrances Inc. It was 95% pure, the impurities being 1.5% α-pinene and 3.5% α-thujene, and was used as such for all the reactions: $[\alpha]^{25}D$ +95° (*c* 20, CCl_4) (lit.[9] +87°), $n^{20}D$ 1.4692 (lit.[9] 1.4681). The infrared spectrum was identical with that of an authentic sample.[30]

(29) A. Dieffenbacher and W. Philipsborn, *Helv. Chem. Acta*, **49**, 897 (1966).

(30) V. Herout, *Chem. Listy*, **46**, 438 (1952).

TABLE I

NMR SPECTRAL DATA[a] FOR THE THUJANE DERIVATIVES

	3-H	4-H	10-CH_2 or 10-CH_3	8-CH_3 or 9-CH_3	9-CH_3 or 8-CH_3	6-H_A	6-H_B	$ArCH_3$	$OCOCH_3$
α-Thujene (2)	4.87 (s)		1.72[b]	0.89[c]	0.93[c]	0.7[d]	0[d]		
Sabinene (1)			4.44 (s)	0.90[c]	0.96[c]	0.66 (s)	0.58[e]		
			4.57 (s)						
3-Thujanol (10)	3.22[f]		0.87[c]	0.97[c]	1.01[c]	−0.13–0.27[g]			
3-Thujanol acetate (10a)	4.23[f]		0.97[h]	0.87[c]	1.01[c]	0.0–0.4[g]			1.93 (s)
3-Thujanol tosylate (10b)	4.15[f]		0.82[h]	0.73[c]	0.9[c]	0.08–0.23[g]		2.4 (s)	
10-Thujanol (6)		2.32[i]	3.40[j]	0.89[c]	0.95[c]	0.0–0.43[g]			
10-Thujyl acetate (6a)		2.45[i]	3.98[j]	0.84[c]	0.94[c]	0.0–0.42[g]			1.97 (s)
10-Isothujanol (7)		2.02[k]	3.28[j]	0.85[c]	0.88[c]	0.3 (s)	0.18[l]		
10-Isothujanol acetate (7a)		2.2[k]	3.89[j]	0.83[c]	0.95[c]	0.34 (s)	0.23[l]		1.98 (s)
cis-Thujane (5)		1.93[m]	0.9[c]	0.9[c]	0.93[c]	0.28 (s)	0.18[l]		
trans-Thujane (4)			0.85[c]	0.93[c]	0.93[c]	0.03–0.42[g]			

[a] All spectra were taken on a Varian A-60A or JOL-60H instruments and the chemical shift is expressed in terms of δ units from tetramethylsilane. The letters in parentheses indicate singlet, doublet, quartet, and multiplet. [b] (q), J = 2 cps. [c] (d), J = 6.5 cps. [d] (q), J = 3 cps. [e] (d), J = 1.5 cps. [f] (q), J = 8 cps. [g] (m), AB pattern of an ABX system. [h] (d), J = 4.5 cps. [i] Broad peak spread over 40 cps. [j] (d), J = 7 cps. [k] (q), J = 7 cps broad peak spread over 24 cps. [l] (d), J = 1.5 cps. [m] Broad peak spread over 32 cps.

The purification of diglyme, tetrahydrofuran, and boron trifluoride–etherate and the preparation of diborane were carried out by the usual procedures.[20] The glpc analyses were made on a Hitachi gas chromatographic analyser KGL-2A with 45-m Golay columns of squalene (A), UC oil IB-550 X (B), Carbowax 20M (C), Ohukara gc analyzer GI-360 with 2-m packed columns of 15% Carbowax 20M on Diasolid (D), F & M Model 500 with 3-m packed columns of 20% Carbowax 20M on Chromosorb W (40/60) (E), F & M Prep Model 770 with 2.5- or 8-m packed columns of 15% Carbowax 20M on Chromosorb W (F and G), and Perkin-Elmer Model 226 with 45-m Golay columns of squalene (H), Carbowax 20M (I), and TCP (tricresyl phosphate) (J). The nmr spectra were taken on the JOL-60H or Varian A-60H. The infrared spectra were run on the Hitachi EPI-G2 or Perkin-Elmer Infracord Model 137.

Hydroboration–Oxidation of (+)-α-Thujene.—In a 250-ml three-necked flask equipped with a thermometer, condenser, pressure-equalizing dropping funnel, and side arm with a serum cap were placed 8.12 g of α-thujene (60 mmol) and 20 ml of tetrahydrofuran. The mixture was cooled to 0° and, under stirring, 27.5 ml of a 1.4 M solution of diborane in tetrahydrofuran (40 mmol of BH_3) was added dropwise. After 2 hr at 0° and 1 hr at 25°, the excess of hydride was destroyed by the careful addition of 1 ml of water in 1 ml of tetrahydrofuran. The reaction mixture was oxidized at 45–50° by adding 13.3 ml of 3 N sodium hydroxide (40 mmol) and 13.3 ml of 30% hydrogen peroxide. After 1 hr the mixture was saturated with potassium carbonate, the tetrahydrofuran layer separated, and the aqueous phase extracted with ether. The combined extracts were dried over $MgSO_4$ and distilled to give 7.2 g of the alcohols, bp 89° (3.2 mm), a yield of 83%. Isopinocampheol and thujyl alcohol were difficult to separate by glpc, but their acetates were easily separable.

(−)-Thujyl Acetate (10a).—The mixture of thujyl alcohol and isopinocampheol (7.2 g, 50 mmol) was dissolved in 11 ml of pyridine and 5.6 ml of acetic anhydride (6 g, 60 mmol) was added and allowed to stand at room temperature overnight. The nmr analysis of this mixture indicated 90% acetylation. Pyridine and acetic anhydride were removed by distillation under reduced pressure at room temperature and the residue was distilled to give 7.8 g of acetates, bp 100–105° (5 mm), a yield of 82%. Thujyl acetate (85%, t_r 80 min) and isopinocampheol acetate, (15% t_r 105 min) were separated on column G at 200°. Pure thujyl acetate had bp 75° (2 mm); $n^{20}D$ 1.4475; $[\alpha]^{24}D$ −58° (c 20, CCl_4).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 74.43; H, 10.27. Found: C, 74.40; H, 10.65.

(−)-Thujyl Alcohol (10).—Thujyl acetate (2.52 g, 12.8 mmol) was allowed to react with 6.5 ml of lithium aluminum hydride in tetrahydrofuran (2.0 M, 13 mmol) overnight. Residual hydride was decomposed with water, a saturated solution of potassium sodium tartrate (6.5 ml) added, the supernatant tetrahydrofuran layer separated, and the aqueous layer extracted with ether. The combined extracts were dried over $MgSO_4$ and distilled to give 1.69 g of thujyl alcohol: bp 72° (1.8 mm); $n^{20}D$ 1.4603; $[\alpha]^{28.5}D$ −46.7 (c 20, CCl_4). Its infrared and nmr spectra were completely superimposable with those of the authentic samples.[22]

(+)-*trans*-Thujane (4).—Thujyl alcohol (0.79 g, 5 mmol) and 5 ml of dry pyridine were mixed. Then 0.95 g of freshly sublimed *p*-toluenesulfonyl chloride (5 mmol) was added at 0° with stirring. The mixture was placed in cold room (0°) for 24 hr. Analysis of the supernatant liquid by nmr indicated 89% tosylation. It was filtered to remove pyridine hydrochloride and the filtrate was evaporated to dryness at 1 mm. The dry product was treated with an ethereal solution of lithium aluminum hydride (7.5 ml of 2 M, 15 mmol) cautiously and left for 2 days with stirring under a nitrogen atmosphere. An insoluble white precipitate formed, ether was removed, and the product was collected at 90° (1 mm) in a Dry Ice cooled trap. Pure *trans*-thujane was isolated by glpc on column E. The yield was 0.310 g (45%); $n^{20}D$ 1.4384; $[\alpha]^{28.5}D$ −37.3° (c 10, CCl_4). Its infrared and nmr spectra were identical with those of the hydrocarbon from the alcohol B, the major alcohol obtained in the hydroboration–oxidation of (+)-sabinene.

(−)-3-Thujone (11).—(−)-3-Thujyl alcohol (10) and ether (2 ml) were treated with aqueous chromic acid in the usual manner.[23] A pure sample of (−)-3-thujone was obtained by glpc on column D: $n^{27}D$ 1.4538 (lit.[24] 1.4508); $[\alpha]$ −27.8° lit.[24] +73.4°). The infrared and nmr spectra were consistent with those of the authentic samples.[22]

Equilibration of (−)-3-Thujone (11) and (+)-Isothujone (12).—(−)-3-Thujone (1 mmol) was added to sodium ethoxide solution (1 ml, 1 M) and stirred at 25°. The progress of the equilibrations was studied by glpc analysis by removing aliquots, extracting the ketones with pentane, and neutralizing the alkali with 1% hydrochloric acid. The results are [time in minutes, per cent (−)-3-thujone] 0, 100; 30, 67.4; 60, 67.7; 120, 68.4.

Catalytic Hydrogenations. A. (+)-α-Thujene on Palladium.—(+)-α-Thujene (0.65 g) in 15 ml of ethanol was hydrogenated over palladium black catalyst (0.2 g) at 25°. After 60 min, the absorption of hydrogen had stopped, and 2 mol equiv of hydrogen had been consumed. The reaction mixture was filtered, diluted with water, and extracted with ether. The ether solution was dried and distilled. Glpc analysis on column A showed a single peak. However no attempt was made to determine whether it was a *cis*- or *trans*-cyclopentane derivative or a mixture of both. The isolated sample by glpc had $[\alpha]D$ −5.40°, $n^{18}D$ 1.4339; nmr, no cyclopropane protons between δ 0 and 0.78 from tetramethylsilane and no olefinic protons.

Anal. Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.38. Found: C, 85.99; H, 14.09.

B. (+)-α-Thujene on Platinum at −20°.—In a Brown□ microhydrogenator was placed 0.1 g of platinum dioxide, 0.2 g of Darco, and 2 ml of diethyl ether. The catalyst was formed with hydrogen from the generator, which contained 2 ml of glacial acetic acid in the flask and sodium borohydride solution (1.197 M in H^-) in the buret. The mixture was allowed to stand for 5 min

to ensure that there was no further absorption of hydrogen. The flask was cooled to −20°, using a Dry Ice–carbon tetrachloride slush. Thujene (1 ml, 0.845 g, 6.2 mmol) was added slowly and the absorption of hydrogen followed by the utilization of sodium borohydride solution: 1.8 ml, 5.72 mmol, over 45 min. The reaction was allowed to continue for a total of 2 hr, but there was no further hydrogen consumption, indicating a clean hydrogenation to a dihydro derivative.[31] The solution was separated from the catalyst and dried over $MgSO_4$. Glpc analysis on column E at 50° indicated two components. The second component (17%) was identified as α-pinene by comparison with an authentic nmr spectrum. The first component on columns H and I gave a single peak but on column J gave two peaks at 50° with 10-lb helium pressure: 85% *trans*-thujane (t_r 10 min) and 15% *cis*-thujane (t_r 11 min). The nmr spectra of the compound indicated the presence of cyclopropane protons δ 0–0.3 (m), but no olefinic protons. It had $[\alpha]^{28}D$ −29.3° (*c* 20, CCl_4), $n^{20}D$ 1.4376.

C. (+)-α-Thujene on Platinum at Room Temperature.—When the hydrogenation was done at room temperature using the Brown□ microhydrogenator under identical conditions and the product analyzed by glpc on column J, three compounds were obtained, 68% *trans*-thujane 4 (t_r 10 min), 14% tetrahydrothujane (t_r 10.5 min), and 18% *cis*-thujane 5 (t_r 11 min.)

D. (+)-Sabinene on Platinum at −20°.—Hydrogenation was done exactly as described for (+)-α-thujene, using exactly the same quantities, but the hydrogenation was over in 20 min. The glpc analysis on column J indicated the presence of two compounds: 15% *trans*-thujane (t_r 10 min) and 85% *cis*-thujane (t_r 11 min). The nmr spectrum of the product indicated the presence of cyclopropane protons at δ 0–0.7 (m), but no olefinic protons. It had $[\alpha]^{27}D$ +9.17 (*c* 20, CCl_4), $n^{20}D$ 1.4390.

E. (+)-Sabinene on Platinum at Room Temperature.—Like (+)-thujene, (+)-sabinene also gave three products at room temperature: *cis*-thujane, 62%, tetrahydrothujane, 25%, and *trans*-thujane, 13%.

F. (+)-Sabinene on Palladium at Room Temperature.—The hydrogenation was over within 40 min and the hydrogen consumed corresponded to 2 mmol for each mole of (+)-sabinene. Glpc analysis showed a single peak on column J.

Isomerization of (+)-Sabinene (1) to (−)-α-Thujene (2). A. With Ethylenediaminolithium.—The reagent was prepared as described earlier[3] using lithium (0.7 g) and ethylenediamine (30 ml). To the reagent (3 ml) was added 1 ml of sabinene (0.845 g) and this was allowed to stir overnight at room temperature. Water (3 ml) was added and the mixture extracted with pentane. Glpc analysis of the pentane extract on column H indicated that it is a mixture of three components: 68% α-thujene (t_r 18.5 min), 7% sabinene (t_r 23 min), and 25% *p*-cymene (t_r 29.5 min). Nmr analysis of the product indicated the presence of 10% conjugated diene, probably in the aromatic fraction: 75% sabinene and thujene, 10% unknown conjugated diene (330 cps), and 15% aromatics (408 cps).

B. With Potassium *t*-Butoxide in Dimethyl Sulfoxide.—A round-bottomed flask, fitted with a side arm with a serum cap, was flushed with nitrogen, and then potassium *t*-butoxide in dimethyl sulfoxide (2 *M*, 5 ml) was added, followed by sabinene (1.7 ml, 10 mmol) in 5 ml of dimethyl sulfoxide. The mixture was heated to 90°. At appropriate intervals 50-μl aliquots were removed and examined by glpc on column E at 79°, isothermally. The time in minutes and the per cent α-thujene formed were as follows: 5, 40; 10, 50; 20, 76; 30, 83; 40, 87; 50, 88; 60, 90; 70, 91; 80, 91; 120, 91; 150, 91. No aromatics formed, as indicated by glpc and nmr. The reaction mixture was decomposed with 5 ml of water and extracted with four 10-ml portions of pentane dried over $MgSO_4$, and passed through a column of silicic acid impregnated with silver nitrate (15%). It was further eluted with pentane (100 ml). Pure α-thujene was then isolated by distilling the solvent. Its infrared and nmr spectra were identical with those of the authentic samples, $n^{20}D$ 1.4512, $[\alpha]^{28.5}D$ −55 (*c* 20, CCl_4). Hence the Dragaco sample of (+)-α-thujene used in the present study and the sample obtained by isomerization of (+)-sabinene are optical antipodes.

Hydroboration–Oxidation of (+)-Sabinene.—Under the same conditions as described for α-thujene, sabinene (1.73 g) was hydroborated by diborane in tetrahydrofuran (4.4 ml of 1.82 *M* in BH_3) and then oxidized by alkaline hydrogen peroxide. It was shown by glpc on column C that the yield of the primary alcohols A and B was 93% and the distribution was 35:65. In the hope of getting more stereoselectivity, the hydroboration was carried out with disiamylborane. The reagent disiamylborane was prepared as described earlier[20] using 14.7 g of 2-methyl-2-butene (210 mmol) and 69 ml of diborane in tetrahydrofuran (1.45 *M* in BH_3, 100 mmol). Sabinene (9.52 g, 70 mmol) was then added to the well-stirred solution of disiamylborane at 0°. The progress of the reaction was studied by removing 1-ml aliquots of the solution and examining it for residual hydride. Within 1 hr 19% of the reaction was over. After 2 hr, at 0°, the reaction mixture was decomposed with water, oxidized with 35 ml of sodium hydroxide (3 *N*) and 35 ml of hydrogen peroxide (30%) at 35–40°, and extracted with ether. The combined extracts were dried over $MgSO_4$ and distilled. The product, 9.2 g, a yield of 90%, contained 32% alcohol A and 68% alcohol B and had the following properties: $n^{18}D$ 1.4652 and $[\alpha]D$ +51.6°. These alcohols gave ill-resolved peaks on glpc and hence could not be separated.

Separation of Alcohols A and B. A. Monophthalate Method.—The mixture of alcohols (2.4 g), freshly distilled phthalic anhydride (2.36 g), and dry pyridine (5 ml) was heated at 100° for 5 hr, and then poured into 30 ml of sodium carbonate solution (5%). Neutral compounds were extracted with petroleum ether. The aqueous phase was acidified to congo red with 30% sulfuric acid. The solid was extracted with ether. The extract was washed with brine and dried over Na_2SO_4. Repeated crystallization from petroleum ether and methanol gave a solid, mp 93.8–94.6°, $[\alpha]D$ −79.2°.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.54; H, 7.39.

The purified acid phthalate (0.156 g), dissolved in alcoholic potassium hydroxide (potassium hydroxide, 0.152 g, and ethanol, 5 ml), was heated at reflux for 1 hr, and steam distilled. The distillate was extracted with ether and dried over $MgSO_4$ and distilled. It was found by glpc to be alcohol B uncontaminated with alcohol A.

Acetate Method.—The mixture of alcohols A and B (7.2 g, 48 mmol), 11 ml of pyridine, and 6 g of acetic anhydride (60 mmol) were mixed and left overnight. It was worked up as described earlier for thujyl acetate. Distillation at 100° (4 mm) gave 7.18 g of the acetate mixture. These acetates (4.8 g) were then separated by preparative glpc on column G at 200° by injecting 200 μl at a time. Three fractions were collected: first fraction, acetate of alcohol A, 100% pure by glpc and nmr (0.758 g, t_r 128 min); second fraction, a 50:50 mixture of acetates of alcohol A and B (0.720 g); and a third fraction, acetate of alcohol B, 100% pure by glpc and nmr (1.324 g, t_r 138 min).

Acetate of Alcohol A (7a).—It had bp 82° (2 mm); $n^{22.5}D$ 1.4525; $[\alpha]^{22.5}D$ +54° (*c* 10, THF), +6.10 (neat 1 dm).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 74.43; H, 10.27. Found: C, 74.40; H, 10.65.

Acetate of Alcohol B (6b).—It had bp 82° (2 mm); $n^{22.5}D$ 1.4520; $[\alpha]^{27}D$ +76.9° (*c* 10, THF), +75.27 (neat).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 74.43; H, 10.27. Found: C, 74.73; H, 10.35.

Alcohol A.—10-Isothujanol (7) was obtained in 90% yield by the lithium aluminum hydride reduction of the acetate of alcohol A (0.650 g) using the same procedure as described earlier. It had bp 80–81° (1.8 mm); $n^{20}D$ 1.4656; $[\alpha]^{24.5}D$ +13.1° (*c* 20, CCl_4).

Alcohol B.—10-Thujanol (6) was also prepared in 92% yield by the above procedure. It had bp 80–81° (1.8 mm); $n^{20}D$ 1.4636; $[\alpha]^{24.5}D$ +91.7° (*c* 20, CCl_4).

(+)-*trans*-Thujane (4).—Alcohol B (0.308 g, 2 mmol), pyridine (2 ml), and *p*-tolylsulphonyl chloride (0.396 g, 2 mmol) were mixed and allowed to react at 0° for 24 hr. The reaction mixture was filtered and the filtrate was evaporated to dryness at 1 mm. To the residue was added lithium aluminum hydride in diethyl ether (5 ml, 2 *M*) and allowed to react at room temperature for 48 hr. It was worked out as described earlier for (−)-*trans*-thujane from thujyl alcohol. Hydrocarbon (0.170 g, 62%) was collected by glpc on column E and was identical by nmr and glpc with that obtained from thujyl alcohol *via* the tosylate reduction, and also corresponded to the major hydrocarbon obtained in the hydrogenation of α-thujene at −20°. Hence the alcohol B is 10-thujanol (6). The hydrocarbon had $n^{20}D$ 1.4367 and $[\alpha]^{25}D$ +84.3° (*c* 20, CCl_4).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.70; H, 13.41.

(−)-*cis*-Thujane (5) was prepared in 57% yield from alcohol using identical conditions. This hydrocarbon was identical with

(31) We are indebted to Dr. Charles A. Brown for disclosing to us the results of his studies of low temperature hydrogenation.

the minor hydrocarbon obtained during hydrogenation of (+)-thujene at −20° and with the major hydrocarbon obtained during the hydrogenation of (+)-sabinene at −20° by glpc and nmr. This compound had $n^{25}D$ 1.4390; $[\alpha]^{28.5}D$ −10.05° (c 20, CCl_4).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 87.04; H, 12.86.

Hydroboration–Isomerization–Oxidation of (+)-α-Thujene.—After hydroboration of α-thujene (0.085 g) with diborane in tetrahydrofuran (0.2 ml, 2.43 *M* in BH_3), diglyme, 2 ml, was added and tetrahydrofuran was removed under vacuum. The reaction mixture was then heated at 170–175° for 2.5 hr, oxidized by alkaline hydrogen peroxide, and analyzed by glpc on column D which indicated the ratio of alcohol **A** to alcohol **B** to be 40:60.

Hydroboration–Isomerization–Oxidation of (+)-Sabinene.—To a mixture of (+)-sabinene (0.1 g) in diglyme (0.5 ml) and sodium borohydride solution in diglyme (1.0 *M*, 0.9 ml) was added at 0° boron trifluoride–diglymate (3.65 *M*, 0.33 ml). The solution was stirred for 2 hr. It was heated at 150–160° for 2.5 hr and oxidized as usual. When analyzed by glpc on column D, the ratio of alcohol **A** to **B** was 40:60.

Oxidation of 10-Thujanol with Chromic Acid.—10-Thujanol (0.1 g) was oxidized with chromic acid under the same conditions as described for thujyl alcohol. Glpc analysis on column A indicated 47% yield of the aldehydes, the ratio of 10-thujylaldehyde (**8**) (t_r 5.0 min) to 10-isothujylaldehyde (**9**) (t_r 4.1) being 97:3. 10-Thujylaldehyde was obtained by preparative glpc. Although a pure analytical sample of 10-thujylaldehyde was not obtained, it was characterized by reducing it back to 10-thujanol with sodium borohydride.

Oxidation of 10-Isothujyl Alcohol with Chromic Acid.—10-Isothujyl alcohol was oxidized under the same conditions as above. The compound gave back pure 10-isothujanol on reduction with sodium borohydride.

Equilibration of 10-Thujylaldehyde.—A mixture of 85% pure 10-thujylaldehyde and 15% 10-isothujylaldehyde (40 mg) was added to sodium ethoxide solution (0.5 *M*, 1 ml) in ethanol. It was stirred at 25° and the progress of the reaction was studied by removing aliquots and neutralizing it with 1% hydrochloric adid. The pentane extract of the neutralized reaction mixture was then analyzed by glpc on column D. The results are (time in minute and per cent thujylaldehyde) 0.85; 30, 76; 60, 63; 120, 59; 200, 59.

Registry No.—(+)-Sabinene, 2009-00-9; (−)-α-thujene, 3917-48-4; (+)-*trans*-thujane, 5523-91-1; (−)-*cis*-thujane, 4423-90-0; (+)-10-thujanol, 20-126-25-4; (+)-10-thujanol acetate, 20-126-26-5; (+)-10-isothujanol, 20-126-27-6; (+)-10-thujanol acid phthalate, 20147-89-1; (+)-10-isothujanol acetate, 20-126-28-7; (−)-3-thujanol, 20-126-29-8; (−)-3-thujanol acetate, 20-126-30-1; 3-thujanol tosylate, 20-126-31-2; (+)-α-thujene, 563-34-8; (−)-*trans*-thujane, 20126-20-9; (+)-*cis*-thujane, 7712-66-5.

The Preparation and Chemistry of 9β-Estr-4-en-3-ones

E. FARKAS, J. M. OWEN, AND D. J. O'TOOLE

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

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Hydrogenation of 17α-substituted estra-4,9(10)-dien-3-ones gave the corresponding 9β-estr-4-en-3-one accompanied by the 10α isomer. Because of inherent strain, the 9β-estr-4-en-3-ones readily isomerized under mild acid or base conditions to yield the analogous 9β-estr-5(10)-en-3-ones; more vigorous conditions resulted in epimerization to the 9β,10α-estr-4-en-3-ones. Reduction of 17β-hydroxy-17α-methyl-9β-estr-4-en-3-one with Li–NH_3 yielded 17β-hydroxy-17α-methyl-5α,9β,10β-estran-3-one.

The preparation of steroids having natural configurations at various ring juncture carbons continues to be a challenge to the synthetic chemist.[1] Although the 9β C_{19} steroid analogs have been prepared,[2] the corresponding 19-nor compounds have not been reported. In an earlier study, the hydrogenation of 17β-hydroxyestra-4,9(10)-dien-3-one to give unnatural 10α,19-nor steroids was described.[1c] As the C_{17} substituent of the dienone was varied, increasing amounts of a new isomer were obtained; changes in catalyst and in solvent also resulted in increased yields of this new isomer.

As an example, when 17β-hydroxy-17α-methylestra-4,9(10)-dien-3-one[3] was hydrogenated in EtOH with Pd–$SrCO_3$ catalyst,[4] there was obtained after fractional crystallization a 26% yield of 17β-hydroxy-17α-methyl-10α-estr-4-en-3-one (**1**) and an 18% yield of the new isomer, 17β-hydroxy-17α-methyl-9β-estr-4-en-3-one (**2**). The structure of **2** was assigned on the basis of spectral studies and chemical transformation. The presence of an α,β-unsaturated ketone was indicated by the uv and ir data. Also, the nmr supported the assignment as an isomeric 19-nor-4-en-3-one, since it revealed the presence of the 4 proton as a broadened singlet at δ 5.86 and the 17- and 18-methyl protons as singlets at δ 1.23 and 1.00, respectively. The 18-methyl proton resonance of the isomeric ketone **1** was at δ 0.82.

Examination of molecular models indicates that the 9β stereochemistry necessitates the presence of a boat conformation in one of the rings; the B ring is generally assigned this conformation since the flexible terminal A ring can assume a conformation which will minimize some of the resultant strain interactions. This conformation is consistent with the nmr data, since the C_{18} angular methyl group would be expected to be deshielded because it is situated on the convex β surface of the molecule.

The circular dichroism (CD) spectrum of **2** exhibits a positive Cotton effect in the long-wavelength region and a negative Cotton effect in the $\pi-\pi^*$ region. This curve is similar to the CD spectrum of 17β-hydroxy-9β,10α-estr-4-en-3-one, except that the short-wavelength Cotton effect is less intense.[5] Because of this lower intensity, the chirality of the chromophore appears to be more nearly planar in the predominant conformer, a situation similar to that with the 9α,10α-estr-4-en-3-

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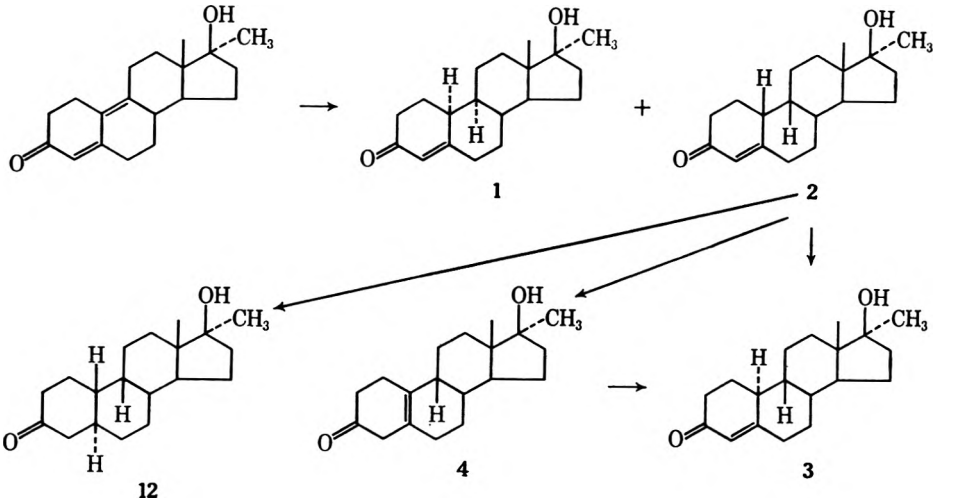
SCHEME I



ones.[1c] Unlike the 9α,10α isomer, the 9β,10β isomer experiences no change in the sign of the Cotton effect in the $\pi-\pi^*$ region on changing solvent from dioxane to methanol.

Treatment of **2** in methanolic HCl gave the isomeric ketone 17β-hydroxy-17α-methyl-9β,10α-estr-4-en-3-one (**3**) (Scheme I). Its CD spectrum was similar to that reported for the analogous C_{19} retro (9β,10α) compounds.[5] Further, the chemical stability of this compound, as evidenced by its method of preparation, favors the all-chair retro assignment.[6] Interestingly, the 18-methyl proton resonance is at δ 0.95; the natural 9α,10β isomer has the chemical shift of these protons at δ 0.91.

Of the four isomeric estr-4-en-3-ones (at C_9 and C_{10}), only the 9β isomer experiences a disappearance of the uv maximum at 243 mμ upon the addition of a few drops of aqueous base. On acidification of this solution, the chromophore does not reappear. These changes can be used as a semiquantitative assay to determine the purity of the 9β isomer. An approximate duplication of these reaction conditions on a preparative scale led to the isolation of 17β-hydroxy-17α-methyl-9β-estr-5(10)-en-3-one (**4**). The 9β assignment can be made by a comparison of physical properties with those of the 9α isomer and also by examination of the rotatory dispersion (RD) spectrum, which shows a Cotton effect minimum in the long-wavelength region while the 9α isomer displays a maximum.[7] In addition, the nmr spectrum does not contain any vinyl protons, and it has the 17-methyl proton resonance at δ 1.13 compared with δ 1.26 for the 9α isomer. This upfield shift is in agreement with the assigned structure, since the double bond at 5(10) in the 9β series could be expected to shield the 17-methyl group protons. The ready deconjugation under these mild conditions reflects the severe strain existing in the molecule. Further, the α face of the dienolate is hindered to protonation at C_{10}, and this situation also favors the formation of the deconjugated ketone.[8]

The ketone **2** can also be deconjugated using dilute mineral acid; this change too can be readily observed in the uv. More concentrated acid or longer reaction time leads to the retro (9β,10α) compound mentioned previously. This 9β,10β-estra-4-en-3-one system, under acidic conditions, leads to a dienol which is protonated at C_4, leading to the deconjugated ketone. In the normal androstenone series, the dienol is protonated with mineral acid at C_6 and with AcOH at C_2.[8] This difference in the site of protonation can again be attributed to the strain inherent with the 9β,10β stereochemistry and to the severe hindrance of the α face of the dienol.

Several other 9β-estra-4-en-3-ones have been prepared by direct hydrogenation. Although it is not clearly the result of steric factors, best yields of the 9β,10β isomer were obtained by hydrogenation of 17α-hydroxyestra-4,9(10)-dien-3-one (**5**). This latter compound was readily prepared[3] from the corresponding 17α-hydroxyestr-5(10)-en-3-one.[9] Hydrogenation of dienone **5** gave almost exclusively 17α-hydroxy-9β-estra-4-en-3-one (**6**) with traces of the 9α,10α isomer (**7**). It is worthy of comment that allylic alcohols, on catalytic hydrogenation, direct the hydrogen to approach the molecule *cis* to the alcohol group.[10] In the present nonallylic situation, the 17α alcohol directs the hydrogen to approach predominantly from the opposite side. The conformation of the D ring undoubtedly contributes to the stereochemical course of this reaction.[11] Compound **6** is extremely sensitive to acid, and even spectral grade $CDCl_3$ results in partial isomerization to the 5(10)-en-3-one compound, necessitating the use of pyridine as solvent for nmr studies. Once again the nmr spectrum of this 9β isomer has the 18-methyl proton resonance considerably farther downfield when compared to the spectra of the other 9,10-isomeric compounds.

Hydrogenation of the epimeric 17β-hydroxyestra-4,9(10)-dien-3-one did not yield any detectable amounts of the 9β isomer under a variety of conditions.[1c] In sharp contrast, it was recently shown that the presence of either a 17α- or a 17β-hydroxyl group, albeit with a different catalyst, results in hydrogenation of a 14(15) double bond from the α face.[12] Thus, in the present

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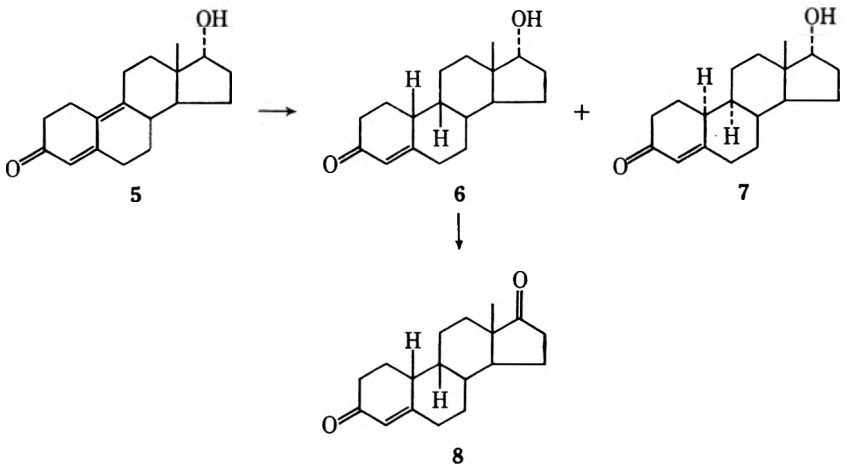
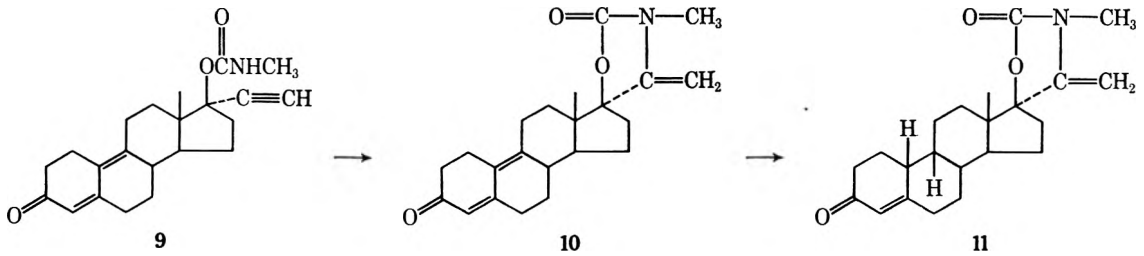
SCHEME II



SCHEME III



study, the 17α-hydroxy compound is of value, because it can be used as an intermediate for the preparation of a variety of other 17-substituted analogs. Using chromic anhydride–pyridine, 17α-hydroxy-9β-estra-4-en-3-one (**6**) can be oxidized in good yield to 9β-estr-4-ene-3,17-dione (**8**) (Scheme II). Chemical transformations of this 17-one compound are currently underway.

Added insight into the steric requirements of β-face hydrogenation was obtained on hydrogenation of N-methyl-N-{1-[17β-hydroxyestra-4,9(10)-dien-3-one-17α-yl]vinyl}carbamic acid γ-lactone (**10**). **10** was readily obtained by cyclization of the methyl carbamate **9**[13] (Scheme III). Hydrogenation using Pd–$BaSO_4$ catalyst led to a 25% yield of the 9β,10β isomer (**11**) as the sole crystalline product. Many of the reaction mixtures from the hydrogenations being reported are composed of mixtures of isomers which appear as a single component in a variety of tlc systems; to date these mixtures have only been resolved by fractional crystallization. The structural assignment of **11** was made on the basis of the disappearance of the uv chromophore with the addition of base and also because the 18-methyl proton resonance occurs farthest downfield when compared with its 9,10 isomers.

In addition to the reactions of the 9β-estra-4-en-3-one system already described, metal–NH_3 reduction was also studied. Compound **2** was readily converted in good yield into 17β-hydroxy-17α-methyl-5α,9β,10β-estran-3-one (**12**). This structural assignment was supported by the RD spectrum of **12**, which was nearly identical in sign and amplitude of its Cotton effect with that of the analogous cholestanone.[14] Once again the nmr spectrum revealed that the chemical shift of the 18-methyl protons again occurs further downfield than the related isomeric estranes. The A/B *trans* protonation of the radical anion obtained during the course of the reduction is consistent with current views of this reaction.[15]

Additional transformations of this novel system are currently underway.

Experimental Section

Melting points are uncorrected. The uv spectra were obtained using a Cary 15 spectrophotometer, while a Perkin-Elmer 21 was used for the ir spectra. Nmr spectra were obtained on a Varian HR-60 with TMS as internal standard. The CD and RD spectra were recorded on a Cary 50 spectropolarimeter.

17β-Hydroxy-17α-methyl-10α- and 17β-Hydroxy-17α-methyl-9β-estr-4-en-3-one (1 and 2).—Using a calibrated atmospheric hydrogenation apparatus, 0.42 g of 2% Pd–$SrCO_3$ in 30 ml of 3A EtOH was prereduced, and then 1 g of 17β-hydroxy-17α-methylestra-4,9(10)-dien-3-one in 30 ml of EtOH was added. The hydrogenation was allowed to proceed until 1.08-equiv uptake occurred (9 min). The catalyst was filtered off, the solvent was evaporated *in vacuo*, and the residue was recrystallized from Et_2O. The first crop (0.26 g), mp 177–183°, was found by uv to be the 10α isomer. Recrystallization gave mp 188–190°; uv λ_{max} (EtOH) 242 mμ (ϵ 15,300). There was no appreciable depression in melting point upon addition of OH^-.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.05; H, 9.64.

The second crop of material (0.18 g) was found to be the 9β isomer, mp 168–174°. Recrystallization from Et_2O gave an analytical sample, mp 186–188°; CD (*c* 0.00097, MeOH) $[\Delta\epsilon]_{365}$ ±0, $[\Delta\epsilon]_{325}$ +1.26, $[\Delta\epsilon]_{285}$ ±0, $[\Delta\epsilon]_{244}$ −8.7, $[\Delta\epsilon]_{223}$ ±0; uv λ_{max} (EtOH) 243 mμ (ϵ 15,500), λ_{max} (EtOH, OH^-) 235 mμ (ϵ 2430).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.84; H, 9.91.

Hydrogenation studies using 5% Pd–$BaSO_4$ in EtOAc in portions indicated above gave similar results.

Acid Isomerization to 17β-Hydroxy-17α-methyl-9β,10α-estr-4-en-3-one (3).—To a solution of 8 ml of MeOH and 0.04 g of **2** was added four drops of concentrated HCl. The course of the reaction was followed by removing aliquot samples and examining their uv spectra. After 20 min, the 243-mμ extinction had almost

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disappeared, while, after 4.5 hr, the extinction had returned to approximately its original magnitude. Much of the solvent was removed *in vacuo*, without heat, and the solution was diluted with iced H_2O. The mixture was extracted with several portions of Et_2O, and this combined solution was washed with $NaHCO_3$ and NaCl solutions. After drying (Na_2SO_4), the solvent was removed *in vacuo*, and the residue was recrystallized from Et_2O to give 0.022 g of **3**, mp 162–164°; CD (*c* 0.00053, MeOH) $[\Delta\epsilon]_{360}$ ±0, $[\Delta\epsilon]_{317}$ +1.89, $[\Delta\epsilon]_{273}$ ±0, $[\Delta\epsilon]_{242}$ −11.6; uv λ_{max} (EtOH) 242 mμ (ε 16,350); nmr ($CDCl_3$) δ 0.95 (s, 3 H, C-18 Me), 1.30 (s, 3 H, C-17 Me), 5.85 (s, 1 H, C-4).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.37; H, 9.70.

Nmr analysis of the noncrystalline residue showed this to be an approximately 1:1 ratio of **3** and **4** (see below).

Base Deconjugation to 17β-Hydroxy-17α-methyl-9β-estr-5(10)-en-3-one (4).—To a solution of 0.15 g of **2** in 25 ml of MeOH which was flushed with N_2 was added 30 drops of a 0.4 *N* solution of $NaOCH_3$ in MeOH. The resultant solution was let stand under a N_2 atmosphere for 1.5 hr. Much of the solvent was then removed *in vacuo* without heating and the solution was poured into iced H_2O which had been acidified with AcOH. This mixture was extracted with several portions of CH_2Cl_2. The combined solution was washed with NaCl solution and dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. Nmr analysis of the crude residue showed this to be predominately **4**. The residue was dissolved in a small volume of 4:1 C_6H_6/Skelly F and was chromatographed over 10 g of grade III neutral alumina. Taking 40-ml fractions, the fractions 8–30 were combined; the solvent was evaporated to dryness *in vacuo;* and the residue was crystallized from Et_2O–Skelly B to give 0.062 g, mp 121–122°; no uv; ORD (*c* 0.0011, dioxane) $[\phi]_{317}$ −3878, $[\phi]_{308}$ −4063; nmr ($CDCl_3$) δ 0.92 (s, 3 H, C-18 Me), 1.14 (s, 3 H, C-17 Me).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.54; H, 10.01.

Base Isomerization to 17β-Hydroxy-17α-methyl-9β,10α-estr-4-en-3-one (3).—A solution of 10 ml of MeOH and 0.1 g of **2** was flushed with N_2 and then 0.85 ml of a 0.4 *N* $NaOCH_3$ in MeOH solution was added. The resultant solution was heated at reflux under N_2 overnight. Much of the solvent was removed *in vacuo* and the solution was poured into iced H_2O. This mixture was extracted with Et_2O in several portions and the combined ethereal solution was washed in turn with $NaHCO_3$ and NaCl solutions and dried (Na_2SO_4). The solvent was evaporated *in vacuo*. Nmr analysis of the residue indicated that it was composed largely of the 9β,10α isomer. Recrystallization of the residue from Et_2O–Skelly B gave 0.041 g, mp 161–163°. This was identical with material described above.

Acid Deconjugation to 4.—To a solution of 0.2 g of **2** in 80 ml of 2 B EtOH was added 4 drops of 0.1 *N* HCl. After 2.25 hr, uv analysis of the solution indicated that the maximum at 243 mμ had diminished 95%. The solution was concentrated *in vacuo* without heat, and this concentrate was poured into iced H_2O. The mixture was extracted with several portions of Et_2O, the ethereal solution was washed with NaCl solution and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was dissolved in a small volume of 4:1 C_6H_6–hexane, and this was chromatographed over 25 g of activity III neutral alumina. Individual fractions of 10 ml were collected and the fractions between 30 and 40 were combined. The solvent was evaporated and the residue was recrystallized from Et_2O to give 0.031 g of **4**, mp 119–122°. The nmr spectrum of this material was identical with material obtained by base deconjugation.

17α-Hydroxyestra-4,9(10)-dien-3-one (5).—A solution of 10 g of 17α-hydroxyestra-5(10)-en-3-one[8] and 275 ml of dry pyridine was cooled in an ice bath, and then 11.7 g of pyridine perbromide hydrobromide was added in portions with swirling. The mixture was let stand in the cold for 1 hr and at room temperature for 3 hr. The mixture was poured into excess iced H_2O, and this was extracted thoroughly with CH_2Cl_2. This latter combined solution was washed eight times with 200-ml portions of 5% HCl solution and with aqueous NaCl solution and dried. The solvent was evaporated *in vacuo* and the residue was crystallized from Et_2O–Skelly F to give 6.9 g of diene, mp 127–129°; uv λ_{max} (EtOH) 304 mμ (ε 20,200).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.40; H, 8.85.

17α-Hydroxy-9β-estr-4-en-3-one (6) and 17α-Hydroxy-10α-estr-4-en-3-one (7).—The hydrogenation was carried out as described above, using 0.21 g of 2% Pd-$SrCO_3$ in 35 ml of 3 A EtOH and 0.5 g of diene. There was a 1.1-equiv uptake in 5 min. After the usual treatment, the residue was crystallized from Et_2O to give 0.13 g of crystals, mp 139–140°; CD (*c* 0.00103, dioxane) $[\Delta\epsilon]_{385}$ ±0, $[\Delta\epsilon]_{362}$ +0.64, $[\Delta\epsilon]_{348}$ +1.15, $[\Delta\epsilon]_{334}$ +1.14, $[\Delta\epsilon]_{324}$ + 0.815, $[\Delta\epsilon]_{295}$ ± 0, $[\Delta\epsilon]_{262}$ ± 0, $[\Delta\epsilon]_{239}$ − 7.82, $[\Delta\epsilon]_{220}$ ± 0; uv λ_{max} (EtOH) 244 mμ (ε 15,500), λ_{max} (EtOH, OH^-) 240 mμ (ε 4900); nmr (pyridine-d_5) δ 0.82 (s, 3 H, C-18 CH_3) and 5.96 (br s, 1 H, C-4 H).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55. Found: C, 79.01; H, 9.71.

A second crop of 0.031 g was obtained, which on recrystallization from Et_2O gave the 10α isomer, mp 177–179°; uv λ_{max} (EtOH) 243 mμ (ε 15,300); nmr (pyridine-d_5) δ 0.63 (s, 3 H, C-18), 5.94 (br s, 1 H, C-4 H).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55. Found: C, 78.65; H, 9.51.

9β-Estr-4-ene-3,17-dione (8).—To a mixture of 0.2 g of CrO_3 in 2 ml of pyridine in an ice bath, a solution of 0.2 g of **6** in 4 ml of pyridine was added, and the mixture was let stand at room temperature for 2 days. The reaction mixture was then poured into excess iced H_2O and extracted with several portions of Et_2O. The solvent was removed from the combined solution *in vacuo* without excessive heat, and the residue was dried using a vacuum pump until the pyridine was removed. The residue was crystallized from Et_2O–Skelly F to give 0.052 g of **7**, mp 174–176°; uv λ_{max} (EtOH, OH^-) 243 (ε 16,050) and 239 mμ (ε 2,700); ir ($CHCl_3$) 1655 and 1727 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.21; H, 8.87.

17α-Ethynyl-17β-hydroxyestra-4,9(10)-dien-3-one Methyl Carbamate (9).—To a solution of 80 ml of CH_3NCO and 0.4 g of Dabco was added 4.0 g of 17α-ethynyl-17β-hydroxyestra-4,9(10)-dien-3-one[3] and the solution was heated at reflux overnight. The solvent was evaporated *in vacuo* and the residue was recrystallized from Et_2O to give 2.1 g of product, mp 158–160°.

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.72; H, 7.90; N, 3.99.

N-Methyl-N-{1-[17β-hydroxyestra-4,9(10)-dien-3-on-17α-yl]-vinyl}carbamic Acid γ-Lactone (10).—A solution comprised of 2.0 g of **9**, 100 ml of MeOH, and 8 ml of 0.4 *N* $NaOCH_3$–MeOH was heated at reflux overnight. After removal of about 1/3 of the solvent *in vacuo*, the solution was poured into excess iced H_2O. The mixture was extracted with several portions of CH_2Cl_2; this combined nonaqueous solution was washed with NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*.

The residue did not crystallize readily and thus was chromatographed on 200 g of neutral activity III alumina using C_6H_6 as solvent. Fractions 30–100 were found to be one spot by tlc analysis and were combined. Recrystallization using Et_2O as solvent gave 0.51 g of **10**, mp 201–203°.

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.78; H, 7.64; N, 3.78.

N-Methyl-N-[(17β-hydroxy-9β-estr-4-en-3-on-17α-yl)vinyl]-carbamic Acid γ-Lactone (11).—Following the procedure described for **2**, 0.21 g of 5% Pd-$BaSO_4$ in 15 ml of EtOAc was prereduced with hydrogen and then 0.5 g of **10** was added. The hydrogenation was carried out until 1.06-equiv uptake (11 min) and the catalyst was filtered. The solvent was removed *in vacuo* and the residue was recrystallized from Et_2O to give 0.149 g of **11**, mp 173–175°; uv λ_{max} (EtOH) 240 mμ sh (ε 13,600, disappears on addition of OH^-); nmr ($CDCl_3$) δ 1.10 (s, 3 H, C-18 Me), 5.90 (s, 1 H, C-4 H).

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.05; H, 8.47; N, 4.31.

17β-Hydroxy-17α-methyl-5α,9β,10β-estran-3-one (12).—To 200 ml of redistilled NH_3 was added 0.4 g of Li while the mixture was cooled in a dry ice bath. A solution of 0.2 g of **2** in 35 ml of dry THF was added with stirring. The reaction mixture was stirred for an additional 20 min and excess NH_4Cl was slowly added. The NH_3 was allowed to evaporate overnight and the residue was taken up with CH_2Cl_2–H_2O. The aqueous solution was further washed with CH_2Cl_2. The combined nonaqueous solution was washed with NaCl solution and dried, and the solvent was evaporated *in vacuo*. The residue was dissolved in a small volume of 3:2 Skelly F–C_6H_6 and this solution was chromatographed over 15 g of activity III neutral alumina. The frac-

tions 10–49 were combined and again the solvent was evaporated *in vacuo*. The residue was crystallized from Et_2O–Skelly F to give 0.127 g of 11, mp 177–178°; ORD (*c* 0.00207, dioxane) $[\phi]_{313}$ +2994, $[\phi]_{291}$ ±0, $[\phi]_{272}$ −1768; nmr δ 1.1 (s, 3 H, C-18 CH_3) and 1.25 (s, 3 H, C-17 CH_3).

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.29; H, 10.35.

Registry No.—**1**, 5670-57-5; **2**, 20708-78-5; **3**, 4258-76-8; **4**, 20708-79-6; **5**, 20790-83-4; **6**, 20708-80-9; **7**, 20708-81-0; **8**, 6827-75-4; **9**, 20708-83-2; **10**, 20708-84-3; **11**, 20708-85-4; **12**, 20708-86-5.

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Selective Transglycosylation of Methylated 2-Acetamido-2-deoxy-β-D-glucopyranosides on a Microscale

WILMAR L. SALO[1] AND HEWITT G. FLETCHER, JR.

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Maryland 20014

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When heated at 125° in butyl acetate solution and in the presence of butyl alcohol and zinc chloride, methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (β **1**) is converted into a mixture of the anomeric butyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranosides (**2**), the β anomer preponderating. Under these conditions, α **1** is not attacked and the anomeric forms of methyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranoside (**3**) are attacked to only a minor extent, and thus it appears that methylated 2-acetamido-2-deoxy-β-D-glucopyranosides may be selectively transglycosylated by this mixture of reagents. Since the anomeric forms of **2** are readily detected by gas–liquid partition chromatography (glpc) and thin layer chromatography (tlc), the method is applicable on a microscale. To explore the method further, it was applied to the chitobiose derivative **4**; the β linkage in this disaccharide was readily cleaved to give **2** and a second product which showed the chromatographic behavior expected of a butyl 2-acetamido-2-deoxy-3,6-di-*O*-methyl-β-D-glucopyranoside (**5**).

We have recently shown[2] that acetylated 2-acetamido-2-deoxy-β-D-glucopyranosides readily undergo a transglycosylation reaction when heated with benzyl alcohol at 125° in the presence of zinc chloride, giving benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside. An acetylated, β-linked disaccharide, "α-chitobiose octaacetate," was also, in part, cleaved under these conditions, and, since neither methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside nor methyl β-D-glucopyranoside tetraacetate was attacked under the transglycosylation conditions used, it is possible that a method of selective solvolysis is actually or potentially available here to cleave oligosaccharide chains at those points where a 2-acylamido-2-deoxyaldose is linked by a *trans* glycosidic bond. We have explored this reaction further, and will now describe the development of a modified transglycosylation procedure which is designed to be used on 1–5-mg quantities of material and which ought, in principle, to yield information regarding the point of attachment of the cleavage-susceptible sugar moiety.

In the earlier paper,[2] we suggested that the relative susceptibility of acetylated 2-acetamido-2-deoxy-β-D-glucopyranosides to transglycosylation arises through anchimeric assistance provided by the acetamido group in cleaving the *trans*-disposed glycosidic linkage. On the basis of evidence[3] obtained in this laboratory, it was assumed that an oxazoline was formed and that this, in turn, was attacked by the benzyl alcohol to form benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucoside. The *O*-acetyl groups were not deemed to be an essential feature of the reaction, except insofar as they masked hydroxyl groups. In adapting the process to small-scale work, gas–liquid partition chromatography of cleavage mixtures was contemplated and *O*-methyl, rather than *O*-acetyl, derivatives were used inasmuch as they would not only give products susceptible to glpc, but also the nature of these products should indicate the points of linkage in an oligosaccharide. Finally, substituted benzyl 2-acetamido-2-deoxy-D-glucopyranosides proved somewhat unsuitable for glpc examination, and we have turned to the more volatile butyl glycosides; this is a fortunate circumstance, since the medium of choice for the transglycosylation is butyl acetate, which, unless carefully purified, frequently contains a significant proportion of butyl alcohol.

At the outset, authentic samples of the anomeric butyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranosides (α and β **2**) were synthesized *via* a conventional glycosylation of 2-acetamido-2-deoxy-D-glucose, followed by methylation and separation of the anomers by chromatography on silica gel; both proved to be readily crystallizable substances.

Turning now to the transglycosylation reaction, the behavior of methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (β **1**) with butyl alcohol and zinc chloride in butyl acetate solution was first examined. After 4 hr at 125°, the reaction mixture was cooled and freed of zinc chloride. Glpc as well as tlc showed that only *ca.* 2.5% of β **1** remained, the bulk of the product being β **2**, along with some α **2**. While the immediate objective here was the development of a microanalytical method, the reaction described above was repeated on a preparative scale and β **2** was isolated in 82% yield.

That α **2** is formed from β **1** was somewhat unexpected in view of the presumed mechanisms involved. Glycosides such as α **1** (as well as α and β **3**) were not anomerized under the transglycosylation conditions,

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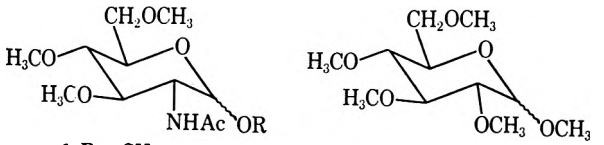

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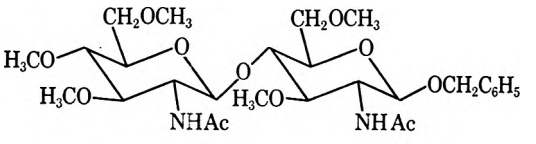
2, R = $CH_3(CH_2)_3$

3



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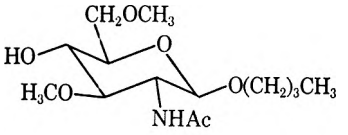

5

and so it is unlikely that the α 2 found arose through the anomerization of the β 2 initially formed. We regard it as more likely that the intermediate oxazoline, formed from β 1, was attacked by adventitious moisture to give 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranose, and that this, in the presence of zinc chloride and butyl alcohol, afforded a mixture of α and β 2. Yoshimura and his coworkers[4] have shown the effectiveness of a variety of Lewis acids in catalyzing the condensation of 2-acylamino-2-deoxy-D-glucoses with alcohols.

In contrast to methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (β 1), its anomer (α 1) was not detectably attacked when subjected to the cleavage conditions. Similarly, the anomeric methyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranosides (α and β 3) appeared to be resistant to cleavage, although minor products, chromatographically identified as the butyl 2,3,4,6-tetra-*O*-methyl- D- glucopyranosides, were detected. We next turned our attention to an intersaccharidic linkage of known structure and anomeric configuration and, for this purpose, chose a derivative of the disaccharide chitobiose, 2-acetamido-4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose. Benzyl 2-acetamido-4-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranosyl)-2-deoxy-3,6-di-*O*-methyl-β-D-glucopyranoside (4) was prepared from the corresponding penta-*O*-acetyl derivative[2,5] and the methylated glycoside (4) was subjected to the transglycosylation conditions. While β 1 remained nearly colorless under these conditions, 4 darkened slightly. Glpc of the product revealed a major (91%) and a minor (9%) component; the former had the retention time of 2 (the anomeric forms of 2 migrate at the same rate in the system used). After trimethylsilylation, the retention time of the major product was unchanged, while that of the minor product was increased; on the basis of this evidence, it is assumed that the minor component is probably butyl 2-acetamido-2-deoxy-3,6-di-*O*-methyl-β-D-glucopyranoside (5). Tlc of the cleavage mixture showed that both anomers of 2 were present as well as a component with the rate of migration of 4; whether this was indeed 4 or, as seems more likely, the corresponding butyl glycoside, was not ascertained. In any event, it is evident that 4 is cleaved under these transglycosylation conditions and that each of the two possible fragments may be detected by glpc. One would, of course, expect that 2 and 5 should be formed in equimolar amounts. That considerably less of 5 than of 2 is detected may be due to some special reactivity of 5, which bears a free hydroxyl group; indeed, the colored materials produced in the cleavage of 4 may arise through the destruction of 5.

While the evidence presented here tends to indicate that the method described is of potential utility in the investigation of oligosaccharide structure, it should be emphasized that many of the parameters involved await further investigation. In particular, a survey of the efficiency of Lewis acids other than zinc chloride would seem desirable.

Experimental Section

Melting points are equivalent to corrected values.

Thin layer chromatography was conducted on silica gel G_{254} (E. Merck AG, Darmstadt), components being detected by spraying with 10% sulfuric acid and heating at *ca.* 100°. Column chromatography was carried out with silica gel no. 7734 (0.05–0.2 mm) of E. Merck AG. Unless otherwise specified, dichloromethane–ether–methanol (20:10:1) was used for both tlc and column chromatography; for the latter, columns were packed in dichloromethane–ether (2:1) prior to use.

Gas–liquid partition chromatography was carried out with a Hewlett–Packard model 5750 chromatograph, using helium as a carrier gas and a flame ionization detector. The following columns were employed: (A) 0.25 in. o.d. × 6.5 ft of Apiezon N on Chromosorb P,[6] used isothermally at 250°; (B) 0.25 in. o.d. × 6.5 ft of 15% diethylene glycol succinate on Chromosorb WAW,[6] used isothermally at 180°. Trimethylsilyl derivatives were prepared using the "Tri-Sil" reagent of the Pierce Chemical Co., Rockford, Ill.

Reagent grade zinc chloride was fused and powdered and then stored over phosphorus pentaoxide. Reagent grade butyl alcohol and butyl acetate were stored over molecular sieve, type 4A (Fisher Scientific Co.), while *N*,*N*-dimethylformamide was stored over barium oxide. A stock solution of anhydrous zinc chloride in butyl acetate (100 mg/ml) was made up and stored over a small quantity of molecular sieve. All transglycosylation reactions were carried out under a reflux condenser equipped with a calcium chloride drying tube.

Nmr spectra were obtained using a Varian A-60 spectrometer and tetramethylsilane as an internal standard.

The Anomeric Methyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranosides (α and β 1).—The α anomer was prepared from methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside[7] by methylation with a mixture of barium oxide, barium hydroxide, methyl iodide, and *N*,*N*-dimethylformamide:[8] mp 153–154.5°, $[\alpha]^{20}D$ 126.5° (*c* 1.35, chloroform) [lit.[9] mp 150°, $[\alpha]^{18}D$ 120.0° (*c* 0.4, chloroform)]. The β anomer was prepared by the direct methylation of 2-acetamido-2-deoxy-D-glucose as described by Kuhn and Trischmann:[8] mp 199.5–200.5° (lit.[8] mp 198–199°).

The Anomeric Butyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranosides (α and β 2).—2-Acetamido-2-deoxy-D-glucose (2.0 g) and *p*-toluenesulfonic acid (200 mg) were added to butyl alcohol (50 ml) and the mixture was boiled under reflux for 5 hr. The clear, colorless solution was cooled and concentrated *in vacuo*, toluene being evaporated *in vacuo* from the residue. The syrup was dissolved in *N*,*N*-dimethylformamide (35 ml) and methylated by treatment with barium hydroxide octahydrate (5 g), barium oxide (7.4 g), and methyl iodide (18 ml) for 18 hr at room temperature. The reaction mixture was worked up in normal fashion and the crude product was chromatographed on a column of silica gel (2.9 × 34 cm). The first com-

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ponent eluted consisted of α 2 (2.56 g, 89%), which was crystallized from cold ether: mp 90–92°, $[\alpha]^{21}D$ 84° (c 2.7, chloroform); nmr ($CDCl_3$) τ 5.27 (H_1, doublet, $J_{1,2}$ = 3.7 Hz), 6.4–6.6 [18 H, 2 peaks, CH_3 and $CH_3(CH_2)_3$], and 8.0 (3 H, AcN).

Anal. Calcd for $C_{15}H_{29}NO_6$ (319.41): C, 56.41; H, 9.15; N, 4.38. Found: C, 56.13; H, 9.14; N, 4.55.

The second component eluted (0.24 g, 8.3%), the β anomer (β 2), was crystallized from cold ethyl acetate: mp 149.5–151°; $[\alpha]^{21}D$ 1.1° (c 0.81, chloroform); nmr ($CDCl_3$) τ 5.22 (doublet, H_1, $J_{1,2}$ = 7.5 Hz), 6.4–6.6 [18 H, 2 peaks, CH_3 and $CH_3(CH_2)_3$], and 8.0 (3 H, AcN).

Anal. Calcd for $C_{15}H_{29}NO_6$ (319.41): C, 56.41; H, 9.15; N, 4.38. Found: C, 56.21; H, 9.00; N, 4.56.

The Anomeric Methyl 2,3,4,6-Tetra-*O*-methyl-D-glucopyranosides (α and β 3).—Methyl α-D-glucopyranoside and its anomer were methylated with methyl iodide and silver oxide in *N*,*N*-dimethylformamide solution.[10] The amorphous products were chromatographically homogeneous when examined by glpc on column B.

Benzyl 2-Acetamido-4-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranosyl)-2-deoxy-3,6-di-*O*-methyl-β-D-glucopyranoside (4).—Benzyl 2-acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranoside[2] (mp 273–274°) was methylated by the procedure of Kuhn and Trischmann[8] to give **4**, which was crystallized from cold chloroform solution: mp 258–260°, $[\alpha]^{21}D$ −40.2° (c 1.11, *N*,*N*-dimethylformamide).

Anal. Calcd for $C_{28}H_{44}N_2O_{11}$ (584.68): C, 57.52; H, 7.59; N, 4.79. Found: C, 57.67; H, 7.35; N, 4.79.

Behavior of Methyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (β 1) with Zinc Chloride and Butyl Alcohol in Butyl Acetate Solution.—Three milligrams (0.0108 mmol) of β 1 was added to butyl acetate (0.64 ml) containing zinc chloride (6.4 mg, 0.047 mmol) and butyl alcohol (10.6 μl, 0.116 mmol). The mixture was heated and stirred at 125° (bath) in a stoppered flask for 4 hr, the faintly yellow reaction mixture was cooled and diluted with dichloromethane, and the resulting solution was washed with water. Moisture was removed with sodium sulfate and the solution was concentrated to a volume of *ca.* 0.5 ml. Glpc of the residue on column A showed but a trace of starting material (2.5 %, estimated by peak areas), the bulk of the product being the anomeric butyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranosides (α and β 2) which are not resolved from each other on this column; a few minor peaks of low retention time were also observed but were not identified. Tlc of the mixture showed that β 2 was the preponderant product, although it was accompanied by some α 2.

In order to ascertain the feasibility of the transglycosylation reaction as a preparative method, β 1 (294 mg) was dissolved in butyl acetate (29.4 ml), and to this solution was added anhydrous zinc chloride (588 mg) and butyl alcohol (1.2 ml). The reaction mixture was heated with stirring at 125° for 3 hr; it was then cooled, diluted with dichloromethane, and washed with water. Moisture was removed with sodium sulfate and the solution was concentrated *in vacuo* to yield a syrup which was dissolved in benzene–ether (1:1) and then chromatographed on a column of silica gel using benzene–ether–methanol (14:14:1) for elution. Fractions containing β 2 were pooled and concentrated, the residue being crystallized from ethyl acetate: yield 277 mg (82%), mp and mmp 150–151°.

Behavior of Methyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranoside (α 1) with Zinc Chloride and Butyl Alcohol in Butyl Acetate Solution.—The methylated glycoside α 1 (5.1 mg) was added to a solution of butyl acetate (1.07 ml) containing zinc chloride (10.7 mg) and butyl alcohol (18 μl). The reaction mixture was stirred and heated at 125° (bath) for 4 hr, remaining clear and colorless during this period; it was then cooled, diluted with dichloromethane (1 ml), and shaken once with water. The organic solution was dried over sodium sulfate, concentrated to a small volume, and examined by glpc on column A. Only one peak was observed, and this had the retention time of α 1. Although this column does not resolve α and β 1, it readily distinguishes these from 2; that no 2 was detected clearly shows that no β 1 was formed.

Behavior of the Anomeric Methyl 2,3,4,6-Tetra-*O*-methyl-D-glucopyranosides (α and β 3) with Zinc Chloride and Butyl Alcohol in Butyl Acetate Solution.—A mixture of methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (α 3, 25.2 mg), zinc chloride (58.5 mg), butyl alcohol (0.098 ml), and butyl acetate (5.85 ml) was heated at 125° (bath) for 4 hr. The cooled mixture was examined directly by glpc on column B and was found to consist largely of unchanged α 3; a small (7%) peak of higher retention time was observed. In a similar fashion, methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside (β 3, 27.5 mg) was heated with zinc chloride (56.8 mg), butyl alcohol (0.107 ml), and butyl acetate (5.14 ml) at 125° for 4 hr. Examination by glpc on column B showed β 3 to preponderate (86.2%); two smaller peaks (8.3% and 5.5%) with longer retention times were observed, but neither had the retention time of α 3. 2,3,4,6-Tetra-*O*-methyl-D-glucopyranose was treated with zinc chloride, butyl alcohol, and butyl acetate at 125° for 4 hr and then examined by glpc on column B. Two peaks, presumably representing the anomeric butyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranosides, were obtained. The retention times of these products were identical with those of the two minor components detected after treatment of β 3. The butyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranoside with the longer retention time was chromatographically identical with the minor component from the treatment of α 3; the butyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranoside with the smaller retention time could not be resolved from α 3 on column B.

Behavior of Benzyl 2-Acetamido-4-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranosyl)-2-deoxy-3,6-di-*O*-methyl-β-D-glucopyranoside (4) with Zinc Chloride and Butyl Alcohol in Butyl Acetate Solution.—Compound **4** (12 mg) was heated at 125° (bath) with a mixture of zinc chloride (24 mg), butyl alcohol (0.04 ml), and butyl acetate (1.2 ml) for 4 hr. The amber-brown mixture was cooled, diluted with dichloromethane (1 ml), and washed once with water. Moisture was removed with sodium sulfate and the solution was concentrated to a small volume (0.5 ml); glpc on column A revealed two major components, the larger of which (91%) had the retention time of β 2. The smaller peak (9%) was presumably **5**; trimethylsilylation caused this smaller peak to shift to a longer retention time while the larger peak was unaffected. Examination of the product by tlc showed the presence of both anomeric forms of **2** as well as of a component which migrated at the same rate as **4** but which may have been the butyl glycoside corresponding to **4**. The reaction mixture was chromatographed on a column (2.9 × 13.5 cm) of silica gel, and the first component to emerge was identical (tlc and glpc) with α 2. The second component was similarly shown to be β 2. Finally, a third component emerged; glpc on column A showed this to be the smaller of the two major peaks observed earlier. As before, its retention time on column A increased with trimethylsilylation. Since the liquid phase of column A (Apiezon N) is a hydrocarbon, trimethylsilylation of a compound such as **5** would be expected to increase the affinity of the compound for the liquid phase and thus increase the retention time.

Registry No.—α 1, 7380-60-1; β 1, 6195-86-4; α 2, 20708-89-8; β 2, 20708-90-1; α 3, 605-81-2; β 3, 3149-65-3; 4, 20708-93-4; zinc chloride, 7646-85-7; butyl alcohol, 71-36-3.

Acknowledgment.—We are indebted to the staff of the Section on Analytical Services and Instrumentation of this institute for elemental analyses and nmr spectra.

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Neighboring-Group Participation in Carbohydrates. The Synthesis of 2,3-Diamino-2,3-dideoxy-L-ribose[1]

ELMER J. REIST AND SANDRA H. CRUSE

Stanford Research Institute, Menlo Park, California 94025

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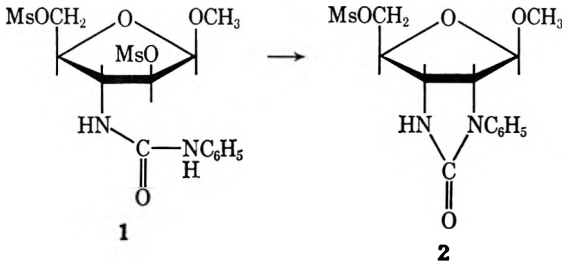
Treatment of methyl 3-deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside with sodium fluoride in DMF effected the elimination of the mesylate at C-4 to give methyl 3-amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-cyclic urethan (**7**). An SN2 displacement on **7** using sodium azide yielded methyl 3-amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (**8**). Hydrogenation of **8** and subsequent deblocking gave 2,3-diamino-2,3-dideoxy-L-ribose (**11**) as its crystalline dihydrochloride.

In recent years, there has been considerable interest in the preparation and chemistry of diaminodideoxy sugars, *e.g.*, derivatives of 2,3-diamino-2,3-dideoxy-D-mannose,[2] 2,3-diamino-2,3-dideoxy-D-allose,[3] 2,3-diamino-2,3-dideoxy-D-altrose,[2a] 4,5-diamino-4,5-dideoxy-D-arabinose,[4] and many others. The widespread occurrence in nature of derivatives of D-ribose made the preparation of diamino analogs an interesting challenge, both from the standpoint of the synthetic problems connected with the preparation of a 2,3-*cis*-diamine and also from the possibility of obtaining compounds which may have interesting biological activity. Baker and Hullar[5] described the preparation of a material which was believed to be a derivative (**2**) of 2,3-diamino-2,3-dideoxy-D-ribose by the displacement of the 2-O-mesylate by the neighboring ureido group of **1**. The de-



blocking of **2**, however, must give an N-phenyl derivative of 2,3-diamino-2,3-dideoxy-D-ribose. To avoid removal of the N-phenyl group of **2**, an alternative method was sought for the preparation of the unsubstituted 2,-3-diamino sugar. The preparation of cyclic carbonates of sugars as intermediates for the synthesis of sugars which contain *cis* related functional groups has been described.[6] It seemed possible to adapt this approach to the synthesis of *cis*-diamino sugars. The synthesis of 2,3-diamino-2,3-dideoxy-L-ribose dihydrochloride from D-arabinose by this approach is described here. The D-ribose analog can be prepared from L-arabinose.

Methyl 3-amino-3-deoxy-β-D-xylopyranoside (**3**),[7] prepared from D-arabinose, was treated with methyl chloroformate in pyridine to give crystalline methyl 3-deoxy-2,4-di-O-methoxycarbonyl-3-methoxycarbonylamino-β-D-xylopyranoside (**4**). Treatment of **4** with methanolic sodium methoxide effected O-deacylation to give methyl 3-deoxy-3-methoxycarbonylamino-β-D-xylopyranoside (**5**). Mesylation of **5** using methanesulfonyl chloride in pyridine gave a good yield of methyl 3-deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside (**6**). When this compound was treated with anhydrous sodium fluoride in DMF, a 58% yield of a crystalline product was obtained which had analytical data that was satisfactory for methyl 3-amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-cyclic urethan (**7**), the product to be expected from the displacement of the O-mesylate at C-4 from **6**. Alternatively, the product of this reaction could be methyl 3-amino-3-deoxy-4-O-methylsulfonyl-β-D-lyxopyranoside 2,3-cyclic urethan (**15**) by displacement of the O-mesylate at C-2 from **6**. That the correct structure was **7** rather than **15** was determined by nmr spectroscopy, which is described later.

Treatment of **7** with sodium azide in DMF effected the displacement of the remaining mesylate to give a quantitative yield of crystalline methyl 3-amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (**8**). Catalytic hydrogenation of **8** using 5% palladium on carbon yielded 90% of crystalline methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (**9**). Removal of the cyclic urethan was carried out using refluxing aqueous barium hydroxide to give a 94% yield of crystalline methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside (**10**). Hydrolysis of **10** with 6 *N* hydrochloric acid gave 2,3-diamino-2,3-dideoxy-L-ribose (**11**), isolated as its crystalline dihydrochloride.

It is interesting to note that the infrared spectra of **7** and all subsequent compounds in which the cyclic urethan is intact failed to show amide II absorption at 6.5 μ. A similar observation was reported by Gross, *et al.*,[8] for cyclic urethans derived from benzyl 2-amino-2-deoxy-α-D-gulopyranoside.

The nmr spectra of the dimesylate **6** and the subsequent reaction products **7**–**9** were examined (Table I); band assignments were made by means of spin decoupling. The formation of the cyclic urethan in **7** to create a fused ring system had little effect on the position of the nmr bands. The displacement of the second mesylate by azide to give **8** and subsequent hydrogenation of the azide to give the free amine **9** caused a pronounced shift upfield in the position of H-2. Thus, the free amine must be on C-2 and the sodium fluoride cyclization product must be **7** rather than the isomeric 4-mesylate **15**.

Efforts to prepare a phenylosazone of **11** by the pro-

(1) This investigation was supported by the U. S. Public Health Service, Research Grants GM 11438 from the General Medical Sciences Institute and NB 07776 from the National Institute of Neurological Diseases and Blindness.

(2) (a) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963). (b) B. R. Baker and T. L. Hullar, *ibid.*, **30**, 4038 (1965).

(3) (a) W. M. zu Reckendorf, *Ber.*, **97**, 1275 (1964); (b) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1057 (1964).

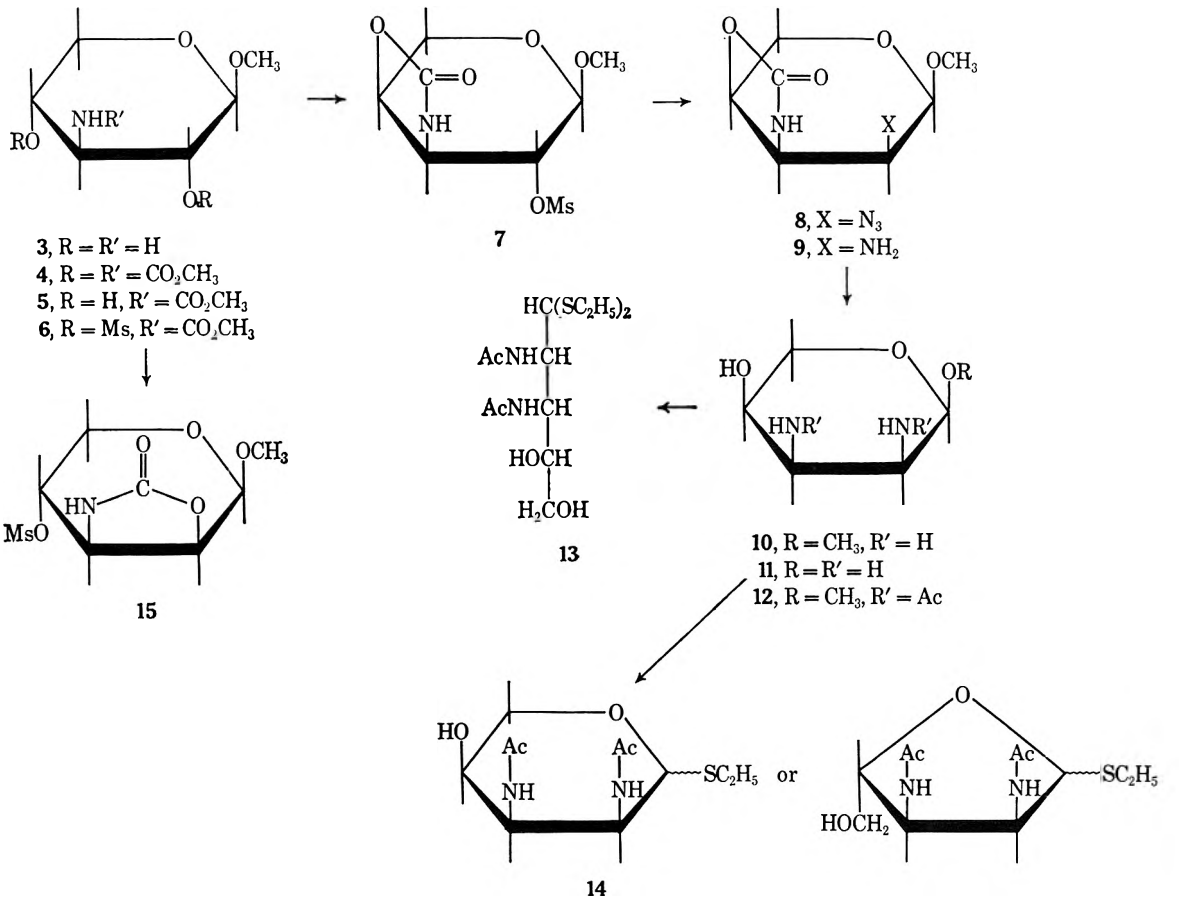
(4) S. Hanessian, *Carbohyd. Res.*, **1**, 178 (1965).

(5) B. R. Baker and T. L. Hullar, *J. Org. Chem.*, **30**, 4053 (1965).

(6) E. J. Reist and S. H. Cruse, *Carbohyd. Res.*, **10**, 289 (1969).

(7) E. J. Reist, D. F. Calkins, and L. Goodman, *J. Amer. Chem. Soc.*, **90**, 3852 (1968).

(8) P. H. Gross, K. Brendel, and H. K. Zimmerman, Jr., *Ann.*, **680**, 159 (1964).



cedure reported[9] for the preparation of such a derivative from D-glucosamine failed and decomposition resulted. The preparation of a dithioacetal by the procedure developed for the preparation of the diethylthioacetal of glucosamine hydrochloride[10] also failed and starting material was recovered. As an alternative route for the preparation of a thioacetal of **11**, the methyl glycoside **10** was N-acetylated to give crystalline methyl 2,3-diacetamido-2,3-dideoxy-α-L-ribopyranoside (**12**). When **12** was treated with ethanethiol in concentrated hydrochloric acid, a low yield of a crystalline derivative was obtained, which analyzed for a thioglycoside (**14**) rather than the thioacetal (**13**) expected from such a procedure.[11] A similar result was observed by Hough and Taha[12] when they treated 2-acetamido-2-deoxy-D-glucose under similar conditions. The isolation of a thioglycoside under these conditions is consistent with the 2,3 diamino structure arising from **7** rather than the isomeric 3,4-diamine derived from **15**.

No evidence could be obtained for the formation of the 2-O-mesylate **15**. The apparently exclusive cyclization of the carbonate of **6** to give **7** is in agreement with the observation of Baker and Schaub,[13] who reported that the reaction of methyl 3-acetamido-3-deoxy-2,4-di-O-methylsulfonyl-β-L-xylopyranoside (**16**) with sodium acetate in ethanol gave a 66% yield of a monomesylate to which they gave the 4-O-mesylate structure **18**. Their tentative assignment was based on the analogous reactivity of the 3-acetamido-2-mesylate

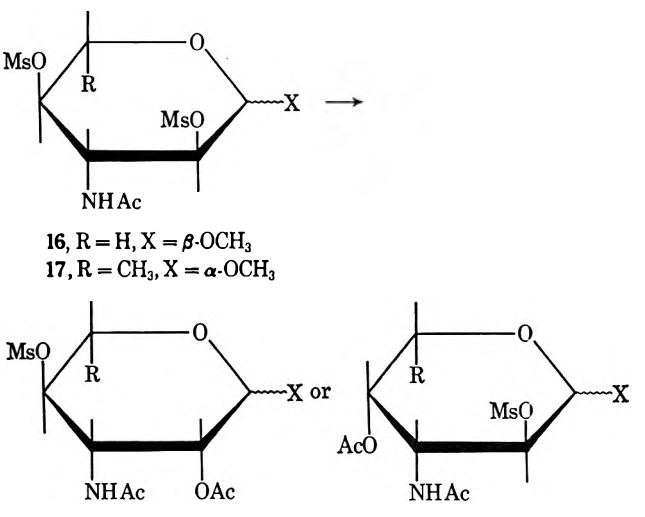
TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

Compd	H-1[a]	H-2	H-3	H-4	H-5e	H-5a
6	5.5 (d)	5.5 (q)	6.0 (m)	5.3 (m)	5.8 (q)	6.4 (q)
7	5.6 (d)	5.6 (q)	6.1 (m)	5.3 (m)	6.1 (q)	6.2 (q)
8	5.7 (d)	6.5 (t)	6.5 (q)	5.4 (m)	5.9 (q)	6.2 (q)
9	5.9 (d)	7.2 (q)	6.5 (q)	5.4 (m)	5.9 (q)	6.2 (q)

[a] Band positions are expressed in τ units.

of methyl 3-acetamido-4,6-benzylidene-3-deoxy-2-O-methylsulfonyl-α-D-altropyranoside toward sodium acetate in ethanol. A subsequent report by Richardson and McLauchlan[14] described a similar treatment of



(9) F. Tiemann, *Ber.*, **19**, 49 (1886).
(10) L. Hough and M. I. Taha, *J. Chem. Soc.*, 3564 (1957).
(11) M. L. Wolfrom, R. U. Lemieux, and S. M. Olin, *J. Amer. Chem. Soc.*, **71**, 2870 (1949).
(12) L. Hough and M. I. Taha, *J. Chem. Soc.*, 2042 (1959).
(13) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954).
(14) A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).

methyl 3-acetamido-3,6-dideoxy-2,4-di-O-methylsulfonyl-α-L-glucoside (17) with sodium acetate in 2-methoxyethanol. They presented convincing evidence that the initial displacement occurred at C-4 to give methyl 3-acetamido-3,6-dideoxy-2-O-methylsulfonyl-α-L-galactopyranoside (21). From these results the suggestion was made[15] that the monosulfonate isolated from 16 was indeed the 2-sulfonate, 20, rather than the 4-sulfonate, 18.

The results reported in this paper on the participation of the N-methoxycarbonyl neighboring group are consistent with the results of Richardson and McLauchlan[14] and support the suggestion[15] that the monomesylate of Baker and Schaub[13] is probably the 2-mesylate 20.

Experimental Section[16]

Methyl 3-Deoxy-2,4-di-O-methoxycarbonyl-3-methoxycarbonylamino-β-D-xylopyranoside (4).—A solution of 10.34 g (62.5 mmol) of methyl-3-amino-3-deoxy-β-D-xylopyranoside[7] (3) in 100 ml of dry pyridine was cooled to 0° under a nitrogen atmosphere, and 25 ml (30.7 g, 327 mmol) of methyl chloroformate was added dropwise with stirring and continued cooling. The reaction was stirred at room temperature for 20 hr, and then stirred for 1 hr with 2 ml of water to decompose the excess methyl chloroformate.

The mixture was diluted with 100 ml of water and extracted with three 80-ml portions of chloroform. The chloroform layers were washed with 50 ml of saturated aqueous sodium bicarbonate and 50 ml of water, combined, dried, and evaporated to dryness *in vacuo* to give 22.3 g of an oil which crystallized on standing. The product was recrystallized from 95% ethanol to give 12.25 g of crystals, mp 118.5–120.0°.

The analytical sample was recrystallized from cyclohexane–benzene (5:3) to give material with mp 126–127.5°; $[\alpha]^{23}D$ −65° (*c* 0.30, chloroform); λ_{max}^{Nujol} 3.0 (NH), 5.70, 5.80, 5.90 (C=O), 7.75, 8.10 μ (C—O—C).

Anal. Calcd for $C_{12}H_{19}NO_{10}$: C, 42.7; H, 5.63; N, 4.15. Found: C, 42.6; H, 5.60; N, 4.25.

Methyl 3-Deoxy-3-methoxycarbonylamino-β-D-xylopyranoside (5).—To a solution of 10.5 g of methyl 3-deoxy-2,4-di-O-methoxycarbonyl-3-methoxycarbonylamino-β-D-xylopyranoside (4) in 200 ml of methanol was added 10 ml of 0.1 *N* methanolic sodium methoxide. The mixture was stored at room temperature for 3 hr and neutralized to pH 7 with IRC 50 (H). The neutralized solution was filtered and evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate to give 6.4 g (93%) of product, mp 159–161°.

The analytical sample, obtained by recrystallization from ethyl acetate, had mp 158–160°; $[\alpha]^{23}D$ −60° (*c* 0.50, water); λ_{max}^{Nujol} 2.90 (OH, NH), 5.75, 5.95 (C=O), 6.45 μ (secondary amide).

Anal. Calcd for $C_8H_{15}NO_6$: C, 43.5; H, 6.78; N, 6.34. Found: C, 43.5; H, 6.95; N, 6.33.

Methyl 3-Deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside (6).—A solution of 7.35 g (33.3 mmol) of methyl 3-deoxy-3-methoxycarbonylamino-β-D-xylopyranoside (5) in 250 ml of dry pyridine was cooled to 0° in an ice bath, and 12 ml (17.8 g, 155 mmol) of methanesulfonyl chloride was added dropwise with stirring and continued cooling. After the exothermic reaction had ceased, the mixture was stirred at room temperature for 18 hr, and the excess methanesulfonyl chloride was decomposed by stirring with 2 ml of water for 0.5 hr.

The reaction mixture was partitioned between 100 ml each of chloroform and water. The chloroform layer was washed with saturated aqueous sodium bicarbonate and water, dried, and evaporated to dryness *in vacuo* to give 11.4 g of product as a yellow solid. Recrystallization from methanol gave 8.25 g (72%) of product as white crystals, mp 139–141°. The analytical sample was recrystallized from methanol: mp 142.5–143.5°; $[\alpha]^{23}D$ −55° (*c* 0.50, chloroform); λ_{max}^{Nujol} 3.0 (NH), 5.95 (C=O), 6.50 μ (secondary amide).

Anal. Calcd for $C_{10}H_{19}NO_{10}S_2$: C, 31.8; H, 5.03; N, 3.72. Found: C, 31.9; H, 5.04; N, 3.47.

Methyl 3-Amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-Cyclic Urethan (7).—A mixture of 6.75 g of methyl 3-deoxy-3-methoxycarbonylamino-2,4-di-O-methylsulfonyl-β-D-xylopyranoside (6) and 6.75 g of sodium fluoride was dried *in vacuo* at 63°, heated with stirring under nitrogen in 125 ml of dry DMF at 130° for 24 hr, and evaporated to dryness *in vacuo*. The residue was partitioned between chloroform and water. The chloroform layer was dried and evaporated to dryness to give 4.0 g of product as an oil. Trituration with 10 ml of ethyl acetate gave 1.10 g of crystalline product, mp 122–125°. Chromatography of the mother liquors on silica gel using ethyl acetate as the eluant gave an additional 1.65 g of crystalline product, mp 125–126°, for a total yield of 58%. The analytical sample was recrystallized from ethyl acetate: mp 128.5–129.5°; $[\alpha]^{23}D$ −12° (*c* 0.36, water); λ_{max}^{Nujol} 3.0 (NH), 5.70 μ (C=O).

Anal. Calcd for $C_8H_{13}NO_7S$: C, 36.0; H, 4.87; N, 5.25. Found: C, 36.1; H, 5.03; N, 5.38.

Methyl 3-Amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-Cyclic Urethan (8).—A mixture of 1.08 g of methyl 3-amino-3-deoxy-2-O-methylsulfonyl-α-L-arabinopyranoside 3,4-cyclic urethan (7) and 1.10 g of sodium azide were suspended in 50 ml of benzene, the benzene was distilled to dryness, 50 ml of dry DMF was added, and the reaction was heated at 140° for 18 hr under nitrogen. The reaction mixture was evaporated to dryness *in vacuo* and the residue was triturated several times with boiling ether. The ether was filtered and evaporated to dryness to give 0.870 g (100%) of white solid which was satisfactory for the next reaction. The analytical sample was obtained by recrystallization from water: mp 108–109°; $[\alpha]^{23}n$ 14° (*c* 0.48, water); λ_{max}^{Nujol} 3.05, 3.15 (NH), 4.70 (N_3), 5.60, 5.80 μ (C=O).

Anal. Calcd for $C_7H_{10}N_4O_4$: C, 39.3; H, 4.68; N, 26.2. Found: C, 39.2; H, 4.71; N, 25.9.

Methyl 2,3-Diamino-2,3-dideoxy-α-L-ribopyranoside 3,4-Cyclic Urethan (9).—A solution of 230 mg of methyl 3-amino-2-azido-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (8) which contained a suspension of 55 mg of 5% palladium on carbon was hydrogenated at atmospheric pressure and room temperature for 6 hr, and the catalyst was removed by filtration through a Celite pad. The filtrate was evaporated to dryness *in vacuo* to give 180 mg of solid which was free of azide in the infrared. The analytical sample was recrystallized from methanol: mp 143–144°; $[\alpha]^{22}D$ −39° (*c* 0.50, water); λ_{max}^{Nujol} 2.95–3.15 (NH, OH), 5.70 (C=O), 6.30 μ (NH_2).

Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.6; H, 6.38; N, 14.9. Found: C, 44.6; H, 6.26; N, 15.1.

Methyl 2,3-Diamino-2,3-dideoxy-α-L-ribopyranoside (10).—To a solution of 57 mg of methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside 3,4-cyclic urethan (9) in 2 ml of water was added 140 mg of barium hydroxide octahydrate. The mixture was heated at reflux for 2 hr, and a heavy white precipitate of barium carbonate began to separate after 0.5 hr. The reaction was cooled, the precipitate was removed by filtration, and carbon dioxide was bubbled through the filtrate to remove the excess barium ions. The precipitated barium carbonate was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was extracted with 20 ml of boiling chloroform. The chloroform was evaporated to dryness to give 46 mg of white solid, mp 148–150°. The analytical sample was recrystallized from chloroform: mp 145–151°; $[\alpha]^{22}D$ −3° (*c* 0.49, water); λ_{max}^{Nujol} 2.95–3.20 (OH, NH), 6.25 μ (NH_2).

Anal. Calcd for $C_6H_{14}N_2O_3$: C, 44.4; H, 8.66; N, 17.3. Found: C, 44.1; H, 8.94; N, 17.3.

2,3-Diamino-2,3-dideoxy-α-L-ribose (11) Dihydrochloride.—A solution of 100 mg of methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside (11) in 4 ml of 6 *N* hydrochloric acid was heated at 110° for 3 hr and evaporated to dryness *in vacuo* at 20°. Two small portions of water were added and lyophilized, and the residue was triturated with 2 ml of absolute ethanol to effect crystallization. The analytical sample was prepared by recrystallization from aqueous acetic acid to give white crystals with mp 175° (gas evolution); $[\alpha]^{17}D$ 113° → 70° (*c* 0.49, water).

Anal. Calcd for $C_5H_{12}N_2O_3 \cdot 2HCl$: C, 27.1; H, 6.33; N, 12.7; Cl^-, 32.1. Found: C, 27.0; H, 6.60; N, 12.6; Cl^-, 31.8.

(15) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967).

(16) Melting points are corrected. Thin layer chromatograms were run on silica gel HF (E. Merck AG, Darmstadt). Spots were detected by iodine vapor. Organic solutions were dried using anhydrous magnesium sulfate. Nmr spectra were recorded with either a Varian A-60 or HA-100 spectrometer, for solutions in chloroform-*d*, with tetramethylsilane (c 1.00) as the internal standard unless otherwise indicated.

Methyl 2,3-Diacetamido-2,3-dideoxy-α-L-ribopyranoside (12).—To a solution of 108 mg of methyl 2,3-diamino-2,3-dideoxy-α-L-ribopyranoside (10) in 1 ml of water was added 0.5 ml of acetic anhydride. The mixture was stirred for 5 min and evaporated to dryness *in vacuo* to give 148 mg of crude product as a white solid. Purification was carried out by trituration with two 1-ml portions of methanol to give 109 mg of white solid, mp >275°, which was homogeneous on tlc with R_f 0.2 using ethyl acetate–methanol (9:1); λ_{max}^{Nujol} 2.83–3.2 (NH), 6.05, 6.15 (C=O), 6.35–6.45 μ (secondary amide).

Anal. Calcd for $C_{10}H_{18}N_2O_5 \cdot 1/3\ H_2O$: C, 47.7; H, 7.40; N, 11.1. Found: C, 47.5; H, 7.23; N, 10.9.

Ethylthio 2,3-Diacetamido-2,3-dideoxy-L-riboside (14).—A solution of 100 mg of 12 in 1.5 ml of concentrated hydrochloric acid and 1.5 ml of ethanethiol was stirred at 0–5° for 20 hr and neutralized with ammonia. The aqueous solution was extracted with chloroform and the aqueous phase was evaporated to dryness *in vacuo*. The dry residue was extracted with several 2–3 ml portions of chloroform. The chloroform extracts were evaporated to dryness *in vacuo* and the solid residue was recrystallized from methanol–ether to give 12 mg of product as a white solid: mp 275° dec; λ_{max}^{Nujol} 3.0 (NH), 6.05 (C=O), 6.5 μ (secondary amide). The nmr spectrum in D_2O showed one ethyl group and two N-acetates.

Anal. Calcd for $C_{11}H_{20}N_2O_4S \cdot {}^3/_4H_2O$: C, 45.6; H, 7.43; N, 9.70. Found: C, 45.9; H, 7.20; N, 9.52.

Registry No.—**4**, 20453-03-6; **5**, 20452-98-6; **6**, 20452-99-7; **7**, 20453-00-3; **8**, 20453-04-7; **9**, 20453-05-8; **10**, 20452-95-3; **11** (2HCl), 20452-96-4; **12**, 20452-97-5; **14**, 20453-06-9.

The Condensation of Glyoxylic Acid with 5α-Androstanolone

MANUEL DEBONO, R. MICHAEL MOLLOY, AND L. E. PATTERSON

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

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The condensation of 5α-androstanolone with glyoxylic acid gave steroids with an α-hydroxyacetic acid side chain at C-2. This side chain then reacts further with the C-3 carbonyl group to give ring-A-fused lactols. The chemistry of these lactols was studied, and the lactols were used to synthesize the novel ring-A-fused pyridazone **6**. When the condensation reaction was carried out in refluxing methanol, the C-2 *trans*-ylidene acetic acid derivative was isolated. The chemistry of these acids was studied, and their derivatives were used for synthesis of ring-A-fused γ-lactones.

Recent interest in the synthesis of ring-A-fused heterocyclic steroids has been prompted by the discovery of the unique biological properties of the steroidal pyrazoles.[1]

The goal of the present study was the synthesis of a 3-keto steroidal intermediate bearing a two-carbon side chain at C-2. This could be subsequently converted to fused steroidal heterocyclic systems possessing six-membered rings bearing two heteroatoms or five-membered rings bearing one heteroatom. This synthesis was accomplished by a modification of the procedure outlined by Newman, *et al.*, and also by Kurath and Cole, for the synthesis of 17-keto-16-*trans*-ylidene acetic acid steroids.[2] Condensation of 5α-androstanolone with glyoxylic acid in aqueous methanol and sodium hydroxide at room temperature gave hydroxyketo acid **1**, which could readily be lactolized to give the methoxylactol **2** when treated with methanolic HCl (Scheme I). An analogous condensation has recently been employed by Pettit[3] for synthesis of the isocardenolide side chain from 20-keto steroids.

The structure of **2** was deduced from its infrared spectrum[4] (1760 cm^{-1}) and from the properties of its diacetoxy derivative (**3**) obtained by refluxing **2** with acetic anhydride containing sodium acetate. The infrared spectrum showed that the lactol carbonyl group was unaltered by these acetylation conditions. Since no enol lactonization was observed under these conditions, it was concluded that the methoxyl group was at C-3 rather than on the side chain.[5] The position of the C-2′ hydroxyl group was confirmed by the observation that the doublet in the nmr of **2** at δ 4.85 shifted to δ 5.85 upon acetylation. The nmr spectrum of **3** (see Figure 1) showed two acetoxy groups as singlets at δ 2.06 and 2.16; the C-2 proton was observed as a quintet at δ 2.74 (J = 5 Hz). The proton at C-2′ was observed as a doublet at δ 5.83 (J = 5 Hz), and the methoxyl group and 17α proton gave signals at δ 3.37 and 4.62, respectively.

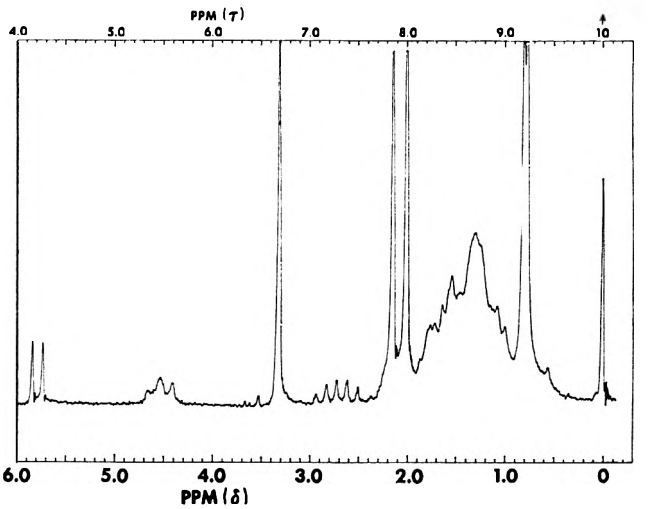


Figure 1.—Nuclear magnetic resonance spectrum of lactol diacetate **3**.

The stereochemistry of ring fusion of the lactol to ring A and its orientation can be deduced from the nmr spectrum of **3** and through the use of conformational analysis. It is well established that γ-lactones prefer a

(1) (a) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Amer. Chem. Soc.*, **81**, 1513 (1959); (b) D. K. Phillips and A. J. Manson, *J. Org. Chem.*, **28**, 2886 (1963), and references cited therein. (c) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *J. Amer. Chem. Soc.*, **86**, 1520 (1964), and references cited therein.

(2) (a) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961); (b) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *ibid.*, **23**, 1832 (1958).

(3) G. R. Pettit, G. L. Dunn, and B. Green, *Chem. Ind. (London)*, 1265 (1964).

(4) R. S. Rasmussen and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1073 (1949).

(5) M. S. Newman and C. A. VanderWerf, *ibid.*, **67**, 233 (1945).

cis fusion to six-membered rings[6] and that large groups prefer the 2α orientation (equatorial) in the 5α-androstane system.[7] Applying these two facts to the lactol diacetate **3**, it is evident that the most favorable ring fusion is at the 2α–3α positions with the methoxyl group situated at 3β-equatorial position. Dreiding models indicate that the methoxyl group severely hinders the β side of the lactol ring, thereby favoring the orientation of the 2′-acetoxyl function toward the α side. That this preference exists can be deduced from the similarity of the coupling between the C-2′–C-2 protons (J = 6.5 Hz, dihedral angle *ca.* 30°) with those reported by Williamson and Johnson in their study of the conformation effects on coupling constants in various α-acetoxycholestanones.[8]

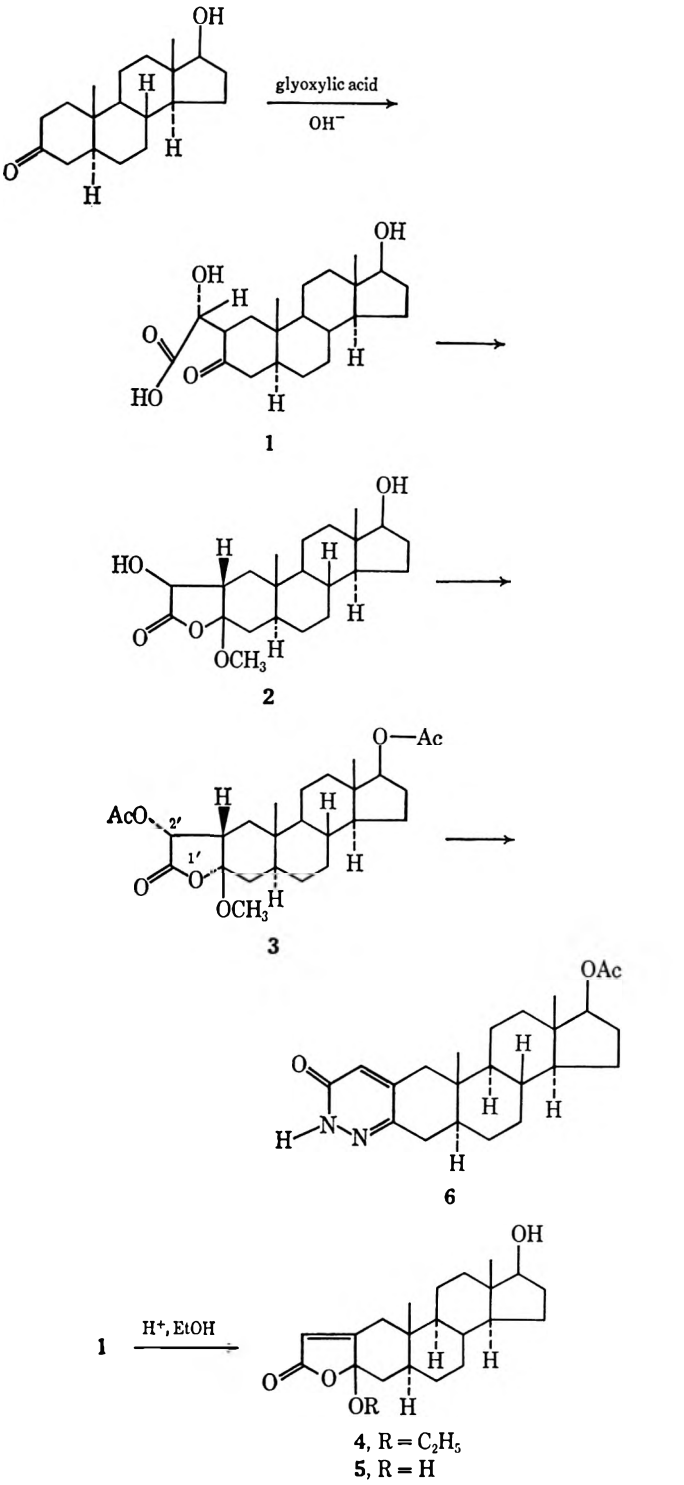
Further chemical proof of the structure of **2** was obtained by isolation of the α,β-unsaturated ethoxylactol **4** when **2** was refluxed in acidic ethanol. Recrystallization of **4** from moist acetone gave the less soluble lactol **5**.

The methoxylactol acetate **3** was transformed to the corresponding ring-A-fused pyridazone **6** by refluxing in ethanolic hydrazine. The nmr spectrum of **6** showed one aromatic proton at δ 6.72, while infrared (1660 cm^{-1}) and ultraviolet spectra (293 mμ) are typical of substituted pyridazines.[9]

The condensation of glyoxylic acid with androstanolone in refluxing aqueous methanolic base gave exclusively 17α-hydroxy-3-oxo-5α-androstan-$\Delta^{2,\alpha}$-acetic acid (**7**) (Scheme II) in 85% yield. The uv spectrum showed an absorption maximum at 240 mμ and an nmr signal at δ 6.28 for the olefinic proton. These properties are in general agreement with those reported by Kurath and Cole for the 16-*trans*-ylidene acetic acid 17-keto steroids.[2a,10] The exclusive formation of the *trans*-ylidene keto acid by this reaction is in full accord with the observation of Zimmerman and Ahramjian that *threo*- and *erythro*-3-hydroxy-2,3-diphenylpropionic acid each give exclusively *trans*-α-phenylcinnamic acid in better than 99% yields.[11]

The acid **7** was reduced to the 3β-hydroxy acid **8** with sodium borohydride. The resulting acid showed no tendency to lactonize, which is in accord with the *trans* orientation of the side chain. Acetylation of **8** gave the diacetoxy acid **9**. In the nmr spectrum of **9** an olefinic proton signal is situated at δ 5.88 and a doublet at δ 4.2 (1 H, J = 15 Hz) which was assigned to the equatorial proton at C-1. This rigid orientation of the *trans*-ylidene side chain at C-2 allows the deshielding plane of the carboxyl group to approach C-1 closely, thereby shifting the equatorial proton downfield.[12] This interpretation was bolstered further by the use of double resonance techniques. Irradiation at precisely 105 Hz upfield from the δ 4.2 signal resulted in the collapse of this broadened doublet to a broad singlet. Conversely, irradiation at δ 4.2 caused a singlet at δ 1.94 to appear through the methylene envelope. The nmr signal at δ 5.25 for the C-3 proton has a band width at half-height

SCHEME I



(6) (a) J. Klein, *J. Amer. Chem. Soc.*, **81**, 3611 (1959). (b) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *ibid.*, **83**, 66 (1961).

(7) (a) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *ibid.*, **77**, 6401 (1955); (b) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(8) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961); the Williamson–Johnson data show that protons on carbon bearing both an acetoxy and a carbonyl group will couple with protons on adjacent carbon atoms having dihedral angles in the vicinity of 30° to produce a coupling constant of about 6.6 Hz.

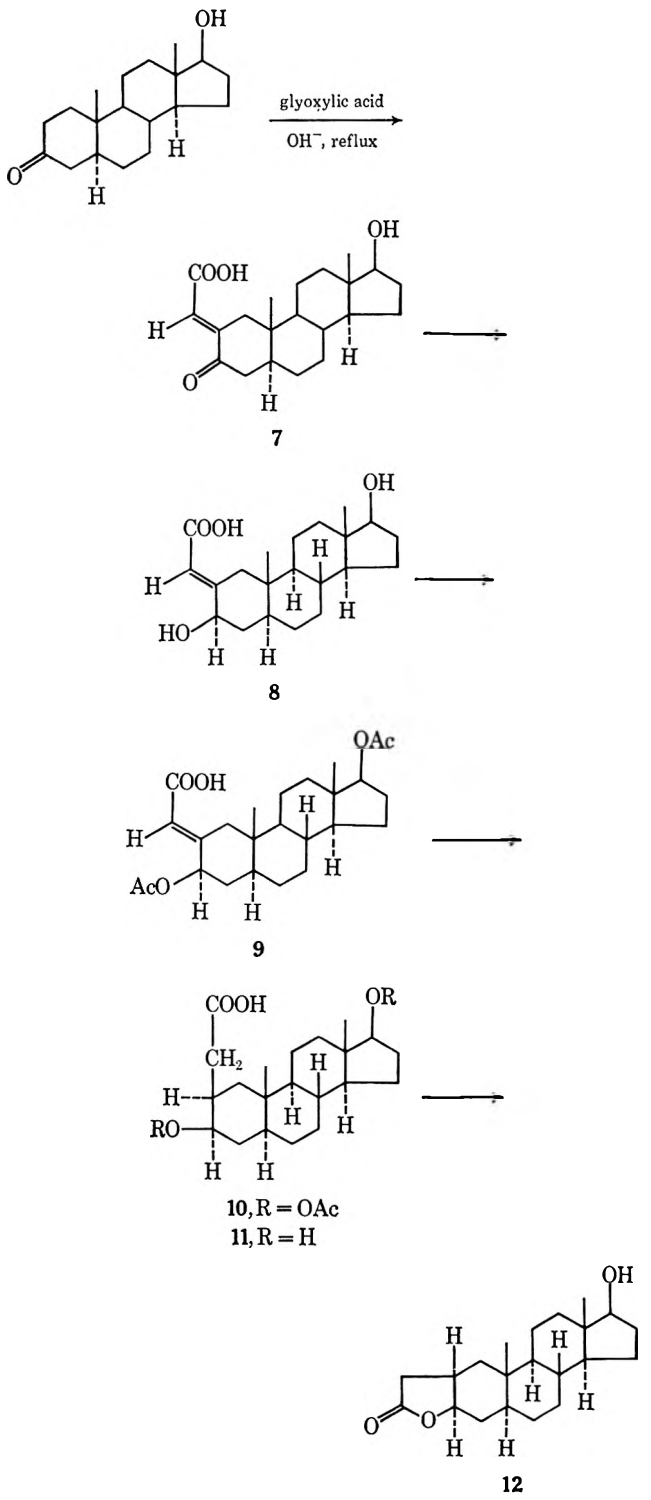
(9) T. L. Jacobs in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 120.

(10) The olefinic proton for 17-keto-16-*trans*-ylidene acetic acid Δ^6-androstan-3β-ol was observed at δ 6.42 and absorbed at 244 mμ (ε 10,000) in the ultraviolet region. The shifts in these properties in going from a 16- to a 2-ylidene side chain reflect the higher degree of planarity achieved between this grouping and the carbonyl function when attached to a five-membered ring. This effect is also reflected in the greater deshielding of the olefinic proton by the carbonyl group in the latter case.

(11) H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81**, 2086 (1959).

(12) Recent studies on the structure of cassaic acid have similarly demonstrated deshielding of methylene groups adjacent to ylidene acetic acid groupings: (a) R. L. Clarke, S. J. Daum, P. E. Shaw, and R. K. Kullnig, *ibid.*, **88**, 5865 (1966); (b) H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965).

SCHEME II



of 17 Hz, indicating that the acetate group at C-3 has the equatorial 3β orientation.[13]

The dihydroxy acid **8** was acetylated to **9**, and the latter was hydrogenated smoothly to the fully saturated diacetoxy acid **10**. Hydrogenation caused the δ 4.2 nmr signal to disappear. Hydrolysis of **10** gave the acid **11**, which was readily lactonized to the fused γ-lactone **12**. On the grounds of greater steric hindrance of the ring-A β face, the main hydrogenation product is assumed to have the C-2 side chain in the 2β position.

(13) (a) J. C. Orr, M. L. Franco, A. D. Cross, and F. Sondheimer, *Steroids*, **3**, 1 (1964); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 79.

The successful syntheses of the fused pyridazone **6** and the lactone **12** demonstrate the usefulness of the condensation of glyoxylic acid with keto steroids for the synthesis of heterocyclic steroid derivatives. The further utility of this method is currently under study.

Experimental Section

Infrared spectra were determined on a Beckman IR-7 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian Model HR-60 spectrometer with internal tetramethylsilane. Ultraviolet spectra were obtained with a Cary Model 15 spectrophotometer. Melting points were determined on a Mel-Temp apparatus and are uncorrected.

Condensation of 5α-Androstanolone with Glyoxylic Acid. Method A.—A slurry of 10 g (0.034 mol) of 5α-androstanolone in 200 ml of 1:1 aqueous MeOH was treated with 7 g of 40% aqueous glyoxylic acid solution and 2.72 g of NaOH. Stirring was continued at room temperature for 18 hr, and the reaction mixture was diluted with 600 ml of H_2O. Ether extraction of this solution gave 1 g of unreacted starting ketone. The alkaline layer was carefully acidified with acetic acid to pH 5–6 and extracted three times with Et_2O, and the extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a foam. The foam crystallized from MeOH–H_2O to give 17β-hydroxy-5α-androstan-2α-(α-hydroxyacetic acid)-3-one (**1**) (6 g): mp 190–191°; ir (Nujol) 1710 cm^{-1}; $[\alpha]^{20}D$ 32.9° (c 1, EtOH).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.10; H, 9.09. Found: C, 68.92; H, 8.84.

A methanolic solution of **1** (3 g in 75 ml of MeOH) was treated with a catalytic amount of methanolic HCl (1 ml of 10% methanolic HCl per 25 ml of methanolic solution of **1**), and the solvent was allowed to evaporate slowly under a slight vacuum and cooling. When the first indication of crystallization occurred, the solution was placed in the refrigerator. A white solid, 3ξ-methoxy-17β-hydroxy-5α-androstan-2α-(α-hydroxyacetic acid)-3-one-lactol (**2**) (2 g) was isolated and recrystallized from MeOH: mp 255–260°; ir (Nujol) 1760 cm^{-1}; $[\alpha]^{20}D$ 85.5° (c 1.17, DMF).

Anal. Calcd for $C_{22}H_{34}O_4 \cdot H_2O$: C, 66.66; H, 9.08. Found: C, 66.62; H, 9.08.

The gross structure of **2** was further verified by conversion to the crystalline diacetoxymethoxylactol **3**, as described below.

Method B.—The procedure outlined by Kurath and Cole for the condensation of glyoxylic acid with 17-keto steroids[2a] was used, except that the reaction mixture was not refluxed after the 18-hr room temperature stirring period. Instead, the mixture was gradually heated to 50° over a 20-min period. The products and yields were comparable with those obtained by method A. The simplicity of using glyoxylic acid directly instead of generating it *in situ* makes method A more attractive.

Acetylation of Methoxylactol 2.—A solution containing 2 g (0.0053 mol) of **2** in 50 ml of Ac_2O was refluxed under nitrogen for 1.5 hr. At this time, 0.5 g of anhydrous NaOAc was added to the brilliant yellow solution; refluxing under nitrogen was continued for 3 hr. The solution was cooled and evaporated to dryness *in vacuo*, and the residue was extracted with Et_2O and filtered. The Et_2O was removed *in vacuo*, and the residual oil was dissolved in Me_2CO to give the solid **3** (0.5 g): mp 171–174° (EtOH); $[\alpha]^{25}D$ – 12.6° (c 0.350, $CHCl_3$); ir ($CHCl_3$) 1760 cm^{-1} (lactone); for nmr ($CDCl_3$) see Figure 1.

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.59; H, 8.29. Found: C, 67.57; H, 8.28.

17β-Acetoxy-6′-(1′H)-oxo-5α-androstano[3,2-*c*]pyridazine (6).—A solution of 0.5 g (0.0011 mol) of **3** in EtOH (50 ml) was treated with 0.5 ml of 85% hydrazine hydrate and refluxed for 3 hr. The solvent was evaporated *in vacuo*, and the residue was recrystallized from absolute EtOH (0.38 g): mp 295–299°; $[\alpha]^{20}D$ 38.5° (c 0.52, $CHCl_3$).

Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.55; H, 8.65; N, 7.27.

The ultraviolet spectrum, λ_{max} (EtOH) 295 mμ (ϵ 2062), was typical of pyridazones.[9]

3ϵ-Ethoxy-17β-hydroxy-5′(2′H)-oxo-5α-androstano[3,2-*b*]furan (4).—A solution containing 0.5 g (0.013 mol) of the hydroxy acid **1** in 50 ml of EtOH was acidified with 5 drops of ethanolic HCl and refluxed overnight. The product was chromatographed on 30 g of Florisil with Et_2O. Elution with this solvent gave 200 mg of **4** as a foam which crystallized from Me_2CO–hexane: mp

169–171°; ir ($CHCl_3$) 1770, 1670 cm^{-1}; uv λ_{max} (EtOH) 215 mμ (ε 13,700); $[\alpha]^{20}D$ −73.8° (*c* 1.35, $CHCl_3$).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.5. Found: C, 73.85; H, 9.23.

Allowing this material to stand in moist Me_2CO caused gradual precipitation of the crystalline product **5**: mp 246–250°; $[\alpha]^{25}D$ −123.4° (*c* 0.95); ir (Nujol) 1750 cm^{-1}; uv λ_{max} (EtOH) 217 mμ (ε 13,350).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.57; H, 8.76.

17β-Hydroxy-3-oxo-5α-androstan-$\Delta^{2,\alpha}$-acetic Acid (7).—A solution of 5.4 g (0.02 mol) of 5α-androstanolone in 100 ml of MeOH and 100 ml of H_2O was treated with 1.6 g of NaOH followed by 7.4 g of commercial 40% glyoxylic acid solution (Eastman Kodak) in 50 ml of MeOH. The milky suspension cleared upon addition of the glyoxylic acid and gradually a gelatinous precipitate formed. The mixture was refluxed for 3 hr. The cooled solution was diluted with H_2O and extracted with Et_2O to remove unreacted starting material. The aqueous layer was acidified to pH 5 with a glacial AcOH and the residual Et_2O was removed by bubbling in a nitrogen stream. A white granular precipitate formed rapidly after most of the residual Et_2O had been removed. The precipitate (5 g) was collected and recrystallized: mp 221–223° dec (MeOH–H_2O); uv λ_{max} (EtOH) 240 (ε 10,000) and 230 mμ (shoulder). The nmr spectrum showed olefinic absorption at δ 6.30; $[\alpha]^{25}D$ 114.3° (*c* 1.05, EtOH).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.90; H, 8.90.

Sodium Borohydride Reduction of 7.—A solution of **7** (0.5 g) in 15 ml of absolute MeOH was cooled to 0° and treated with 15 ml of an aqueous solution of 0.3 g of $NaBH_4$. The ice bath was removed after 30 min, and stirring was continued for 30 min at room temperature. The reaction was refluxed for 30 min and then cooled. After the dropwise addition of 25 ml of 25% NaOH solution, the solvent was removed *in vacuo* and the residual solid was slurried with H_2O. Acidification of the alkaline mixture gave a white precipitate of **8** which was crystallized from MeOH (0.35 g): mp 278–282° dec; uv λ_{max} (EtOH) 220 mμ (ε 20,000); $[\alpha]^{25}D$ −3.6° (*c* 0.684, $CHCl_3$); nmr (DMSO) δ 5.88 (olefinic proton).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.02; H, 9.53.

This dihydroxy acid was further characterized by conversion into its diacetate by dissolving 0.3 g in 30 ml of 1:1 pyridine–Ac_2O and allowing the solution to stand overnight at room temperature. Water (20 ml) was added very carefully with cooling, and the solution was heated for 2 hr on a steam bath and added to 100 ml of ice–water. The precipitate **9** was collected and recrystallized from MeOH (0.25 g): mp 206–210°; $[\alpha]^{25}D$ −2.90° (*c* 0.831, $CHCl_3$); uv λ_{max} (EtOH) 222 mμ (ε 20,000).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.41; H, 8.45.

3β,17β-Dihydroxy-5α-androstan-2β-acetic Acid 3,17-Diacetate (10).—A solution of 10.0 g of **9** in 250 ml of HOAc containing 1.0 g of PtO_2 was hydrogenated in a Parr shaker until the rate of hydrogenation diminished to a low level. The product was isolated, and its uv spectrum showed 55% starting material still remaining. This material was diluted with HOAc (250 ml), fresh catalyst was added (0.6 g), and the mixture was hydrogenated at atmospheric pressure until the level of starting material was reduced to 10–15% (assayed by uv). The product was isolated as an oil, dissolved in 3:1 petroleum ether (30–60°)–Et_2O, and chilled. An amorphous solid was precipitated (2.33 g) which was recrystallized from Me_2CO–petroleum ether to give a crystalline solid **10**, mp 220–224°, which was identical with 3β,17β-dihydroxy-5α-androstan-2β-acetic acid 3,17-diacetate obtained by us in another study.[14] The mother liquors were concentrated further to give an amorphous solid, mp 103–107° (7.3 g). When a sample of the latter was hydrolyzed and lactonized (see accompanying procedure for preparation of **12**), it was judged to be a mixture of epimers at C-2. The 2β isomer was present in approximately 60–70% as indicated by the nmr signal of the C-19 methyl group; the chemical shifts of the two epimers occur at 54 and 58 cps, with the latter signal predominating slightly. Attempts at purifying this mixture further were not successful.

3β,17β-Dihydroxy-5α-androstan-2β-acetic Acid (11).—A solution of **10** (2 g, 0.46 mmol) was dissolved in 270 ml of H_2O and 30 ml of 2 *N* methanolic KOH. After standing for 4 hr at room temperature, the reaction mixture was concentrated to half volume and extracted with three 100-ml portions of Et_2O. The extract was dried over $MgSO_4$ and evaporated to give 43 mg of starting material. The basic layer was acidified to pH 2 and extracted with Et_2O. The dried extract was evaporated to give 1.51 g of **11** as a white solid which was recrystallized from Me_2CO–petroleum ether: mp 177–180° (resolidifies, melts at 202–204°).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.06; H, 9.71.

Lactonization of 3β,17β-Dihydroxy-5α-androstan-2β-acetic Acid (11).—A solution of 0.68 g of **11** in 75 ml of C_6H_6 and 50 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 4 hr until tlc showed no starting material remaining. The solution was cooled and more C_6H_6 was added. After washing with saturated $NaHCO_3$ solution and drying over $MgSO_4$, the solvent was evaporated to dryness and the resulting oil was crystallized from MeOH to give lactone **12** as a white solid (0.7 g): mp 199–201° (MeOH); ir ($CHCl_3$) 1750 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.58; H, 9.54.

Registry No.—Glyoxylic acid, 298-12-4.

Acknowledgment.—The authors are indebted to Drs. E. Farkas and R. T. Rapala for their timely advice and criticisms during this work, as well as to the members of the physicochemical and microanalytical sections of the Lilly Laboratories for technical support.

(14) M. Debono and R. M. Molloy, *J. Org. Chem.*, in press.

N-Pyruvoylanthranilic Acid. Evidence against a Cyclol Structure[1]

PAUL F. WEGFAHRT AND HENRY RAPOPORT

Department of Chemistry, University of California at Berkeley, Berkeley, California 94720

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N-Pyruvoylanthranilic acid and several of its derivatives, metabolites of a number of microorganisms, were examined for the presence of a cyclol form in solution. The nmr spectra in several solvents failed to provide evidence for such a form, although a hemiketal was observed in protic solvents. Selective exchange with $H_2{}^{18}O$ at the ketone carbonyl, followed by cyclization to 1-acetyl-3-methylene-4,1-benzoxazepine-2,5-dione and subsequent ^{18}O analysis, showed complete retention of the isotope label. The previously[2] postulated cyclol intermediate, invoked to explain the nmr spectrum and formation of the benzoxazepine, is inconsistent with this evidence. An alternate mechanism for the formation of benzoxazepine is proposed.

Recent investigations of bacterial and mold metabolites have uncovered several derivatives of N-pyruvoylanthranilic acid (**1a**). In *Aerobacter aerogenes*, **1a** has been proposed as an intermediate in the biosynthesis of anthranilic acid.[3] Fermentations of *Pencillium chrysogenum* and *P. notatum* were found to produce N-pyruvoylanthranilamide (**1b**).[4] A related compound, 2-(3-hydroxy-3-phenylpyruvoylamino)-N-methylben-

(1) Supported in part by the U. S. Army Research Office, Durham, N. C.

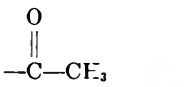
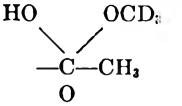
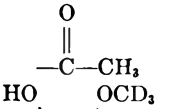
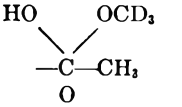
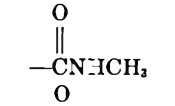
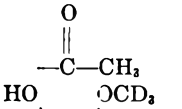
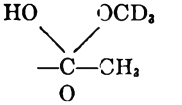
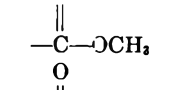
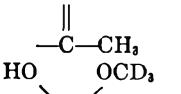
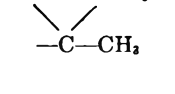
(2) F. Lingens and B. Sprössler, *Ann.*, **702**, 169 (1967).

(3) C. Ratledge, *Nature*, **203**, 428 (1964).

(4) P. J. Suter and W. B. Turner, *J. Chem. Soc., C*, 2240 (1967).

TABLE I

METHYL SIGNALS IN THE NMR SPECTRA[a] OF N-PYRUVOYLANTHRANILIC ACID AND SOME OF ITS DERIVATIVES

Compound	Solvent: DMSO-d_6	Solvent: C_5H_5N	Solvent: CD_3OD	Assignment
N-Pyruvoylanthranilic acid (1a)	2.44 (3)	2.06 (3)	2.49 (2)	
			1.57 (1)	
N-Pyruvoylanthranilamide (1b)	2.45 (3)	2.09 (3)	2.47 (2)	
			1.55 (1)	
N-Pyruvoylanthranilic acid N-methylamide (1c)	2.88 (3)		2.90 (3)	
	2.43 (3)		2.45 (2)	
			1.55 (1)	
Methyl N-pyruvoylanthranilate (1d)	3.90 (3)	3.33 (3)	3.92 (3)	
	2.45 (3)	2.07 (3)	2.47 (2)	
			1.56 (1)	

[a] δ values, relative to internal TMS (δ 0), followed by number of protons in parenthesis.

zamide (2) has been proposed as an intermediate in the rearrangement of cyclopenin (3) to viridicatin (4).[5]

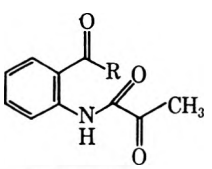
Lingens and Sprössler[2] reported the synthesis of N-pyruvoylanthranilic acid (1a) and concluded that in methanol solution this compound existed, in part, as the seven-membered cyclol, 5a. They subsequently invoked this form as an intermediate to explain the facile cyclization of N-pyruvoylanthranilic acid to 1-acetyl-3-methylene-4,1-benzoxazepine-2,5-dione (7) in acetic anhydride–pyridine. The supporting evidence for the cyclol postulate consisted of a time-dependent shift in the ultraviolet (uv) absorption in methanol and the separation of the methyl peak in the nmr spectrum in deuteriomethanol into two peaks at δ 2.5 and 1.6 in a ratio of 2:1, assigned to the methyl ketone and cyclol forms, respectively. Several model compounds, including the dimethyl ketal of 1a, were prepared to confirm the nmr positions. Interestingly, the cyclol methyl ether, 5b, was not observed in the preparation of the dimethyl ketal.

Our interest in the mold metabolite cyclopenin[6] prompted us to investigate this phenomenon. If a similar cyclization of the amide analog of 1a could be accomplished, then an alternate synthetic route and a possible biosynthetic path to cyclopenin could be envisioned. There is sufficient precedent to believe that amide nitrogen–carbonyl interaction could produce a similar cyclol.[7]

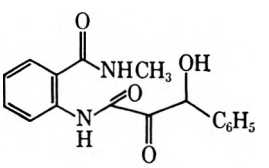
(5) Y. S. Mohammed and M. Luckner, *Tetrahedron Lett.*, 1953 (1963).
(6) H. Smith, P. Wegfahrt, and H. Rapoport, *J. Amer. Chem. Soc.*, **90**, 1668 (1968).
(7) G. I. Glover, R. B. Smith, and H. Rapoport, *ibid.*, **87**, 2003 (1965).

Nmr Studies.—The compounds 1a–1d (Chart I) were investigated by nmr at 60 MHz in a variety of solvents, to clarify the nature of the interaction. The

CHART I



1a, R = OH
b, R = NH_2
c, R = $NHCH_3$
d, R = OCH_3



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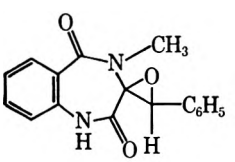

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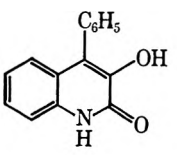

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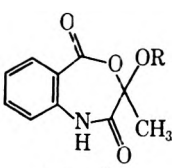
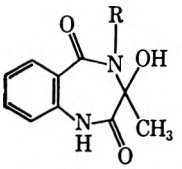
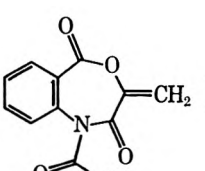


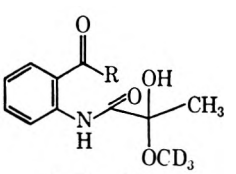
5a, R = H
b, R = CH_3



6a, R = H
b, R = CH_3

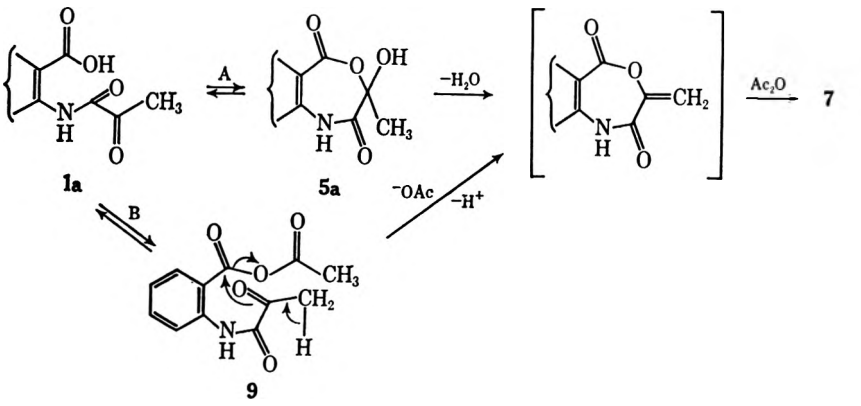


7



8a, R = OH
b, R = NH_2
c, R = $NHCH_3$
d, R = OCD_3

SCHEME I



results, shown in Table I, make it abundantly clear that what is being observed is not cyclol formation.

Splitting of the pyruvoyl methyl signal of compounds **1a**–**1d** was observed only in deuteriomethanol, or in other solvents only after methanol had been added. For all compounds in methanol, the positions and relative intensities of the two peaks attributable to the pyruvoyl methyl were the same. The high-field signal (δ 1.6) was previously assigned to the methyl of the hydroxylactone form **5a**,[2] *i.e.*, methyl on carbon bearing two oxygens. Such a methyl group would not be expected, on the basis of shielding effects, to have the same chemical shift as the methyl of the amide cyclols **6a** and **6b**, *i.e.*, methyl on carbon bearing oxygen and nitrogen, nor would the equilibrium amounts of amide and carboxylic acid cyclols be expected to be the same.

The strongest evidence against existence of any appreciable amount of cyclol form is found in the spectrum of the methyl ester, **1d**, a compound where cyclol formation is not possible, but where the same pattern of methyl splitting is observed. The most reasonable interpretation of the data is that in the presence of methanol the hemiketals **8a**–**8d** are in equilibrium with the ketone, and the position of equilibrium is independent of the carboxylate substituent.

The spectra in nonprotic solvents gave no evidence for a cyclol form in solution, although this alone is not sufficient proof that none exists. Time averaging of the two methyl signals or a very small equilibrium amount of cyclol would be undetectable by the method used. Thus the conversion of **1a** into benzoxazepine **7** still could have proceeded *via* the previously postulated cyclol **5a** followed by dehydration.

^{18}O Studies.—Inspection of the cyclol mechanism for benzoxazepine formation (path A) suggests a method for testing its validity, since the ketonic oxygen would be lost during reaction by this path. An alternate path which proceeds *via* the mixed anhydride **9** (path B) retains the ketone oxygen in the benzoxazepine ring. Selective ^{18}O exchange at the ketone carbonyl, cyclization to **7**, and ^{18}O analysis of the cyclic product would differentiate between the two paths (see Scheme I).

The apparent ease of hemiketal formation suggested that the ketone oxygen could be exchanged with $H_2{}^{18}O$ under quite mild conditions. Accordingly, **1a** was dissolved in 10:1 tetrahydrofuran–water (1.71% ^{18}O) without catalysis, and samples were withdrawn periodically over a 72-hr period. The ^{18}O content, determined by nonoxidative pyrolysis of the crystalline material and mass spectroscopy of the resulting carbon dioxide,[8] increased regularly, reached a maximum value after 24 hr, and remained constant. Since the ^{18}O content of **1a** after exchange had ceased was only 25% that of the water (Table II), only one of the four oxygens had exchanged, and that presumably was the ketonic oxygen since amides and carboxylic acids usually require more vigorous conditions for oxygen exchange.[9]

TABLE II

^{18}O ANALYSES OF N-PYRUVOYLANTHRANILIC ACIDS (**1a**) AND 2-ACETYL-3-METHYLENE-4,1-BENZOXAZEPINE-2,5-DIONE (**7**)

Compound	% ^{18}O, total[a]	Calcd % ^{18}O of ketone oxygen[b]
H_2O	1.71 ± 0.01	
1a control	0.20 ± 0.01	0.20
1a exchanged	0.57 ± 0.01	1.68 ± 0.04
7[c]	0.58 ± 0.01	1.73 ± 0.04

[a] Determined by mass spectroscopy of pyrolysate, average of two determinations. [b] Calculated assuming that ^{18}O enrichment occurred only in the ketone carbonyl oxygen; % ^{18}O (ketone) = [total ^{18}O − 0.20 (natural abundance)] × number of oxygen atoms + 0.20. [c] Prepared from **1a** − exchanged.

To establish firmly the position of the oxygen which had exchanged, N-pyruvoylanthranilic acid (**1a**) was equilibrated with 30.2% $H_2{}^{18}O$ (containing a large amount of deuterium) and the mass spectrum of this exchanged material was compared with that of the unlabeled compound (Figure 1). The molecular ion of the exchanged material had significant peaks from *m/e* 207, M^+ of the original material, to *m/e* 211 (M + 4). The M + 4 ion contains one atom of ^{18}O and two atoms of deuterium since the absence of a significant M + 5 peak implies that only one oxygen and the two hydrogens, on the amide and acid groups, are exchangeable.

The position of oxygen exchange becomes apparent on inspection of the first fragmentation peak, which occurs at *m/e* 164 (M − 43), and can be attributed to the loss of acetyl. The absence of peaks at *m/e* 167 and 168 and the intensities of the ions at *m/e* 165 and 166 show that the ^{18}O label has been lost and that only deuterium remains. Additionally, the presence of the ^{18}O in the acetyl group can be seen in the greatly enhanced ratio of *m/e* 45 to *m/e* 43 in the exchanged material over that found in the spectrum of unlabeled **1a**.

(8) C. D. Snyder and H. Rapoport, *Biochemistry*, **7**, 2318 (1968).

(9) D. Samuel in "Oxygenases," O. Hayashi, Ed., Academic Press Inc., New York, N. Y., 1962, pp 31–86.

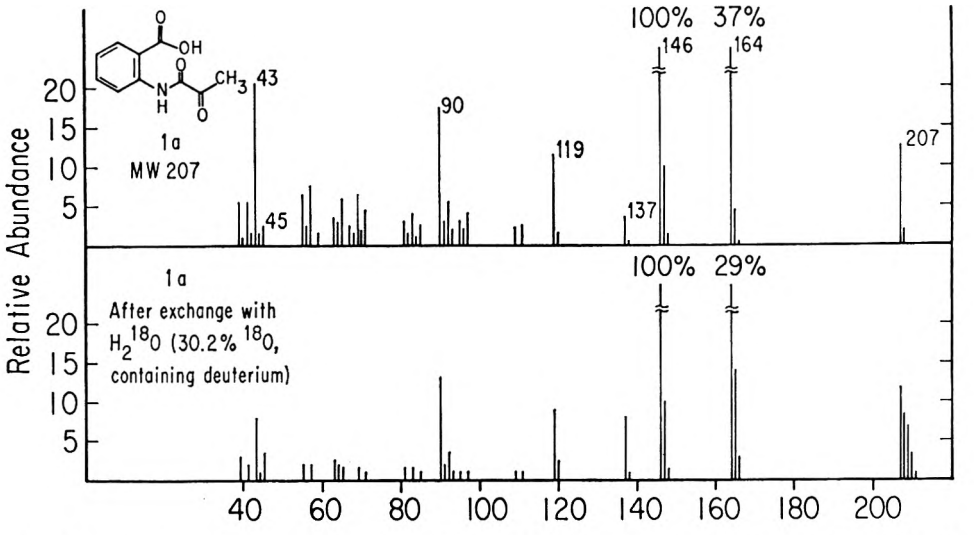
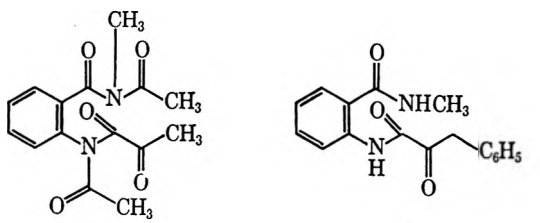


Figure 1.—Mass spectra of N-pyruvoylanthranilic acid (1a) before and after exchange with $H_2{}^{18}O$–$D_2{}^{18}O$.

Loss of the elements of water from the *m/e* 164 ion gives the base peak at *m/e* 146 in which the isotopic content is identical with that of the corresponding peak in the spectrum of unlabeled **1a**. This confirms that the ketone carbonyl was the sole position of ^{18}O exchange.

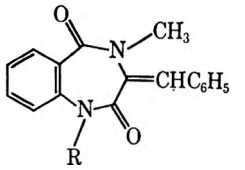
The isotopically labeled material was then converted into the benzoxazepine **7** as described.[2] Analysis of ^{18}O in the product showed complete retention of the isotopic label (Table II). Thus the cyclol intermediate (path A) cannot be contributing to benzoxazepine formation. Path B, which involves displacement of the mixed anhydride, is supported by the evidence.

Although the cyclization *via* the mixed anhydride is not applicable to the amide analogs, the possibility of cyclolization to form a benzodiazepine (**6**) is still possible. In fact, it could be argued that, with the acid **1a**, cyclization *via* path A was merely suppressed by the existence of a more favorable route. Such a route does not exist for the amide; consequently the amide **1c** was subjected to the same conditions that gave cyclization of the acid. Two compounds were isolated from the reaction mixture, which on characterization by mass and nmr spectroscopy appeared to be isomeric diacetyl derivatives of **1c**. Attempts to interconvert thermally the two materials by heating at temperatures up to 150° led only to decomposition. No attempt was made to define rigorously the structure of those materials, but they are believed to be isomers of **10**.



10

11



12a, R = H
b, R = $COCH_3$

As a final attempt to detect benzodiazepine formation *via* cyclolization of ring-open compounds, the phenylpyruvoyl analog **11** was prepared and subjected to the same cyclization conditions. Comparisons by thin layer chromatography (tlc) of the products of the reaction with authentic samples of the anticipated products **12a** and **12b**, prepared by a different route,[6] failed to give any evidence of benzodiazepine formation.

It must be concluded that there is no evidence to support the existence of a cyclol form in pyruvoylanthranilates. Molecular models indicate that the desired ring system is significantly strained, and, although the ring has been formed by closure of the 3–4 bond,[6,10] this has occurred only under irreversible conditions.

Experimental Section

Pyruvoyl Chloride.—Reagent grade thionyl chloride (12 g, 0.10 mol), 95% pyruvic acid (5.0 g, 0.05 mol), and 200 ml of anhydrous ether were boiled in a nitrogen atmosphere for 4 hr. The solvent and excess thionyl chloride were removed *in vacuo* to give 4.2 g (80%) of crude pyruvoyl chloride as a yellow oil, which was used without further purification.

N-Pyruvoylanthranilic acid (1a) was prepared as described[2] in 30% yield after seven recrystallizations: mp 194–195° (lit.[2] mp 194–195°).

N-Pyruvoylanthranilamide (1b).—The crude pyruvoyl chloride (4.2 g, 0.04 mol) in 50 ml of methylene chloride was added over 1 hr to a stirred solution of anthranilamide (5.5 g, 0.04 mol) and pyridine (3.2 g, 0.04 mol) in 200 ml of methylene chloride at 0° and stirred at room temperature for 6 hr. The resulting solution was filtered and washed three times with 1 *N* hydrochloric acid, then with 5% aqueous sodium bicarbonate and water. The solvent was evaporated and the residue was crystallized from methylene chloride–pentane: yield 3.7 g (45%); mp 180–182° (lit.[4] mp 181–184°).

N-Pyruvoylanthranilic acid N-methylamide (1c) was prepared from anthranilic acid N-methylamide and pyruvoyl chloride following the procedure used for preparing anthranilamide. Silica gel chromatography of the crude product gave 2.7 g (31% yield) after crystallization from methylene chloride–pentane: mp 142–144°; $\lambda_{max}^{CH_3OH}$ 302 nm (ϵ 5900), 241 (9600).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7. Found: C, 60.2; H, 5.5; N, 12.6.

Methyl N-pyruvoylanthranilate (1d) was prepared in 64% yield from methyl anthranilate and pyruvoyl chloride: mp 111–112° (lit.[2,4] mp 111–112°).

N-Phenylpyruvoylanthranilic Acid N-Methylamide (11).—Phenylpyruvic acid (1.63 g, 0.01 mol) was dissolved in 20 ml of reagent grade thionyl chloride and warmed under nitrogen at

(10) C. Lee, *J. Heterocycl. Chem.*, **1**, 235 (1964).

50° for 3 hr. The excess reagent was removed *in vacuo* to give 1.8 g of a yellow oil. This material was dissolved in 50 ml of chloroform and added over 1 hr to a stirred solution of anthranilic acid N-methylamide (1.5 g, 0.01 mol) and pyridine (0.9 g, 0.011 mol) in 150 ml of chloroform at 0°. The solution was stirred overnight at room temperature, refluxed for 1 hr, washed with 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water, and dried over sodium sulfate, and the solvent was removed *in vacuo*. Chromatography on silica gel and crystallization from ethyl acetate gave 1.2 g (41%) of **11** as fine needles: mp 182–185° dec; $\lambda_{max}^{C_2H_4OH}$ 302 nm (ε 7900), 249 (12,800); nmr (DMSO-d_6) δ 2.82 (3, d), 4.15 (2, s), 6.9–7.9 (9, m), 8.9–9.1 (2, br).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.4; N, 9.5. Found: C, 69.0; H, 5.2; N, 9.4.

1-Acetyl-3-methylene-4,1-benzoxazepine-2,5-dione (7) was prepared from **1a** in acetic anhydride, by the method described,[2] in 70% yield: mp 95° (lit.[2] mp 95–96°).

Treatment of N-Pyruvoylanthranilic Acid N-Methylamide (1c) with Acetic Anhydride–Pyridine.—A solution of 0.5 g of **1c** in 5 ml of 1:1 acetic anhydride–pyridine was allowed to stand for 2 days at room temperature and then heated on a steam bath for 6 hr. The solution was diluted with ether, washed with 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water, and dried over sodium sulfate. Chromatography on silica gel gave two major products: A [150 mg; mp 134–135°; M^+ 304; $\lambda_{max}^{CH_3OH}$ 294, 240, 221 nm; nmr ($CDCl_3$) δ 1.59 (3, s), 1.62 (3, s), 2.10 (3, s), 2.98 (3, s), 7.0–8.0 (4, m)] and B [65 mg; mp 157–159°; M^+ 304; $\lambda_{max}^{CH_3OH}$ 291, 240, 218 nm; nmr ($CDCl_3$) δ 1.65 (3, s), 1.78 (3, s), 2.00 (3, s), 3.00 (3, s), 7.1–8.2 (4, m)].

^{18}O Exchange of Ia.—Analytically pure N-pyruvoylanthranilic acid (**1a**, 200 mg) was dissolved in 10 ml of dry tetrahydrofuran in a capped serum vial, 1 ml of $H_2{}^{18}O$ (1.71% ^{18}O) was added, and the solution was allowed to stand at room temperature for 72 hr. Aliquots (5 mg), taken periodically to measure the extent of exchange, were added to pyrolysis tubes and the solvent was removed immediately under a nitrogen stream. Succeeding exchanges were run for 24 hr only. Rigorously dried solvents and glassware were used through all ^{18}O experiments. The samples (5 mg) of the material to be analyzed were dried thoroughly under high vacuum and then pyrolyzed at 500° for 4 hr as previously described.[7] The pyrolysis tube was cooled in a methanol–Dry Ice bath and the resulting gases were examined on a mass spectrometer. Since the yield of carbon monoxide was insufficient for the purposes of analysis, the carbon dioxide peak was used. Background hydrocarbons were minimal and the analysis was straightforward. The ^{18}O content of the water was determined by equilibration of a sample with CO_2 in a pyrolysis tube at 500° followed by mass spectroscopy of the gas. The isotope content of the CO_2 was calculated from formula 1

$$^{18}O\ (\%) = \frac{[46]/([44] + [45]) \times 0.96}{2 + \{[46]/([44] + [45])\}} \times 100 \qquad (1)$$

where [44], [45], and [46] are the relative intensities of the *m/e* 44, 45, and 46 peaks.

Registry No.—**1a**, 14469-11-5; **1b**, 18326-62-0; **1c**, 20452-61-3; **1d**, 13748-93-1; **11**, 20453-01-4.

The Synthesis of 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene and Its Rearrangement to *trans*-β-Carotene

J. D. SURMATIS, J. GIBAS, AND R. THOMMEN

Technical Development Department, Hoffmann-La Roche, Inc., Nutley, New Jersey

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A novel synthesis of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (**6**) and its rearrangement to *trans*-β-carotene are reported. A new type of carotenoid with a cross-conjugated keto function (**4**) was used as an intermediate for the synthesis of **6**.

The first synthesis of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (**6**) was reported in 1956.[1] In spite of its structural similarity to β-carotene, very little is known about this carotenoid; it has not been found in nature nor reported to play a role in the biosynthesis of naturally occurring carotenoids. The ease with which it was transformed into β-carotene may explain its absence in natural products. By using a readily available intermediate (**1**) of an industrial vitamin A synthesis,[2,3] **6** was prepared in high yield and rearranged to *trans*-β-carotene.

A search of the literature resulted in one reference[4] describing a carotenoid with a cross-conjugated keto function. Its structure had not been fully established yet, as the work was hampered by a lack of material and published data on this type of configuration. This was an "open-ring" carotenoid belonging to a class represented by lycopene.

The C-20 diol (**1**) was oxidized with manganese dioxide[5] in methylene chloride to afford a cross-conjugated keto aldehyde, **2** (65%), as yellow crystals, mp 74°. The condensation of **2** with retinylphosphonium sulfate (**3**) resulted in a new type of keto carotenoid, **4** (60%), mp 156°. Compound **4** crystallized as dark violet hexagonal prisms from benzene–methanol and as red rhombic crystals from heptane. The color of a solution of **4** in benzene or heptane was similar to that of *trans*-β-carotene of equal concentration. Compound **4** was approximately twice as soluble in heptane as *trans*-β-carotene.

The nuclear magnetic resonance (nmr) spectrum was compatible with the structure assigned to **4** (Figure 1).

The ultraviolet spectrum of **4** showed a weaker absorption than that of *trans*-β-carotene, and the curve exhibited only one maximum (Figure 2).

The retinyltriphenylphosphonium sulfate (**3**) was obtained as a yellow crystalline monohydrate on react-

(1) O. Isler, M. Montavon, R. Ruegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 454 (1956).

(2) O. Isler, A. Ronco, W. Guex, N. C. Hindley, W. Huber, K. Dialer, and M. Koffler, *ibid.*, **32**, 489 (1949).

(3) J. D. Surmatis, U. S. Patent 2,610,208 (1952).

(4) S. L. Jensen and K. Schmidt, *Arch. Mikrobiol.*, **46**, 138 (1963).

(5) Available from General Metallics Oxides Corp., Jersey City, N. J. (Manganese hydrate no. 37).

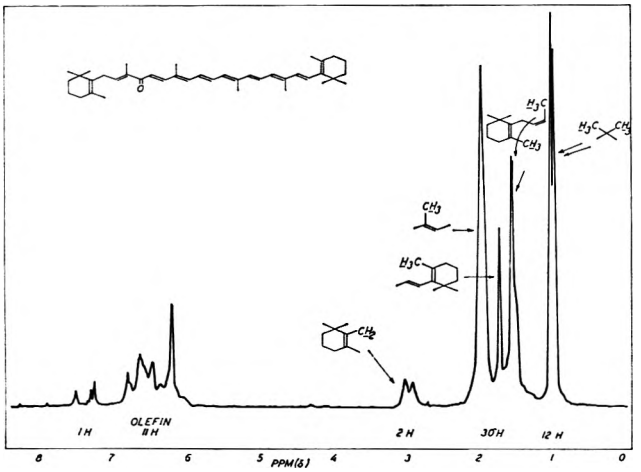


Figure 1.—Nuclear magnetic resonance spectrum of **4**.

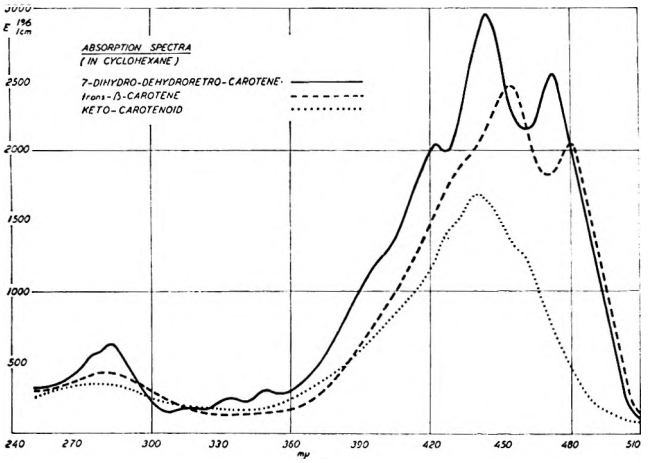


Figure 2.—Ultraviolet spectrum of **4**.

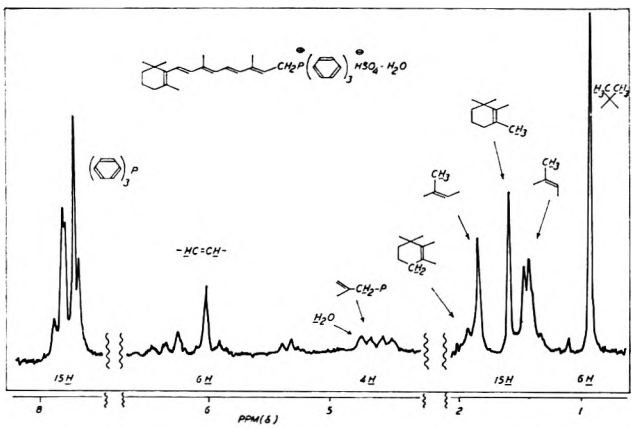


Figure 3.—Nuclear magnetic resonance spectrum of **3**.

ion of vitamin A acetate with triphenylphosphonium sulfate. The presence of a doublet of doublets in the nmr spectrum ($J_{CH,P}$ = 17.5 cps; J_{CH,CH_2} = 7.5 cps) for the CH_2P group indicated the presence of the =CH-CH_2P moiety instead of the retro structure which results when vitamin A is treated with a mineral acid (Figure 3).

Reduction of **4** with sodium borohydride in methanol–pyridine afforded the hydroxy carotenoid (**5**). Samples of **4** and **5** were tested for biological activity in comparison with *trans*-β-carotene, using the rat liver storage[6,7] and curative-growth assays. Although both compounds supported growth at a dose level of 200 μg per day, the calculated vitamin A activities were only 60,000 and 130,000 USP units per gram for **4** and **5**, respectively.

(6) J. R. Foy and K. Morgarlidge, *Anal. Chem.*, **20**, 304 (1948).
(7) K. Guggenheim and W. Koch, *Biochem. J.*, **38**, 256 (1944).

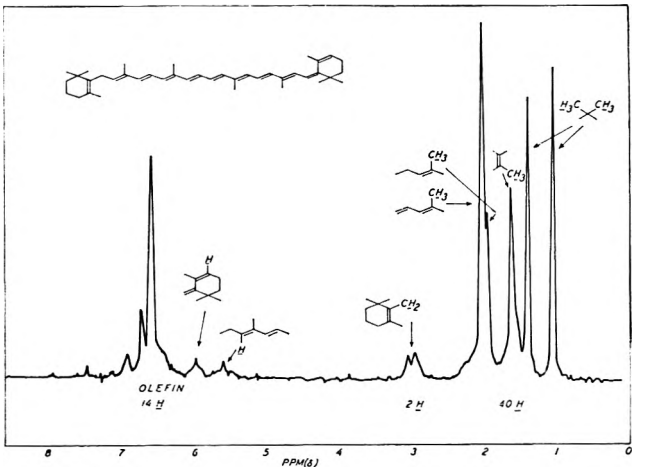


Figure 4.—Nuclear magnetic resonance spectrum of **6**.

When **5** was dehydrated by stirring an acetone solution at 25–30° for 4 hr in the presence of hydrobromic acid, *trans*-β-carotene was afforded in 70% yield; at 0°, a new carotenoid was obtained (73%), mp 168°. The uv spectrum showed three well-defined maxima with typical high absorption displayed by the retro structure (Figure 2). The nmr spectrum was compatible with the structure assigned to 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (**6**) (Figure 4). Compound **6** was found to be unstable under acidic conditions. On stirring a suspension of **6** in acetone containing a trace of hydrobromic acid for 4 hr at 25–30°, *trans*-β-carotene (96%), mp 181°, was obtained (Chart I).

Experimental Section[8,9]

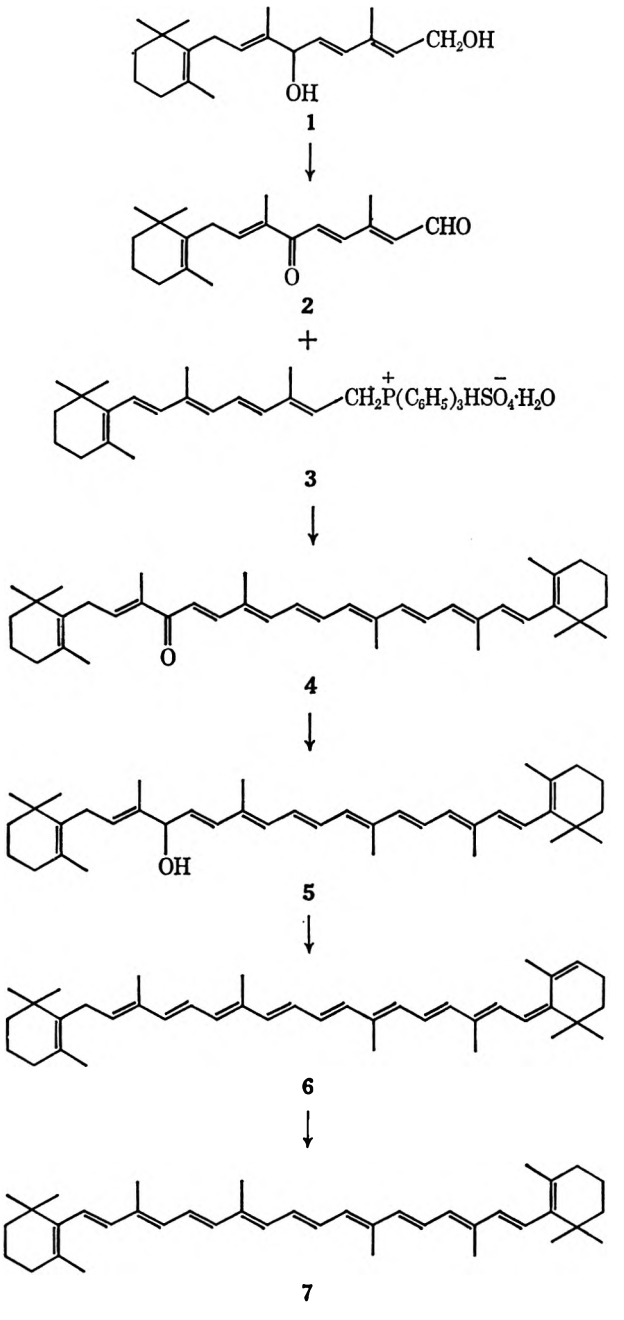
3,7-Dimethyl-6-oxo-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,7-nonatrienal (2).—C-20 diol **1** (609 g), CH_2Cl_2 (4.8 l.), and MnO_2 (2.4 kg) were placed in a 12-l., round-bottom flask fitted with a mechanical stirrer, and agitated for 24 hr under N_2. Additional MnO_2 (2.4 kg) was added, and the stirring was continued for 24 hr. The spent MnO_2 was filtered off and then washed with CH_2Cl_2. The solvent was removed from the combined filtrate and washings, and the residue was crystallized from hexane to give 390.6 g (65%) of **2** as pale yellow crystals, mp 74°; uv (C_2H_5OH), 290 mμ ($\epsilon^{1\%}_{1\,cm}$ 1014).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.90; H, 9.34.

Retinyltriphenylphosphonium Sulfate (3).—Triphenylphosphine (315 g), CH_3OH (3.0 l.), and concentrated H_2SO_4 (56 ml) were placed in a 5-l. flask and stirred for 30 min. Crystalline vitamin A acetate (328 g) was added all at once, and the reaction was stirred under N_2 for 24 hr. The solvent was removed by vacuum distillation, and the residue was crystallized by dissolving in 2.5 l. of boiling acetone and then cooling to 10° for 24 hr. The yellow crystalline product was filtered, washed with acetone, and dried in a vacuum oven at 50°. The retinyltriphenylphosphonium sulfate, which was obtained as a hydrate, weighed 380 g (58.7%), mp 202°.

(8) The nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as the internal reference (δ = 0 ppm).
(9) The boiling and melting points are uncorrected; melting points were determined in vacuum capillaries.

CHART I



Anal. Calcd for $C_{38}H_{47}O_5PS$: C, 70.56; H, 7.32. Found: C, 70.86; H, 7.32.

3,7,12,16-Tetramethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,5,7,9,11,13,15,17-octadecaoctaen-4-one (4).—To a cold (10°) solution of retinyltriphenylphosphonium sulfate (64 g) in CH_3OH (1200 ml), a solution of the C-20 aldehyde **2** (30 g) in a mixture of CH_3OH (200 ml) and pyridine (10 ml) and a solution of KOH (10 g) in CH_3OH (100 ml) were added simultaneously with vigorous stirring over a period of 2 hr. The cooling bath then was removed and the reaction mixture was stirred for 12 hr under N_2. The resulting red crystalline solid was filtered and washed with CH_3OH (1000 ml), H_2O (1000 ml), and finally with CH_3OH (500 ml). The crude product was dried in a vacuum oven (20 mm) at 50° and recrystallized from heptane to obtain 33.2 g (50%) of **4**, mp 156°; uv (cyclohexane) 438 mμ ($\epsilon^{1\%}_{1\,cm}$ 1682).

Anal. Calcd for $C_{40}H_{56}O$: C, 86.90; H, 10.23. Found: C, 86.25; H, 10.23.

3,7,12,16-Tetramethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,5,7,9,11,13,15,17-octadecaoctaen-4-ol (5).—A solution of **5** (60 g) in CH_3OH (600 ml) and pyridine (600 ml) was reduced with sodium borohydride (15 g) by stirring for 24 hr under N_2 at room temperature. The reaction mixture was poured into ice–water (2 l.) in a separator provided with a stirrer, and the product was extracted with CH_2Cl_2. The extract was washed with H_2O and concentrated to a syrup *in vacuo* at 50°. The hydroxy carotenoid **5** was obtained as a yellow resinous solid (58 g), uv (cyclohexane), 405 mμ ($\epsilon^{1\%}_{1\,cm}$ 1613).

Anal. Calcd for $C_{40}H_{58}O$: C, 86.57; H, 10.53. Found: C, 86.16; H, 10.40.

The Dehydration of 5 to *trans*-β-Carotene.—A solution of 63% HBr (20 ml) in acetone (150 ml) was dropped into a solution of the hydroxy carotenoid **5** (55.5 g) in acetone (800 ml) at 25–30° in 30 min. Stirring then was continued under N_2 for 4 hr. The red crystalline solid which was formed was filtered and washed with 5% aqueous $NaHCO_3$ and then with acetone. Recrystallization of the crude product from CH_2Cl_2 afforded 37.6 g (70%) of *trans*-β-carotene, mp 181°; uv (cyclohexane) 456 mμ ($\epsilon^{1\%}_{1\,cm}$ 2500).

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,-18-octadecanonaene (6).—To a stirred solution of **5** (316 g) in acetone (3000 ml), 63% HBr (100 ml) dissolved in 500 ml of acetone was added dropwise at 0° over a period of 1 hr. The crystalline solid that formed was filtered, washed with 5% $NaHCO_3$ solution, and then washed with acetone. Recrystallization from benzene–methanol containing 0.1% of pyridine gave 251 g (72.8%) of **6**, mp 168°; uv (cyclohexane) 444 mμ ($\epsilon^{1\%}_{1\,cm}$ 2936).

Anal. Calcd for $C_{40}H_{56}$: C, 89.48; H, 10.52. Found: C, 89.22; H, 10.37.

Rearrangement of 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (6) to *trans*-β-Carotene (7).—To a suspension of **6** (100 g) in acetone (1.5 l.), a solution of 63% HBr (5 ml) in acetone (500 ml) was added all at once, and the mixture was stirred for 4 hr at room temperature (25–30°). The red crystalline solid was filtered, washed with 5% $NaHCO_3$ solution and then washed with acetone (2 l.), and dried *in vacuo* (20 mm) at 50°. Recrystallization from CH_2Cl_2 afforded 96 g (96%) of *trans*-β-carotene, mp 181°; 456 uv (cyclohexane) 456 mμ ($\epsilon^{1\%}_{1\,cm}$ 2495).

Registry No.—**2**, 20843-63-4; **3**, 20930-45-4; **4**, 20941-64-4; **5**, 20843-65-6: **6**, 20843-64-5; **7**, 116-32-5.

Acknowledgment.—We wish to thank Dr. F. Vane and Dr. P. Bommer for the nmr spectra, Dr. F. Forrester for the uv spectra, Dr. A. Steyermark for the microanalyses, and Mr. E. De Ritter for the determination of biological activities.

Lithium Metal in the α Butylation of Dimethylaniline[1a]

A. R. LEPLEY, V. C. DOHM, AND A. G. GIUMANINI[1b]

Department of Chemistry, Marshall University, Huntington, West Virginia 25701

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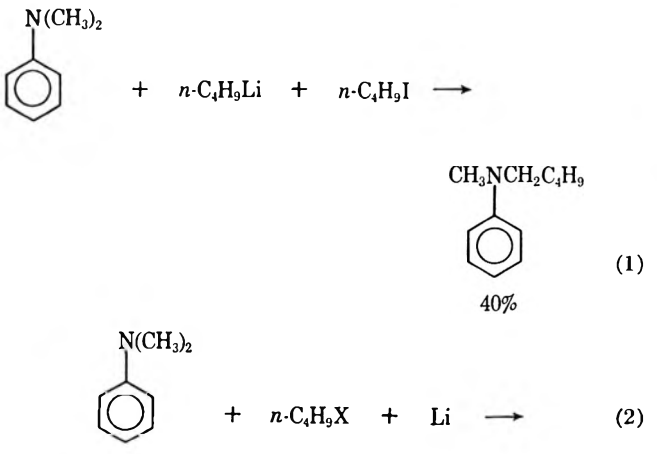
The use of lithium metal in place of *n*-butyllithium as a reagent in the direct butylation of N,N-dimethylaniline was studied. *n*-Butyl halides react with lithium in dimethylaniline to give the normally competing products in α alkylation, N-methyl-N-(1-pentyl)aniline and *n*-octane. Trace amounts of α-amine butylation were observed with 1-chlorobutane; none was reported in previous reactions with butyllithium. Bromobutane with lithium gave less alkylation and more Wurtz product than was observed with alkyllithium reagents. However, yields of N-methyl-N-(1-pentyl)aniline were 62–68% in the reactions of 1-iodobutane. An additional compound, N-methyl-N-(1-butyl)aniline, was observed in small quantities in chloro- and bromobutane reactions. The formation of *n*-butyllithium in the solvent dimethylaniline was demonstrated in the chloro and bromo reactions. Slow room temperature conversion of dimethylaniline–*n*-butyllithium mixtures into aromatic ring metalated products was evident from reaction with hexafluoroacetone.

Alkylation on carbon of a tertiary amine was recently observed in the reaction of N,N-dimethylaniline with iodobenzene and *n*-butyllithium, which produced N-methyl-N-benzylaniline and N-methyl-N-(1-pentyl)-aniline.[2] Subsequent studies have demonstrated that this reaction (1) is limited to the α position of the amine,[3,4] (2) will occur with simple aliphatic amines as well as with aniline derivatives,[4] and (3) takes place when aliphatic iodides or bromides, but not chlorides, replace the original aryl halide.[5] Furthermore, investigations aimed at clarifying the reaction mechanism indicate that the reaction occurs by a direct substitution which, in most cases, does not involve α carbanion,[6] quaternary ammonium salt,[3,4] carbene, or benzyne intermediates.[7]

These alkylations (*e.g.*, eq 1) are clearly in completion with Wurtz coupling,[2-5] and the product distributions are influenced by halogen–metal interchange.[2,3,5] The diversity of the possible reactions, the question of the stability of organolithium compounds in tertiary amine solvents, and the increase in amine α alkylation with a decrease in competing or diluting solvents[3,5] led to the current investigation of organolithium generation in pure, anhydrous, tertiary amines.

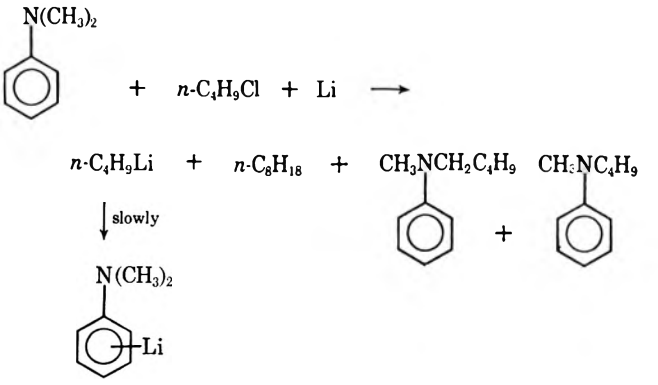


N,N-Dimethylaniline was chosen as solvent and *n*-butyl halides as the organolithium generating species (eq 2) because of the availability of pertinent data from previous related studies.[2-5]

Results and Discussion

Each of the alkyl halides, 1-chloro-, 1-bromo-, and 1-iodobutane, was allowed to react with lithium metal in N,N-dimethylaniline. Enough alkyl halide was used in each case to allow for both *n*-butyllithium generation and amine α alkylation or other carbanion consuming reactions. N,N-Dimethylaniline was used in a considerable excess to provide both reactant and supporting solvent.

1-Chlorobutane reactions furnished the principal evidence for *n*-butyllithium formation. Initial yields of the measured reaction products were quite low despite the rapid disappearance of lithium metal.



After 24 hr, *n*-octane was the major product with 3% yield, while the α-alkylation product, N-methyl-N-(1-pentyl)aniline, was less than 1% although initially formed quite rapidly. N-Methyl-N-(1-butyl)aniline, a product not observed previously in similar reactions, was formed by the chlorobutane–lithium reaction. Initial N-(1-butyl) formation was less than N-(1-pentyl) production, but exceeded the yield of that compound after 24 hr. Thereafter, the N-(1-butyl) product continued to form slowly. These products accounted for less than 6% of the starting amounts of alkyl halide or lithium metal. The remaining material was in the form of organolithium compound.

Addition of 1-iodobutane to the 1-chlorobutane reaction mixture after 24 hr increased the formation of N-methyl-N-(1-pentyl)aniline, which varied with the tem-

(1) (a) Presented in part before the IUPAC 3rd International Symposium on Organometallic Chemistry, Munich, Germany, Aug 1967, Abstracts, p 76. (b) Institute of Organic Chemistry, University of Bologna, 40136 Bologna, Italy.

(2) A. R. Lepley and A. G. Giumanini, *Chem. Ind.* (London) 1035 (1965).

(3) A. R. Lepley and A. G. Giumanini, *J. Org. Chem.*, **31**, 2055 (1966).

(4) A. R. Lepley and W. A. Khan, *ibid.*, **31**, 2061 (1966).

(5) A. R. Lepley and W. A. Khan, *ibid.*, **31**, 2064 (1966).

(6) A. R. Lepley, W. A. Khan, A. B. Giumanini, and A. G. Giumanini, *ibid.*, **31**, 2047 (1966).

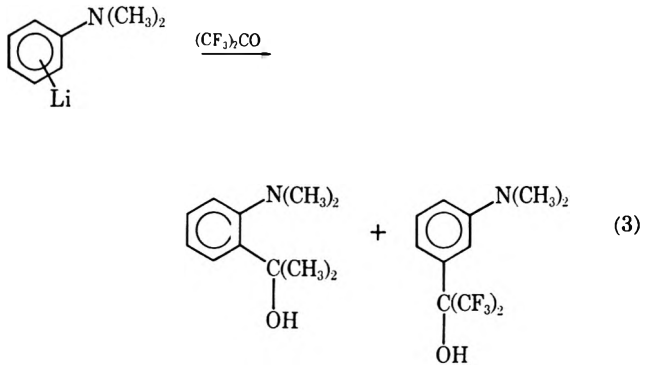
(7) A. R. Lepley, A. G. Giumanini, A. B. Giumanini, and W. A. Khan, *ibid.*, **31**, 2051 (1966).

Table I
N-Methyl-N-(1-pentyl)aniline Production from the Reactions of 1-Haloalkanes with Lithium Metal in N,N-Dimethylaniline

Halide (X)	Yield, % n-C4H9I added[a] 24 hr	26 hr	28 hr	Addition temp, °C
Cl	<1	21	22	26–28
Cl	<1	30	36	0
Br	6	8	13	0
I	66	64	66	0

[a] Added immediately after removal of 24-hr sample

perature of iodide addition (Table I), to 50–90% of the amounts previously obtained[3,5] when *n*-butyllithium in hexane was allowed to react directly with iodobutane in dimethylaniline. Thus, the chlorobutane reaction mixture acted as if it contained a significant amount of *n*-butyllithium. Also, the mixture from the chlorobutane reaction, after 7 days, was treated with hexafluoroacetone and gave almost quantitative yields of *o*-and *m*-dimethylaminophenylbis(trifluoromethyl)carbinol (eq 3). Normally, metalation of N,N-dimethyl-



(3)

aniline with *n*-butyllithium in hexane requires several hours of reflux.[6] The 13:1 ratio of these products, *ortho*:*meta*, was very close to the hydrogen acidities of N,N-dimethylaniline observed on potassium amide catalyzed deuterium exchanges in liquid ammonia at 25°.[8] However, these room temperature results were considerably higher than the 5:1 ratio observed after 24 hr in refluxing hexane.[6] The equilibrium established therefore is highly dependent upon temperature or solvent. Since metalated dimethylaniline was ineffectual as a base in the α-alkylation reaction,[6] the current results are an indication of excellent conversions of chlorobutane into *n*-butyllithium in N,N-dimethylaniline.

1-Bromobutane and lithium metal gave a considerable increase in secondary reactions of the initially formed *n*-butyllithium. *n*-Octane was the principal product identified. This hydrocarbon continued to be formed smoothly after the disappearance of lithium metal from the reaction mixture. Other products showed similar behavior. The general trends were interpreted as an indication that *n*-butyllithium was a required reagent in the formation of all of the observed products. N-Methyl-N-(1-pentyl)aniline and N-methyl-N-(1-butyl)aniline were observed after 24 hr, in 6 and 3% yields, respectively, together with 15% *n*-octane.

1-Iodobutane gave the most dramatic change in this series of reactions. Only M-methyl-N-(1-pentyl)-aniline was observed as an amine product; this compound was rapidly formed, reaching a maximum yield of 62–68% after 4 hr. The amount of 1-pentyl product was not enhanced on the subsequent addition of more 1-iodobutane. Since such enhancement was an indication of the formation of *n*-butyllithium in the reactions with 1-chlorobutane, it seems apparent that any *n*-butyllithium formed in the presence of 1-iodobutane rapidly underwent further reaction by either α alkylation or Wurtz coupling processes. *n*-Octane was observed, but was inadequately separated from the starting 1-iodobutane for quantitative gc determination; *cf.* Table II.

In the 1-bromobutane reaction, n-butyllithium was produced more rapidly than it was consumed by product forming reactions. Addition of 1-iodobutane to this reaction mixture after 24 hr gave a significant (doubling after 4 hr) enhancement of the α-alkylation product, Table I; yet the mass balance was poor. However, when 1-bromobutane was allowed to react for 2 days without 1-iodobutane addition, a 49% yield of *n*-octane and 4.2% yield of N-methyl-N(1-butyl)aniline were determined, which raised the mass balance to more than 60% of the starting halide. This trend toward more Wurtz reaction and less α alkylation agreed with previous studies using *n*-butyllithium and 1-bromobutane.[5]

Only a single new amine was observed when iodobutane was used with lithium metal. This single product accounted for more of the starting materials than all products in either the chloro or bromo reaction. Iodobutane α alkylation was more than 1.5 times that obtained with commercial *n*-butyllithium.[3] Concentrated *n*-butyllithium in hexane solutions produced up to 50% yield of α alkylation[5] but never the more than 60% currently observed with lithium metal. Three factors may contribute to this reaction control: (1) temperature, (2) low organometallic reagent concentrations, and (3) the solvent composition. The current results warrant a further study of these previously observed[5] variables.

The primary reaction process occurs on the metal surface. Generation of *n*-butyllithium, in hydrocarbon solvents (eq 4), is accelerated by the use of a

$$6\,n\text{-}C_4H_9X + 12Li \longrightarrow (n\text{-}C_4H_9Li)_6 + 6LiX \qquad (4)$$

metal dispersion to increase the surface for halide reaction. The surface area requirement reflects the solvation in nonpolar and nonassociative alkanes. *n*-Butyllithium is a hexamer[9] in hydrocarbons where the metal atoms form a cluster surrounded by the alkyl chains. However, branched chain and tertiary alkyl groups form only tetramers. The external hydrocarbon coat interacts with the similar solvent structure to solvate the organolithium clusters. The removal of the *n*-butyllithium from the metal surface thus depends on the formation of some minimum number of RM units capable of solvation. The greater the steric requirements to reach this number, the more dependent the reaction will be on surface conditions.

The tertiary amine significantly changes this solvation. Reactions take place readily even when the metal is not finely divided and when initially covered with a

(8) A. I. Shatenshtein and Y. I. Ranneva, *J. Gen. Chem. USSR*, **31**, 1317 (1961).

(9) T. L. Brown, R. L. Gerteis, D. A. Bafus, and J. A. Ladd, *J. Amer. Chem. Soc.*, **86**, 2135 (1964).

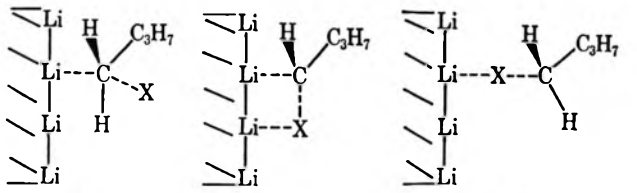
TABLE II

GAS CHROMATOGRAPHIC RETENTION RATIOS FOR PRODUCTS AND OTHER COMPOUNDS RELATED TO THE REACTIONS OF 1-HALOBUTANES WITH LITHIUM METAL IN N,N-DIMETHYLANILINE

	Retention ratios			
	Silicon rubber[a]		GE-SF96[b]	
Compd	Calibration	Reaction products	Calibration	Reaction products
1-Chlorobutane	0.117			
1-Bromobutane	0.168			
n-Octane	0.199	0.197–0.200 (Cl, Br)		
1-Iodobutane	0.210			
1-Bromopentane	0.276			
n-Nonane	0.323		0.378	
n-Decane	0.570		0.524	
n-Undecane	0.705			
N,N-Dimethylaniline	0.711		0.704	
n-Dodecane	1.000[c]		1.000[d]	
m-Dimethylaminophenylbis(trifluoromethyl)carbinol	1.14		1.15	
o-Dimethylaminophenylbis(trifluoromethyl)carbinol	1.38		1.58	
N-Methyl-N-(1-butyl)aniline		1.43–1.48 (Cl, Br)	1.66	1.68 (Cl)
N-Methyl-N-(1-pentyl)aniline	1.71	1.69–1.79 (Cl, Br, I)	2.41 ± 0.03	2.37 (Cl) 2.35 (I)
N,N,N′,N′-Tetramethylbenzidine		1.77 (I)		3.07 (I)
N-Methyl-N-(1-hexyl)aniline	2.08		3.27	
Benzhydryldimethylamine			4.52	4.32 (added to I)

[a] Commercial column supplied by F & M, 0.25 in. × 4 ft, programmed from 80 to 180° at 5°/min, 50 cc/min He flow (80°). [b] A 0.25 in. × 10 ft column of 20% GE-SF96 on 40–60 mesh Chromosorb W; at 185°, 100 cc/min He flow. [c] Standard for qualitative and quantitative analysis, retention time 10.6 ± 0.5 min, peak width at half-height 0.43 ± 0.04 min. [d] Standard for qualitative and quantitative analysis, retention time 3.5 ± 0.3 min, peak width at half-height 0.20 ± 0.05 min.

thin oxide and nitride coat. Thus freshly cut metal, after exposure to the laboratory atmosphere for 5 to 10 min, can be used with the halide in dimethylaniline. This solvent does not appreciably solvate halide ions; *cf.* the insolubility of trialkylanilinium halides. Thus, *n*-butyllithium formation requires a four-center mechanism where both halide and alkyl groups associate with the metal surface as in B rather than the displacement



A B C

type intermediate A. However, *n*-butyl group displacement in C favors the free-radical formation observed[10,11] with iodo and to a lesser extent with bromo compounds.

The enhanced solubility of *n*-butyllithium is then accounted for by an alternative solvation process. The nonbonding, lone pair electrons of the solvent forms an outersphere complex[9,12] with the metal of the alkyllithium. This complex (*e.g.*, the trimer in eq 5) con-

$$2\ n\text{-}C_4H_9X + 4Li + R_3N: \longrightarrow (n\text{-}C_4H_9Li)_2{:}NR_3 + 2LiX \quad (5)$$

tains a solvent molecule which aids solvation. Limited precipitation, apparent during the initial reaction period except when the iodide was used, is consistent with complex formation since halides form weak complexes with organolithium compounds.[13] Organolithium–amine complexes were only studied with trialkylamines;[9,12] thus, the extent of dialkylaniline participation is not yet known.

The secondary reaction processes lead to amine and hydrocarbon products. The yields of N-methyl-N-(1-pentyl)aniline are significantly higher in the 1-iodobutane–lithium reaction than those obtained from *n*-butyllithium in hexane indicating product may occur at the metal surface. However, yields do increase with amine concentration,[5] and the optimum yields now obtained do not exceed those anticipated for this concentration. Thus, there is no evidence supporting direct participation of the metal in this most important, secondary reaction.

The 1-pentyl product was much less important in the chloro- and bromobutane reactions. *n*-Octane from Wurtz coupling (eq 6) accounted for 15% of the bromo compound after 14 hr of reaction and 49% after 48 hr of reaction. The octane formation after lithium

$$2\ n\text{-}C_4H_9X + 2Li \longrightarrow n\text{-}C_8H_{18} + 2LiX \quad (6)$$

metal disappearance (second day) was evidence for the initial formation of *n*-butyllithium and its subsequent reaction with a second mole of the halide (eq 7). How-

$$\begin{aligned} n\text{-}C_4H_9X + 2Li &\longrightarrow n\text{-}C_4H_9Li + LiX \\ n\text{-}C_4H_9X + n\text{-}C_4H_9Li &\longrightarrow n\text{-}C_8H_{18} + LiX \end{aligned} \quad (7)$$

ever, octane formation reached 3.6% in 24 hr and increased to 4.3% at 48 hr, when chlorobutane was allowed to react with metallic lithium. Since disappearance of the metal was slower and *n*-butyllithium concentrations after 1 day were higher than with bromobutane, the predominant formation of *n*-octane from chlorobutane evidently occurs in the presence of the metal. An alternative to free-radical *n*-octane formation which occurs with bromobutane[11] is thus bimo-

(10) A. R. Lepley, *Chem. Commun.*, 64 (1969); A. R. Lepley and R. Landau, *J. Amer. Chem. Soc.*, **91**, 748 (1969); A. R. Lepley, *ibid.*, **90**, 2710 (1968).

(11) D. Bryce-Smith, *J. Chem. Soc.*, 1603 (1956); H. R. Ward, *J. Amer. Chem. Soc.*, **89**, 5517 (1967); H. R. Ward and R. G. Lawler, *ibid.*, **89**, 5518 (1967); H. R. Ward, R. G. Lawler, and R. A. Cooper, *ibid.*, **91**, 746 (1969); F. S. D'yachkovskii and A. E. Shilov, *J. Gen. Chem. USSR*, **33**, 400 (1963); *Russ. Chem. Rev.*, **35**, 300 (1966).

(12) J. F. Eastham and G. W. Gibson, *J. Amer. Chem. Soc.*, **85**, 2171 (1963); Z. K. Cheema, G. W. Gibson, and J. F. Eastham, *ibid.*, **85**, 3517 (1963); F. A. Settle, M. Haggerty, and J. F. Eastham, *ibid.*, **86**, 2076 (1964); C. G. Screttas and J. F. Eastham, *ibid.*, **87**, 3276 (1965).

(13) W. Glaze and R. West, *ibid.*, **82**, 4437 (1960).

lecular reaction of the halide absorbed on the metal surface or reaction with a surface layer of previously formed alkyllithium.

The final product, N-methyl-N-(1-butyl)aniline, was formed in small amounts and was evident only in the chloro- and bromobutane reactions. The highest yields of this product occurred in bromobutane reactions, where the yield after 24 hr slowly increased to 4% at 48 hr. In the chlorobutane reaction, the N-butyl compound was observed at less than 2% after 1 day and increased to only 2.5% with an additional day of reaction. Three possible mechanisms might be anticipated: (1) quaternary salt formation followed by elimination; (2) dealkylation followed by addition to the secondary amine formed; or (3) some type of double displacement or direct alkyl group exchange. Although the occurrence of amine dealkylation has been suggested to result from treatment of some tertiary amines with alkyllithium reagents, only alkyl groups with protons β to the amino nitrogen atom participate,[14] thus excluding the current reactant dimethylaniline. The major formation of N-pentyl product occurs where N-butyl compound is absent and is only comparable to the latter in the chlorobutane reactions. Thus initial formation of the pentyl compound followed by dealkylation and addition steps is improbable. Since a double displacement is uncommon in tertiary amines, including the anilines, a quaternary anilinium salt intermediate seems most plausible. The N,N-dimethyl-N-butyl salt does not form readily,[3] but such salts can undergo displacement reactions as well as Hofmann elimination.[15] The participation of *n*-butyllithium in such displacement reactions has been considered elsewhere.[16] This salt can revert to dimethylaniline by either butene elimination or by displacement, giving *n*-octane. These paths may thus account for part of the hydrocarbon observed. The N-butyl product under consideration is the result of methyl, rather than butyl, group displacement. However, if a significant amount of quaternary salt occurred, other products such as N-methyl-N-(*sec*-pentyl)aniline might be expected from a Stevens rearrangement. Thus limited salt formation is indicated by both the absence of other products and low yield of N-butyl product.

$$C_6H_5N(CH_3)_2 + n\text{-}C_4H_9X \longrightarrow C_6H_5N^+(CH_3)_2C_4H_9\ X^-$$
$$\downarrow RLi$$
$$C_6H_5N(CH_3)_2 + C_6H_5N(CH_3)C_4H_9$$

Experimental Section

Physical Properties.—Proton magnetic resonance (pmr) spectra of synthetic material were measured on a Varian A-60A spectrometer using 0.5-ml samples of 20% v/v solutions in carbon tetrachloride with approximately 1% tetramethylsilane (TMS) as an internal standard. Reaction products were collected from gc as 5–10-mg samples, diluted to 35 μl with 1% TMS in carbon tetrachloride, and measured in a 30-μl spherical cavity tube.

Infrared (ir) measurements were made on the pure liquids or on potassium bromide disks for solids using a Perkin-Elmer Model 137 spectrophotometer. Wavelengths and intensities are given as previously described.[17]

Gas Chromatography.—Columns and conditions used on an F & M Model 700 chromatograph are given in Table II. Retention ratios, peak resolution, and product yields (see tables) were determined using an internal standard method.[5,17] Qualitative and quantitative analyses were made on 0.4 and 1.0 μl of samples from the reaction mixtures. The weighed dodecane, introduced initially in preparing reaction mixtures, was used as the standard for quantitative analysis. Calibration factors for weight ratios of particular classes of compounds were alkanes 1.00, N,N-dialkylanilines and 1-haloalkanes 0.68, and *o*- or *m*-(dimethylamino)phenylbistrifluoromethylcarbinols 0.46. Measured variation in calibration factors was ±0.04. Calculated yields are ±3% of the value given (*e.g.*, 20.0 ± 0.6).

Preparative gc samples were obtained from an F & M Model 500 using a 0.25 in. × 10 ft GF-SF96 column with operating conditions as in Table II. Samples of 50–200 μl were injected and the individual products collected, as each emerged, in cooled 1.5–2.0 × 100 mm open-ended capillary tubes. Normally, several samples were run to collect the 10–15 mg of a product required for ir and pmr spectra and, where appropriate, melting points.

Chemicals.—*n*-Nonane, *n*-decane, *n*-undecane, *n*-dodecane (olefin free, 99%+), and 1-iodobutane were obtained from Matheson Coleman and Bell. *n*-Octane, 1-bromobutane, and 1-bromopentane came from Eastman. 1-Chlorobutane and reagent grade N,N-dimethylaniline were from Fisher Scientific. The latter was dried over sodium wire before use. N-Methyl-N-(1-butyl)aniline, N-methyl-N-(1-pentyl)aniline, N-methyl-N-(1-hexyl)aniline, benzhydryldimethylamine, and *o*- and *m*-dimethylaminophenylbis(trifluoromethyl)carbinol were available from previous studies.[6] Hexafluoroacetone was obtained from Columbia Organic Chemicals and Foote Mineral 0.5 in. × 1 ft lithium metal rod was used. N,N,N′,N′-Tetramethylbenzidine was obtained from Aldrich.

General Procedure for α Alkylation of N,N-Dimethylaniline Using Lithium Metal.—An alkyl halide (0.1 mol) was added to a freshly prepared magnetically stirred mixture of freshly cut lithium metal (0.7 g, 0.1 g-atom), dry N,N-dimethylaniline (38 ml, 0.3 mol), and an accurately weighed amount of *n*-dodecane (*ca.* 3 g) in a 100-ml round-bottomed flask fitted with a drying tube. Samples (1 ml) were removed at various intervals and quenched immediately with distilled water (3 ml). The organic phase was decanted and used for gc analysis. The gc retention ratios of the products were compared with those of synthetic materials. Identification was made through pmr and ir spectra of the products isolated by preparative gc.

Reaction of 1-Iodobutane, N,N-Dimethylaniline, and Lithium.—1-Iodobutane (11.4 ml, 0.10 mol) was allowed to react with lithium (0.79 g, 0.12 g-atom) and N,N-dimethylaniline (38 ml, 0.3 mol) as described in the general procedure. The mixture became warm initially and was allowed to react at room temperature. Samples for analysis were removed after 0.5, 2, and 4 hr, and 1, 2, and 9 days. One gc peak with retention ratio 1.70, (silicon rubber) or 2.35 (GE-SF96) was rapidly formed. After 4 hr the peak was almost as large as that observed after 1 day. By 9 days the peak had slowly decreased in intensity to about two-thirds of its maximum. The ir and pmr spectra of a preparative gc sample of this peak were identical with the spectra[3] of N-methyl-N-(1 pentyl)aniline. Based on this assignment, maximum yield varied from 62 to 68%. Since the starting material, 1 iodobutane, was inadequately separated from a second peak which preceded it, direct qualitative or quantitative identification was not made. However, based on previous experiments using *n*-butyllithium, this peak was assumed to be that of *n*-octane. After 9 days the reaction mixture turned deep blue and an additional peak appeared at a gc retention ratio of 1.77 (silicon rubber) or 3.07 (GE SF96). A preparative gc sample of this material had a melting point of 72°, and pmr bands were at δ 2.82 (CH_3 on aryl nitrogen) and a symmetric pair of aromatic multiplets were centered at 6.27 and 7.24 ppm, with relative intensity ratios of 3:1:1, respectively. The ir spectrum in KBr had bands at 2910 w, 2830 w, 1600 m, 1500 m, 1450 w, 1360 m, 1230 w, 1200 w, 1135 w, 1170 w, 952 vw, 810 s*, and 750 cm^{-1} w. Both the pmr spectrum and ir bands, except that at 750 cm^{-1}, were comparable with data measured for a commercial sample of N,N,N′,N′-tetramethylbenzidine. This product and the blue color of the reaction mixture indicate that air oxidation takes place under the conditions of these studies only long after completion of the organometallic and amine reactions.

(14) K. P. Klein, D. N. van Eenam, and C. R. Hauser, *J. Org. Chem.*, **32**, 1155 (1967).

(15) C. L. Bumgardner and H. Iwerks, *Chem. Commun.*, 431 (1968); D. A. Archer and H. Booth, *J. Chem. Soc.*, 322 (1963).

(16) A. R. Lepley and A. G. Giumanini, *J. Org. Chem.*, **32**, 1706 (1967).

(17) A. R. Lepley and R. H. Becker, *Tetrahedron*, **21**, 2365 (1965).

Reaction of 1-Bromobutane, N,N Dimethylaniline, and Lithium.—1-Bromobutane (13.7 ml, 0.13 mol) was allowed to react with lithium (0.85 g, 0.12 g-atom) and N,N-dimethylaniline (38 ml, 0.3 mol) as described in the general prodedure. No heat evolution was observed. Samples were taken and analyzed after 0.5, 4, and 18 hr, and 1, 2, 7, and 22 days. The halide with retention ratio 0.164 (silicon rubber) decreased to less than one-third its original concentration during the first day. Thereafter, its disappearance was very gradual, reaching one-sixth the initial amount after 3 weeks. *n*-Octane was adequately separated (retention ratio 0.23, silicon rubber) from the halide for quantitative analysis. This hydrocarbon formation lagged behind the halide loss rate, accounting for only 15.4% after 24 hr and 49% after 2 days. During the subsequent reaction period the increase in octane was no more than 10% that of the first 48 hr. A compound which was not apparent in the iodobutane reaction appeared during the first day and then slowly increased for the first week. Its retention ratios were 1.38 (silicon rubber) and 1.68 (GE-SF96) and the ir spectrum of a gc separated sample was identical with that of N-methyl-N-(1-pentyl)aniline except for the lack of a band at 950 w and the presence of a band at 930 cm^{-1} w. The pmr spectrum had a multiplet of two major parts centered at δ 1.08 ppm (aliphatic CH_3 + CH_2's), a singlet at 2.74 (CH_3 on aryl N), a triplet at 3.18 (CH_2 on aryl N), and parts of the aromatic multiplet centered at 6.49 and 6.97 ppm. The relative integrated intensity ratio for these peaks was 7:3:2:3:2, respectively. Both spectra and retention ratios are comparable with the data for N-methyl-N-(1-butyl)aniline.[3] On the basis of this assignment, yield were 3.0, 4.2, and 5.1% at 1, 2, and 7 days, respectively. A slightly greater amount of a second amine, N-methyl-N-(1-pentyl)aniline, was formed more gradually. This product with a retention ratio of 1.64 (silicon rubber) at 4 hr, 1, 2, and 7 days was produced in 3.6, 6.4, 9.2, and 10.6% yields, respectively. If higher molecular weight compounds were present, they were below the level of gc detection under the conditions employed.

Reaction of 1-Chlorobutane, N,N-Dimethylaniline, and Lithium.—A reaction was run using 10.3 ml (0.10 mol) of 1-chlorobutane and 0.91 g (0.13 g-atom) of lithium as described in the general procedure. Samples were taken and analyzed after 1.5, 5, and 18 hr, and 1, 2, 3, and 5 days. The chlorobutane present, retention ratio 0.115 (silicon rubber), decreased to one-quarter its initial amount during the first day and thereafter remained essentially constant. All of the products observed in the 1-bromobutane reaction were present in this reaction, but the yields were significantly lower. All reached maximum amounts after 2 days. *n*-Octane was present in 2.2% at 5 hr and in 3.6% after 1 day, and increased to 4.3% after 2 days. N-Methyl-N-(1-butyl)aniline was less than 2% at 24 hr and 2.5% at 2 days, while N-methyl-N-(1-pentyl)aniline was less than 1% and increased to 1.2% at these same two times. After 7 days, hexafluoroacetone was bubbled through the reaction for 6.5 hr. When this mixture was quenched with water and analyzed with gc, two major product peaks were observed. The first of these, retention ratios 1.14 (silicon rubber) and 1.15 (GE-SF96), was present in 6.4% yield, while the second, retention ratios 1.38 (silicon rubber) and 1.58 (GE-SF96), was formed in 82% yield. These peaks and melting points of collected products were identical with those of *m*- and *o*-(dimethylamino)phenylbistrifluoromethylcarbinol,[6] respectively.

General Procedure for α Alkylation of N,N-Dimethylaniline with Addition of 1-Iodobutane at 24 Hr.—These reactions used the amounts and general procedure described above. All reactions were carried out at 20 ± 2° by running tap water through a copper coil in an insulated water bath. Heating from the magnetic stirrer, surroundings, and exothermic reaction was thus limited. After 24 hr a sample was removed and the mixture was cooled in an ice bath for 15 min before adding 11.4 ml (0.10 mol) of 1-iodobutane. Reaction was allowed to continue for 2 hr (total time 26 hr) in the ice bath. A sample was then taken and the ice bath was replaced with the original water bath. A final sample was taken after 2 hr (total time 28 hr) in the water bath. Gc analysis was used for both qualitative and quantitative determination of N-methyl-N-(1-pentyl)aniline, which was the only product monitored in this series of reactions. Identification was based on comparisons with results from previous experiments. The ice cooling procedure, applied to reactions of the chloro-, bromo-, and iodobutane, was based on the observations in the following example experiments. The results of this series of reactions are summarized in Table I.

Reaction of 1-Chlorobutane, N,N-Dimethylaniline, and Lithium with Addition of 1-Iodobutane.—1-Chlorobutane (10.3 ml, 0.10 mol) was allowed to react with lithium (0.74 g, 0.11 g-atom) and N,N-dimethylaniline (38.1 ml, 0.30 mol) as described in the general procedure with addition of 1-iodobutane (11.4 ml, 0.10 mol) to the cooled mixture at 24 hr.

The reaction was smooth and controllable, giving the yields of N-methyl-N-(1-pentyl)aniline listed in Table I. When the reaction was run without ice cooling prior to iodobutane addition [*i.e.*, run in water bath (20°) for all stages of reaction], 1 min after iodobutane addition the reaction became quite vigorous and exothermic. The color of this reaction rapidly changed from the usual dark brown to a bright coral and an unidentified coral solid separated on prolonged standing (1 day). Yields of N-methyl-N-(1-pentyl)aniline were approximately two-thirds those obtained when cooling was applied prior to iodobutane addition (see Table I). Therefore, the precooling procedure was used in reactions with 1-bromo- and 1-iodobutane.

Registry No.—N,N-Dimethylaniline, 121-69-7; N-methyl-N-(1-pentyl)aniline, 3299-39-6.

Truxanes. II.[1a] Stereoisomerism in the 1,1′-Disubstituted *syn,trans*-Truxane System[1b]

F. L. SETLIFF, A. G. ANASTASSIOU, AND G. W. GRIFFIN[1c]

Departments of Chemistry, Tulane University and Louisiana State University, New Orleans, Louisiana, and Yale University, New Haven, Connecticut

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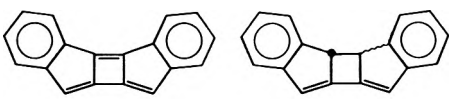
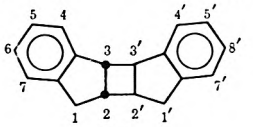
A number of potential precursors for the novel 18-π-electron system dibenzo[*a,g*]tricyclo[5.3.0.0^{2,6}]decapentaene have been prepared. Several stereoisomeric modifications of these precursors (1,1′-disubstituted *syn,trans*-truxanes) and their reaction products have been isolated. A general method for determining stereochemistry at the 1 and 1′ positions in this series of compounds is also presented.

In continuing our efforts to generate diene **2**, a direct progenitor of the potentially aromatic dibenzo[*a,g*]tricyclo[5.3.0.0^{2,6}]decapentaene **1**, we have prepared several 1,1′-disubstituted *syn,trans*-truxanes in a variety of stereochemical modifications. At this time we wish to describe the formation of these truxane derivatives and to demonstrate how nmr spectroscopy may be utilized to differentiate the various possible stereoisomeric forms of these compounds.



1 **2**

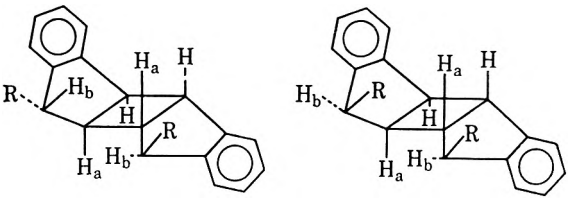


3

A potentially useful precursor for **1**, namely *syn,trans*-truxane (**3**), is readily accessible through photosensitized dimerization of indene.[1a] In principle, 1,1′-disubstituted truxanes may assume one of the three stereoisomeric modifications depicted in **4**, **5**, and **6**, to which we will henceforth refer as *exo,exo*, *exo,endo*, and *endo,endo*, respectively.

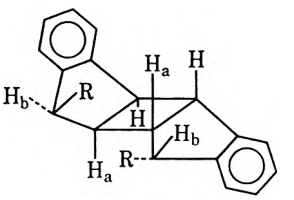
We have found that nmr spectroscopy serves as a valuable tool in distinguishing among these 1,1′-disubstituted *syn,trans*-truxanes. Inspection of simple molecular models indicates that in the *exo,exo*-substituent orientation the dihedral angle between the benzylic proton H_b and the adjacent cyclobutane proton H_a is on the order of 100°, while the corresponding angle for these protons in the *endo,endo*-disubstituted arrangement is nearly 0°. The coupling constants associated with these dihedral angles should be less than 2 Hz for the *exo,exo* orientation and approximately 8 Hz for the *endo,endo* disposition.[2] One would therefore expect that the nmr spectra of **4**, **5**, and **6** should display H_b as a 2 H singlet, 1 H singlet and 1 H doublet, and a 2 H doublet, respectively. This expectation is borne out by the observed spectral properties of the three dimethoxytruxanes **4b**, **5b**, and **6b** (Table I).

Treatment of the *exo,exo*-dibromide **4a**[1a] (H_b, 2 H singlet at τ 4.45[3]) with various bases commonly employed to bring about dehydrohalogenation failed to afford the desired diene **2**.[4] In some cases low yields of substitution products were obtained. For example, ethyl ethers **5a** and **6a** and methyl ethers **5b** and **6b** were isolated when the dibromide was treated with ethanolic and methanolic potassium hydroxide, respectively.



exo,exo **4a**, R = Br
b, R = OCH_3
c, R = I
d, R = $N^+(CH_3)_3I^-$
e, R = $N^+(CH_3)_3OH^-$
f, R = OTs
g, R = OH
h, R = Cl

exo,endo **5a**, R = OCH_2CH_3
b, R = OCH_3
c, R = $N(CH_3)_2$
d, R = $N^+(CH_3)_3I^-$
e, R = $N^+(CH_3)_3$-OH^-
f, R = $N(CH_3)_2$ (O)



endo,endo **6a**, R = OCH_2CH_3
b, R = OCH_3
c, R = Cl

The production of the *endo,endo*-diethers **6a** and **6b** from the *exo,exo*-dibromide **4a** is not unexpected in view of the strongly nucleophilic, nonpolar medium employed which should favor backside displacement. The observed formation of *exo,endo* products **5a** and **5b** is mechanistically less obvious, especially since it was demonstrated by separate experiment that epimerization of the corresponding *endo,endo*-ethers under the conditions of the reaction does not occur.

The remaining isomeric 1,1′-dimethoxytruxane **4b** was prepared by methanolysis of **4a** in a more polar medium (aqueous methanol containing sodium car-

(1) (a) For the first paper in this series, see A. G. Anastassiou and G. W. Griffin, *J. Org. Chem.*, **33**, 3441 (1968). (b) Abstracted from the Ph.D. dissertations of F. L. S. (Tulane University, 1966) and A. G. A. (Yale University, 1963). (c) To whom inquiries and reprint requests should be addressed at the Department of Chemistry, Louisiana State University in New Orleans, Lakefront, New Orleans, La. 70122.

(2) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(3) The H_a and the methine benzylic (3,3′) cyclobutane protons in **4a** appear as 2 H doublets at τ 7.00 and τ 6.25, respectively. That all aliphatic proton peak assignments are correct is supported by the spectrum of *exo,exo*-1,1′-dibromo-3,3′-dichloro-*syn,trans*-truxane in which both H_b (τ 4.55) and H_a (τ 7.16) appear as clean singlets: U. Heep and G. W. Griffin, unpublished results.

(4) Treatment of **4a** with potassium amide in liquid ammonia or **4c** with potassium *t*-butoxide resulted in opening of the cyclobutane ring to yield *sym*-dibenzfulvalene; see A. G. Anastassiou, F. L. Setliff, and G. W. Griffin, *J. Org. Chem.*, **31**, 2705 (1966).

TABLE I

CHEMICAL SHIFTS (τ) FOR THE BENZYLIC (H_b) AND METHOXY PROTONS OF THE THREE 1,1′-DIMETHOXY-*syn,trans*-TRUXANES

Compd	H_b	OCH_3
exo,exo **4b**	5.52 (2 H singlet)	6.76 (6 H singlet)
exo,endo **5b**	5.30 (1 H singlet)	6.45 (3 H singlet)
	4.95 (1 H doublet), J = 8 Hz	6.70 (3 H singlet)
endo,endo **6b**	5.10 (2 H doublet), J = 8 Hz	6.38 (6 H singlet)

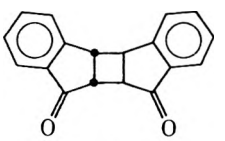
bonate). Reaction under these conditions probably proceeds through initial heterolysis of the C—Br bonds followed by entry of the nucleophilic solvent from the least hindered *exo* side.

Treatment of the dibromide **4a** with sodium iodide in acetone produced the *exo,exo*-diiodide **4c** (H_b, 2 H singlet at τ 4.25). The over-all retention of stereochemistry observed in this transformation suggests that a double displacement[5] has occurred at the 1 and 1′ positions, which is not unexpected in view of the relatively low polarity of the reaction medium. It thus appears that any *endo*-iodides introduced initially are readily displaced to give ultimately the thermodynamically most favorable *exo,exo* modification.

Treatment of **4c** with alcoholic hydroxide, as in the case of **4a**, led to ethers **5b**, **6b**, and **5a**, **6a** rather than **2**.[4] Treatment of **4c** with aqueous trimethylamine produced the *exo,exo* bisquaternary iodide **4d**, which in turn was converted into the *exo,exo* Hofmann base **4e**. Pyrolysis of **4e** under a variety of conditions yielded only intractable materials.

The failure to obtain **2** under strongly basic conditions is perhaps better ascribed to its inability to withstand the reaction conditions rather than to its resistance to form.[6] Indeed, from a stereochemical standpoint the *exo,exo* derivatives are potentially the most promising precursors for **2**, since the leaving groups (H_a and R) can assume the favorable coplanar transition state required for smooth bimolecular elimination, even though a *cis* elimination is required.

Since the ease with which tosylates undergo *cis* bimolecular elimination had been demonstrated previously,[7] we next undertook the synthesis of the *exo,exo*-ditosylate **4f**, in the hope that this compound would respond favorably to mild elimination conditions. The dibromotruxane **4a** was first converted into the *exo,exo*-diol **4g** by treatment with sodium carbonate in aqueous acetone. An SN1 displacement similar to that proposed for the formation of **4b** is undoubtedly operative in the present case as well. Oxidation of **4g** to the known[1a] *syn,trans*-truxone **7** confirmed that the gross structure had been retained.



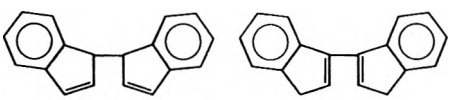
7

Attempts to prepare the ditosylate from this diol in pyridine solution at 0° resulted in the unexpected formation of the *endo,endo*-dichloride **6c** (H_b, 2 H doublet, J = 8 Hz, centered at τ 4.37). The dichloride is presumably formed *via* SN2 displacement of the evanescent ditosylate by chloride present as pyridinium hydrochloride. The facile conversion of **6c** into *exo,exo*-diiodide **4c** on treatment with sodium iodide in acetone provided a useful cross check of gross structure.

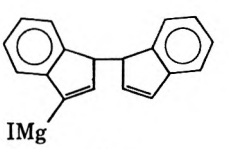
To validate further the applicability of nmr spectroscopy to the characterization of these systems, the *exo,exo*-dichloride **4h** was prepared from the diol **4g** with thionyl chloride in pyridine. The dichloride, which was anticipated to have *exo,exo* stereochemistry,[8] exhibited the expected singlet for H_b (τ 4.62), and was converted into the *exo,exo*-diodide **4c** by sodium iodide in acetone. Double displacement by iodide to produce the most thermodynamically favorable *exo,exo* modification is apparently also operative here.

Our observations on the 1,1′-bisquaternary salt **5d** further substantiates our contention that the *exo,exo* configuration is favored thermodynamically in these *syn,trans*-truxane systems. The *exo,endo* bisquaternary iodide **5d**,[9] prepared by exhaustive methylation of the amine **5c**, which was in turn obtained by aminolysis of the dibromide **4a**,[10] was epimerized (80%) to the *exo,exo* modification **4d** on treatment with boiling aqueous potassium hydroxide. It is not surprising that equilibration under such conditions should favor the less sterically crowded *exo,exo* isomer. The quaternary iodide **4d**, which had been previously prepared from the diiodide **4c** and aqueous trimethylamine, exhibited the characteristic singlet for H_b (τ 4.85).

An interesting transformation was observed in one experiment designed to yield **2** *via* halogen–metal interchange. Dibromide **4a** reacted smoothly with methylmagnesium iodide[11,12] to yield 1,1′-biindenyl (**8**), which was identified by its spectral properties and the consistency of its melting point with the reported value.[13]



8 9



10

Furthermore, **8** underwent facile isomerization to the conjugated 3,3′-biindenyl (**9**) on treatment with meth-

(5) Multiple displacements involving iodide are not uncommon; *cf.* E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1959, p 262.

(6) Although **2** would appear to suffer from considerable strain, we had hoped that elimination would be accompanied by epimerization at a methine benzylic (3,3′) center to offer some relief of strain.

(7) C. H. DePuy, R. D. Thurn, and G. F. Morris, *J. Amer. Chem. Soc.*, **84**, 1314 (1962).

(8) Although inversion of configuration might have been expected to occur in this instance owing to the presence of pyridine, internal displacement of the intermediate chlorosulfite ester resulting in ultimate retention of configuration, as was apparently the case here, is commonly observed if phenyl groups are attached to the carbon atom undergoing reaction; *cf.* W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

(9) Neither treatment of this quaternary iodide with a variety of bases nor pyrolysis of the derived quaternary hydroxide **5e**, or amine oxide **5f**, gave any evidence of the generation of diene **2**.

(10) The course of this transformation remains to be established.

(11) Methyllithium and phenyllithium led to intractable materials.

(12) The successful use of methylmagnesium iodide as a base in elimination reactions has been demonstrated previously: M. S. Kharasch, F. Englemann, and W. H. Urry, *J. Amer. Chem. Soc.*, **66**, 365 (1944).

(13) C. Courtot, *Ann. Chim.*, **10** (4), 79 (1915).

oxide, a conversion which had been observed previously by other workers.[14]

Two reasonable mechanistic alternatives for the formation of **8** from **4a** include either 1,4 elimination of HBr by methide followed by Grignard exchange yielding **10**, then hydrolysis of the Grignard derivative in work-up or 1,4 elimination initiated by nucleophilic attack of methide upon a bromine atom.

Experimental Section[15,16]

Reaction of the *exo,exo*-Dibromide 4a[1a] with Ethanolic Potassium Hydroxide. Formation of the *endo,endo*- and *exo,endo*-Ethers 6a and 5a.[17]—To a solution of potassium hydroxide (10.0 g) in absolute ethanol (50 ml) maintained at room temperature was added 2.0 g (6.8 mmol) of the dibromide **4a**. The resulting suspension was stirred at 75° for 20 hr. Removal of the volatile solvent under reduced pressure afforded a dark residue which was suspended in water (50 ml) and extracted with ether (two 75-ml portions). The ether extracts were combined and washed in turn with 5% hydrochloric acid (100 ml) and water (200 ml). The ether solution was dried over sodium sulfate and evaporated. The residual dark orange oil was dissolved in the minimum amount of benzene, and the benzene solution was applied to a 2 × 30 cm chromatographic column packed with neutral aluminum oxide. Elution was performed with 1:4 benzene–cyclohexane (200 ml), 1:2 benzene–cyclohexane (150 ml), and benzene (250 ml). Evaporation of the first 300 ml of eluted solvent (collected in 50-ml fractions) afforded the crude *endo,endo* isomer **6a** as a yellow-orange solid. Recrystallization from methanol (Norit) provided pure material (140 mg, 11%) as fluffy white needles: mp 136–138°; ir 1345, 1120, and 750 cm^{-1}; nmr ($CDCl_3$) τ 2.68 (s), 4.91 (d), 6.2 (q), 6.47 (m), and 8.7 (t) in the respective area ratio of 4:1:2:2:3.

Anal. Calcd for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.40; H, 7.50.

Evaporation of the later-eluted solvents (300 ml) yielded yellow oils which were combined, dissolved in hot methanol, and filtered free of insoluble material. The filtrate was evaporated to leave a slightly colored solid, which upon recrystallization from a small amount of methanol provided the pure *exo,endo* isomer **5a** (70 mg, 6%) as a white solid: mp 94–96°; ir 1345, 1128, 1110, 1090, 760, and 748 cm^{-1}; nmr ($CDCl_3$) τ 2.65 (m), 4.91 (d), 5.20 (s), 6.2–6.9 (m), 7.2 (t), and 8.5–9.0 (two overlapping triplets) in the area ratio of 8:1:1:7:1:6.

Anal. Calcd for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.25; H, 7.36.

Treatment of the *exo,exo*-Dibromide 4a with Methanolic Potassium Hydroxide. Formation of *endo,endo*- and *exo,endo*-Ethers 6b and 5b.[17]—The dibromide **4a** (1.5 g, 3.85 mmol) was added at room temperature to a solution of 10.0 g of potassium hydroxide in dry methanol (distilled from magnesium turnings). The resulting mixture was stirred at the reflux temperature for 20 hr. A small amount of inorganic material was removed by filtration and the filtrate taken to near dryness on a rotary evaporator. The residual material was suspended in water (30 ml) and extracted with two 50-ml portions of ether. The ether extracts were combined, washed successively with 5% hydrochloric acid and water (100 ml each), and dried over sodium sulfate; the volatile solvent was evaporated. The residual yellow-orange oil was dissolved in a minimum amount of benzene and the resulting solution applied to a 2 × 30 cm column packed with neutral aluminum oxide. Elution was performed with 1:4 benzene–cyclohexane (100 ml), 1:2 benzene–cyclohexane (100 ml), 1:1 benzene–cyclohexane (100 ml), and pure benzene (300 ml). Evaporation of the first 300 ml of eluted solvent afforded the crude *endo,endo*-diether **6b** as a white solid. Recrystallization from a small amount of 95% ethanol provided pure material (145 mg, 12%) as white needles: mp 115–116°; ir 1365, 1110, 1100, 755, and 740 cm^{-1}; nmr ($CDCl_3$) τ 2.65 (s), 5.10 (d), 6.38 (s), and 6.55 (m) in the area ratio of 4:1:3:2.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.19; H, 6.85. Found: C, 82.22; H, 6.98.

Evaporation of the subsequently eluted fractions afforded the *exo,endo* isomer **5b** as a clear, viscous oil which solidified on standing. Recrystallization from a small quantity of 95% ethanol provided pure material (105 mg, 8%) as small needles: mp 86–87°; ir 1360, 1110, 1080, 765, 750, and 730 cm^{-1}; nmr ($CDCl_3$) τ 2.6 (m), 4.95 (d), 5.3 (s), 6.2–6.8 (m), 6.45 (s), 6.70 (s), and 7.15 (t) in the respective area ratio of 8:1:1:3:3:3:1.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.19; H, 6.85. Found: C, 82.13; H, 7.00.

Methanolysis of the Dibromide 4a. Formation of the *exo,exo*-Dimethoxytruxane 4b.—To a stirred solution of the dibromide **4a** (1.5 g, 3.87 mmol) in 60 ml of methanol maintained at the reflux temperature was added dropwise a solution of sodium carbonate (1.5 g) in 20 ml of water. The resulting suspension was stirred under reflux for 24 hr. After concentration of the reaction mixture to a volume of approximately 15 ml, water (50 ml) was added and the resulting aqueous suspension extracted with ether (75 ml). The ether extract was dried over sodium sulfate and evaporated affording the crude diether. Recrystallization from aqueous ethanol provided white needles (850 mg, 75%): mp 76–78°; ir 1350, 1085, 760, and 750 cm^{-1}; nmr ($CDCl_3$) τ 2.55 (m), 5.22 (s), 6.40 (d), 6.76 (s), and 7.38 (d) in the respective area ratio of 4:1:1:3:1.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.19; H, 6.85. Found: C, 82.09; H, 6.99.

Reaction of the Dibromide 4a with Sodium Iodide. Preparation of the *exo,exo*-Diiodide 4c.—A mixture of **4a** (6.0 g, 15.4 mmol), sodium iodide (6.3 g, 42 mmol), and 100 ml of dry acetone (distilled from potassium carbonate) was heated under reflux with stirring for 1.5 hr. The reddish brown reaction mixture was cooled to room temperature, the precipitated sodium bromide was collected on a filter, and the filtrate was subjected to slow evaporation in an air stream. The solid material remaining was washed in turn with water (50 ml) and cold, absolute ethanol (100 ml). The light yellow solid decomposes[18] at 83–85°, but remains unmelted up to 300°. Two recrystallizations from cyclohexane afforded an analytical sample that decomposed at 83–85°: ir 760, 745, 615, and 495 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (s), 4.25 (s), 6.35 (d), and 6.95 (d) in the respective area ratio of 4:1:1:1.

Anal. Calcd for $C_{18}H_{14}I_2$: C, 44.60; H, 2.89; I, 52.48. Found: C, 44.82; H, 3.01; I, 52.70.

Treatment of the *exo,exo*-Diodide 4c with Trimethylamine. Formation of the *exo,exo* Bisquaternary Iodide 4d.—A mixture of the diiodide **4c** (1.0 g, 2.1 mmol) and 90% aqueous trimethylamine was maintained at 75° for 6 hr in an aerosol compatibility tube[19] equipped with coupling and needle valve. The reaction vessel was then cooled to 0° and opened; the solvent was allowed to evaporate at room temperature. The white solid remaining (0.6 g, 50%) melted at 240–244° dec. Two recrystallizations from 95% ethanol produced an analytical sample (mp 243–245° dec): ir 3475, 1475, 960, 885, 848, 788, 778, and 763 cm^{-1}; nmr [D_2O at 70°, $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$ as internal standard] τ 2.22 (m), 4.85 (s), 6.16 (broad), 7.69 (broad), and 7.01 (s) in the respective area ratio of 4:1:1:1:9.

Anal. Calcd for $C_{24}H_{32}N_2I_2$: C, 47.84; H, 5.31; N, 4.65. Found: C, 47.65; H, 5.49; N, 4.54.

The Hofmann base **4e** was generated by treatment of **4d** with silver oxide in the usual manner. The nmr spectrum of a 35% aqueous solution of **4e**, with $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$ as internal standard, exhibited signals at τ 2.09 (m), 4.61 (s), 6.02 (d), 6.60 (d), and 6.88 (s) in the respective area ratio of 4:1:1:1:9.

Pyrolysis of **4e** under vacuum in a preheated glass column led only to intractable materials.

Hydrolysis of the Dibromide 4a with Aqueous Sodium Carbonate. Formation of the *exo,exo*-1,1′-Dihydroxytruxane 4g.—To a stirred solution of the dibromide (3.0 g, 7.7 mmol) in 100 ml of acetone maintained at the reflux temperature was added dropwise over a 20-min period a solution of sodium carbonate (3.5 g) in 50 ml of water. The resulting mixture was stirred at the reflux

(14) F. Straus, R. Kuhnel, and R. Haensel, *Chem. Ber.*, **66**, 1847 (1933).

(15) All melting points are uncorrected. Infrared spectra were recorded in potassium bromide on either a Perkin-Elmer Model 337 or a Beckman IR-8 spectrophotometer. Ultraviolet spectra were obtained using a Perkin-Elmer model 202 ultraviolet-visible spectrophotometer. All nmr spectra were obtained on a Varian A-60 instrument at room temperature with tetramethylsilane as internal standard unless otherwise specified. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(16) In the description of nmr data the abbreviations s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet are employed.

(17) This same procedure also yields the two ethers from the diiodide **4c**.

(18) This iodide is extremely sensitive to light and turns brown on prolonged exposure; however, it may be stored indefinitely without decomposition in an opaque container at 0°.

(19) Fischer Porter Co., Lab Crest Scientific Division, Warminster, Penn.

temperature for 24 hr. The reaction mixture was then concentrated to a volume of approximately 15 ml (rotary evaporator), and the remaining suspension diluted with 50 ml of water. The water-insoluble material was collected on a filter, and the filtrate was extracted with two 100-ml portions of ether. The solid residue obtained on evaporation of the ether was combined with the solid material originally filtered, and the entire crude product was recrystallized from aqueous acetone to afford 1.55 g (77.5%) of pure truxanediol 4g: mp 159–161°; ir 3225 (broad), 1030, 755, 748, and 740 cm^{-1}; nmr (acetone D_6) τ 2.55 (m), 4.98 (s), 5.90 (broad), 6.45 (d), and 7.55 (d) in the respective area ratio of 4:1:1:1:1.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.67; H, 6.26.

Oxidation of the *exo,exo*-Diol 4g with Chromic Anhydride. Formation of *syn,trans*-Truxone 7.—A solution of the truxanediol (175 mg, 0.66 mmol) in pyridine (3 ml) was added over a 15-min period to a stirred suspension of the pyridine–chromic anhydride complex generated by adding 1.0 g of chromic anhydride to 10 ml of pyridine at 15°. The temperature of the reaction mixture was maintained at 20° during the course of the addition. After being stirred at room temperature for 18 hr, the dark solution was poured into water (150 ml), and the aqueous suspension extracted with 100 ml of ether. The ether extract was washed successively with 10% hydrochloric acid (50 ml) and water (100 ml), and dried over sodium sulfate. Removal of the volatile solvent provided the crude truxone 7 (80 mg, 46%) as a white solid, mp 218–222°. Pure material was obtained by recrystallization from methanol (mp 220–222°, lit.[18] mp 221–223°). The infrared spectrum was superimposable on that of authentic material,[18] and a mixture melting point determination showed no depression.

Treatment of the *exo,exo*-Diol 4g with *p*-Toluenesulfonyl Chloride. Formation of the *endo,endo*-Dichlorotruxane 6c.—To a stirred solution of the diol (1.5 g, 5.6 mmol) in 15 ml of dry pyridine (commercial Karl Fischer reagent redistilled from potassium hydroxide) maintained at 0° was added a precooled solution of 2.5 g of acid-free *p*-toluenesulfonyl chloride in 15 ml of dry pyridine in 1–2-ml portions over a period of 30 min. The resulting reaction mixture was stirred for 4 hr at 0–5° and subsequently allowed to warm gradually to room temperature where stirring was continued for an additional 4 hr. The orange solution was then poured into a mixture of 20 ml of concentrated hydrochloric acid, 20 ml of water, and 50 g of crushed ice, and the precipitated white solid was extracted with 150 ml of ether. The ether extract was washed successively with a saturated sodium bicarbonate solution (two 75 ml-portions) and water (100 ml), and dried over sodium sulfate. Removal of the ether (rotary evaporator) yielded the crude dichloride as a crystalline solid, which was washed free of a small amount of adhering oil with cold methanol. The solid material (75 mg, 4.5%) on recrystallization from methylcyclohexane melted at 219–221°: ir 1485, 1235, 845, 752, 746, and 660 cm^{-1}; nmr ($CDCl_3$) τ 2.62 (m), 4.38 (d), and 6.38 (m) in the respective area ratio of 4:1:2.

Anal. Calcd for $C_{18}H_{14}Cl_2$: C, 71.42; H, 4.65. Found: C, 71.60; H, 4.91.

Reaction of the Diol 4g with Thionyl Chloride. Formation of the *exo,exo*-Dichlorotruxane 4h.—Freshly distilled thionyl chloride (2 ml, 27.7 mmol) was added in small portions over a period of 30 min to a stirred solution of the diol (1.5 g, 5.7 mmol) in dry pyridine (Karl Fischer Reagent) maintained at 0–5°. The reaction mixture was allowed to warm gradually to room temperature, and stirring was continued for 6 hr. The dark reddish brown solution was then poured with stirring into 300 ml of ice water and the precipitated yellow solid extracted with 150 ml of ether. The ether extracts were washed in turn with 10% hydrochloric acid (two 75-ml portions) and water (100 ml) and subsequently dried over sodium sulfate. Removal of the ether (rotary evaporator) yielded the crude dichloride as a white solid. After being washed free of adhering oils with cold 95% ethanol the crude material (450 mg, 26.5%) was recrystallized from methylcyclohexane affording white crystals: mp 183–185°; ir 1480, 1240, 845, 769, 740, 700, 663, and 510 cm^{-1}; nmr ($CDCl_3$) τ 2.62 (s), 4.62 (s), 6.28 (d) and 7.10 (d), in the respective area ratio of 4:1:1:1.

Anal. Calcd for $C_{18}H_{14}Cl_2$: C, 71.42; H, 4.65. Found: C, 71.54; H, 4.70.

Formation of 4c from 4h upon Treatment with Sodium Iodide.—A mixture of the dichloride (270 mg, 0.9 mmol) and sodium iodide (400 mg, 2.6 mmol) in 20 ml of dry acetone was heated under reflux for 18 hr. The precipitated sodium chloride was collected on a filter, and the filtrate evaporated in an air stream. The residue was washed with cold, absolute alcohol and recrystallized from cyclohexane yielding 200 mg (46%) of *exo,exo*-1,1′-diiodo-*syn,trans*-truxane (4c) (dec pt 80–85°). The infrared spectrum was identical with that of authentic 4c.

Preparation of 4c from 6c with Sodium Iodide in Acetone.—By a procedure analogous to that described in the preceding experiment, the *endo,endo*-dichloride 6c (60 mg, 0.2 mmol) on stirring under reflux 8 hr with sodium iodide (150 mg, 1.0 mmol) in 15 ml of boiling acetone afforded 55 mg (57%) of the *exo,exo*-diiodide 4c.

Reaction of the Dibromide 4c with Excess Dimethylamine. Formation of the *exo,endo*-Bisdimethylaminotruxane 5c.—A mixture of the dibromotruxane 4a (6.0 g, 0.015 mol) and anhydrous dimethylamine (50 ml) was heated at 75° for 24 hr. An aerosol compatibility tube[19] equipped with coupling and needle valve served as the reaction vessel. The reaction mixture was cooled to 0°, the aerosol tube opened, and the excess dimethylamine was allowed to evaporate in an air stream. The residual dark brown viscous oil was dissolved in 20% aqueous hydrochloric acid (75 ml). The resulting acid solution was filtered and subsequently extracted with benzene (60 ml). The aqueous acid solution was then made basic with 10% potassium hydroxide solution. After being warmed to 50° to remove any residual dimethylamine, the oily, aqueous solution was extracted with ether (200 ml). The ether solution was dried over sodium sulfate, the volatile solvents were removed under reduced pressure, and 4.1 g (83%) of the crude amine 5c remained as a dark brown oil. Further purification was achieved by molecular distillation (95–100°, 0.2 mm): ir (neat, salt plates) 1480, 1455, 1025, and 740 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (m), 5.6–6.0 (m), 6.3–6.9 (m), 7.45 (unsymmetrical doublet), and 8.0 (s) in the respective area ratio of 8:2:3:7:6. A picrate generated in the normal manner melted at 209–210° dec after recrystallization from methanol.

Anal. Calcd for $C_{34}H_{32}N_8O_{14}$ (dipicrate): C, 52.57; H, 4.12; N, 14.43. Found: C, 52.30; H, 4.21; N, 14.31.

Oxidation of 5c with 30% Hydrogen Peroxide. Formation of the Bisamine Oxide 5f.—A solution of 30% hydrogen peroxide (65 ml), which had been precooled to −15°, was added in one portion to a stirred solution of the crude amine 5c (3.5 g) in 70 ml of 95% ethanol maintained at 0–5°. The resulting mixture was stirred at 5° for 30 min and allowed to warm to room temperature where stirring was continued for 90 hr. At this point the reaction mixture was neutral to phenolphthalein, indicating that oxidation was complete. The excess peroxide was decomposed by adding 10–20 mg of platinum black catalyst to the reaction mixture with subsequent stirring for 16 hr. The catalyst was removed by filtration and the light yellow filtrate was evaporated to dryness (rotary evaporator), affording the amine oxide as a yellow-orange glass (3.62 g, 94%). This material is extremely hygroscopic and turns to liquid on exposure to the atmosphere. A picrate generated in the normal manner melted at 173–173.5°.

Anal. Calcd for $C_{34}H_{32}N_8O_{16}$ (dipicrate): C, 50.49; H, 3.96; N, 13.86. Found: C, 50.64; H, 4.20; N, 13.78.

Pyrolysis of 5f under reduced pressure in a preheated glass column led only to intractable materials.

Quaternization of the Amine 5c. Formation of the *exo,endo* Bisquaternary Iodide 5d.—A solution of 8.0 g (0.025 mol) of the crude amine 5c and excess methyl iodide (10 ml) in absolute ethanol (100 ml) was heated under gentle reflux for 3 hr. The reaction mixture was then cooled to room temperature, and the crude quaternary salt which deposited was collected by filtration. Subsequent recrystallization from 95% ethanol (Norit) afforded 11.1 g (74%) of white crystalline material: mp 226–228°; ir 3450 (broad), 1475, 960, 880, 853, 785, 760, 750, and 722 cm^{-1}; nmr [D_2O at 70° $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$ as an internal standard] τ 2.3 (m), 4.62 (d), 4.84 (s), 6.49 (s), and 7.00 (s) in the respective area ratio of 8:1:1:9:9.[20]

Anal. Calcd for $C_{24}H_{32}N_2I_2$: C, 47.84; H, 5.31; N, 4.65. Found: C, 47.64; H, 5.26; N, 4.53.

Isomerization of the *exo,endo* Bisquaternary Iodide 5d to the *exo,exo* Configuration 4d.—The *exo,endo* quaternary salt 5d (15.5 g, 0.026 mol) was suspended in a solution of potassium hydroxide (12.5 g) in water (250 ml) and the resulting mixture heated under reflux for 24 hr. The gray solution was decolorized (Norit) and taken to dryness on a rotary evaporator. The

(20) The cyclobutane protons were not visible in the spectrum.

residual solid was recrystallized from 80% ethanol affording 12.3 g (80%) of the *exo,exo* quaternary salt **4d** as white needles, mp 243–245° dec. The ir spectrum was identical with that of the product obtained from the reaction of the *exo,exo*-diiodide **4c** with aqueous trimethylamine. A mixture melting point determination showed no depression.

Treatment of the Dibromide 4a with Methylmagnesium Iodide. Formation of 1,1′-Biindenyl (8).—Excess magnesium was quickly removed from a freshly prepared solution of methylmagnesium iodide generated from magnesium turnings (0.73 g, 0.03 g-atom) and methyl iodide (1.25 ml) in 15 ml of dry ether. A solution of the dibromotruxane **4a** (3.0 g, 7.7 mmol) in dry benzene (30 ml) was then added dropwise over a 15-min period with manual agitation. The temperature of the reaction mixture rose to 37° during the addition. The reaction mixture was then heated under gentle reflux for 19 hr. After being cooled to room temperature, the light yellow solution was shaken in turn with 30 ml of cold 10% hydrochloric acid and 100 ml of water, and finally dried over sodium sulfate. Removal of the volatile solvents under reduced pressure afforded a light yellow-orange amorphous solid which was boiled in 95% ethanol. The hot ethanolic solution was decanted from insoluble oils and then diluted with water until the solution became cloudy. On standing overnight at room temperature the alcoholic solution deposited 95 mg (5.3%) of 1,1′-biindenyl, mp 93–99°. A pure sample (mp 97–99°, lit.[13] mp 98°) was prepared by recrystallization from 95% ethanol: ir 1465, 803, 770, 760, 733, and 718 cm^{-1}; nmr ($CDCl_3$) τ 2.35–2.98 (m), 3.33 (d), 4.17 (d), and 5.85 (s) in the respective area ratio of 4:1:1:1.

Isomerization of 1,1′-Biindenyl (8) to 3,3′-Biindenyl (9).—To a solution of 1,1′-biindenyl (85 mg) in 2 ml of dry methanol was added 5 drops of a 5% potassium methoxide solution. The resulting reddish brown solution was boiled gently for 5 min and subsequently refrigerated at −10° for 1 hr. The precipitated yellow-brown solid was collected on a filter and recrystallized from petroleum ether (bp 60–90°) to afford 3,3′-biindenyl (55 mg, 65%) melting at 129–131° (lit.[14] mp 130–131°). The ir spectrum was identical in all respects with that of an authentic sample of 9 prepared by reductive dehalogenation of 1,1′-dibromo-3,3′-diindenylene.[14]

Registry No.—**4b**, 20286-93-5; **4c**, 10425-94-2; **4d**, 20286-95-7; **4g**, 20286-96-8; **4h**, 20286-97-9; **5a**, 20286-98-0; **5b**, 20286-99-1; **5c**, 20287-00-7; **5c**, dipicrate, 20287-01-8; **5d**, 20287-02-9; **5f**, dipicrate, 20287-03-0; **6a**, 20287-04-1; **6b**, 20287-05-2; **6c**, 20287-06-3.

Acknowledgment.—We are indebted to the National Science Foundation (Grants G-12759, G.P. 3764, and G.P. 2543) for financial support of this work.

Chemistry of Allene. IV. Catalyzed Cyclodimerization of Allene and a New Allene Pentamer

F. W. HOOVER AND R. V. LINDSEY, JR.

Contribution No. 1547 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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Allene undergoes cyclodimerization to 1,3- and 1,2-dimethylenecyclobutane in the vapor phase over phosphine-modified nickel carbonyls. A polymeric complex of composition $[p\text{-}(C_6H_5)_2PC_6H_4P(C_6H_5)_2 \cdot Ni(CO)_2]_x$ is a particularly effective catalyst. This same complex catalyzes the cyclomerization of allene in the liquid phase to a tetramer, a pentamer, and higher oligomers.

Catalyzed 1,2 cycloadditions involving carbon–carbon double bonds have previously been observed only with norbornadiene,[1] benzonorbornadiene,[2] a tetracyclononene,[2] and butadiene,[3] all in the liquid phase.

We now report the first example of such a metal-catalyzed cyclodimerization in the vapor phase and a novel type of catalyst for this reaction. Thus, 1,3- and 1,2-dimethylenecyclobutane, along with higher oligomers, are obtained when allene is passed over certain phosphine-modified nickel carbonyls at elevated temperatures.

Our most effective catalyst (catalyst I) is a complex of empirical composition $[(C_6H_5)_2PC_6H_4P(C_6H_5)_2 \cdot Ni(CO)_2]$, prepared by reaction of an equimolar mixture of 1,4-bis(diphenylphosphino)benzene and nickel tetracarbonyl. During the reaction, 2 mol of carbon monoxide are evolved/mol of the bisphosphine and the complex precipitates as a white powder of surprising thermal stability. The complex is presumed to be polymeric (linear or macrocyclic) from consideration of its stoichiometry and ligand geometry. The phosphorus–phosphorus distance in the ligand, which is of the order of 6 Å, is too large to permit chelate formation.

The closely related monomeric complex, $[(C_6H_5)_3P]_2Ni(CO)_2$, also catalyzes the cyclodimerization of allene in the vapor phase but is less effective, possibly because of lower thermal stability. It was previously reported[4] to catalyze the cyclomerization of allene in the liquid phase to trimers and higher oligomers, but not dimers.

Oligomerizations were conducted by passing allene diluted with helium over a mixture of catalyst and 20-mesh quartz in a tube attached directly to a gas chromatography column. With catalyst I at 200°, 61% of the allene was converted into volatile products containing 60% 1,3-dimethylenecyclobutane, 13% 1,2-dimethylenecyclobutane, and 27% trimers, mainly 1,2,4-trimethylenecyclohexane. With $[(C_6H_5)_3P]_2Ni(CO)_2$ as catalyst at 175°, 43% of the allene was converted into volatile products consisting of 11% 1,3-dimethylenecyclobutane, 4% 1,2 isomer, and 74% trimer. The dimers were positively identified by means of their retention times, infrared spectra, and proton magnetic resonance spectra. The trimer was identified by comparison with an authentic sample.

It is of interest that the predominant dimer in the catalyzed process is 1,3-dimethylenecyclobutane. In contrast, thermal dimerizations either in the liquid phase at about 140° or in the gas phase at 400–

(1) For a review, see G. N. Schrauzer, *Advan. Catal.*, **18**, 377 (1968).

(2) T. J. Katz, J. C. Carnahan, Jr., and R. Boecke, *J. Org. Chem.*, **32**, 1301 (1967).

(3) P. Heimbach and W. Brenner, *Angew. Chem. Intern. Ed. Engl.*, **6**, 800 (1967).

(4) R. E. Benson and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.*, **81**, 4247 (1959).

600° give 1,2-dimethylenecyclobutane as the principal isomer.[5]

The dimers are quite stable and are essentially unchanged when passed over catalyst I at 225°. However, little trimer is recovered under these conditions. No oligomerization was observed when allene was passed over quartz at 200° in the absence of catalyst.

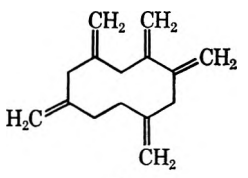
On a preparative scale, the catalyzed oligomerization is highly exothermic and difficult to control. It is advantageous to use very low ratios of nickel complex to inert support and either to dilute the allene with nitrogen or to operate under reduced pressure. Even with these precautions, the relative amounts of products, particularly the ratio of dimers to trimers, varied considerably and conversions into volatile products were generally lower than those reported above. In a typical run at 200° with a nitrogen/allene ratio of 5:1 about 10 g of volatile product/g of catalyst I was formed before activity was lost, presumably because of buildup of nonvolatile products.

The addition of carbon monoxide to the allene inhibits the reaction. However, reaction resumes when the addition is stopped. This indicates that allene cannot compete favorably with carbon monoxide for coordination sites on nickel.

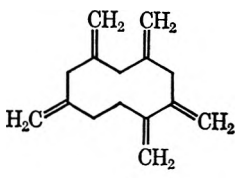
We have also examined the reaction of allene with catalyst I in the liquid phase to complete the comparison with $[(C_6H_5)_3P]_2Ni(CO)_2$. The products obtained were a tetramer, a pentamer, and higher boiling oligomers. No dimers were observed.

The tetramer is identical with the tetramethylenecyclooctane obtained previously with $[(C_6H_5)_3P]_2Ni(CO)_2$ catalyst.[4]

The pentamer, which is different from the one of undetermined structure obtained with $[(C_6H_5)_3P]_3$-RhCl catalyst,[6] has been assigned structure **8a** or **8b** on the basis of the following spectral evidence.[7] Mass spectroscopy gave the parent peak of 200 required for the pentamer. The ultraviolet spectrum showed λ_{max}^{EtOH} 235 mμ (ε 5140), consistent with one conjugated diene group. Both the near-ir and nmr spectra indicated an equal number of hydrogens on saturated and unsaturated carbon atoms. The nmr spectrum determined in $CDCl_3$ showed peaks at δ 2.28 (4 H), 2.80 (2 H), 3.00 (4 H), 4.82 (4 H), 4.91 (4 H, broad), and 5.19 (2 H, triplet J = 2 Hz). This spectrum clearly established the presence of ten vinylic and ten allylic protons, consistent only with a pentamethylenecyclodecane structure. On the basis of established[5] chemical-shift correlations, the peaks at δ 2.28 can be related to the four singly allylic protons in **8a** or **8b** and the peaks at 2.80 and 3.00 to six doubly allylic protons. The ir spectrum showed strongest absorptions at 3100, 2990, 2920, 2860, 1650, 1600, and 890 cm^{-1}. Neither the ir nor the nmr spectrum suggests the presence of CH_2=CH– or –CH=CH– groups.



8a



8b

Experimental Section[8]

Reaction of 1,4-Bis(diphenylphosphino)benzene with Nickel Tetracarbonyl. Preparation of Catalyst I.—To a solution of 22.3 g (0.05 mol) of 1,4-bis(diphenylphosphino)benzene[9] and 600 ml of tetrahydrofuran was added 8.5 g (0.05 mol) of $Ni(CO)_4$ in 100 ml of tetrahydrofuran at 25°. After the initial rapid carbon monoxide evolution had subsided, the reaction was completed by heating the mixture for 1 hr at 65°. A total of 0.10 mol of CO was liberated. The product separated as a white, powdery solid and was collected by filtration: yield 25.4 g (91%). *Anal.* Calcd for $C_{32}H_{24}NiO_2P_2$: C, 68.4; H, 4.3; Ni, 10.4. Found: C, 68.1; H, 4.8; Ni, 10.0.

On thermogravimetric analysis, catalyst I showed a weight loss of only 5% when heated slowly to 200°. Differential thermal analysis under N_2 showed a shallow exotherm near 165° with the degradation endotherm at 265–290°.

Vapor Phase Cyclization of Allene.—Vapor phase cyclization of allene was conducted in a 290 × 13 mm i.d. Inconel tube attached to a gas chromatography column packed with 1,2,3-tris(2-cyanoethoxy)propane on firebrick. The tube was packed with an intimate mixture of catalyst (3 g) and 20-mesh quartz (30 ml). Allene (1–4 ml) contained in glass loops fitted with a four-way 2V-bore stopcock was carried into the reactor with helium. The dimers and trimers were identified by their retention times and by comparison of their ir spectra and/or nmr spectra with those of authentic samples.

On a preparative scale, an allene–nitrogen mixture (1:5) was passed over a mixture of 1 g of catalyst I and 40 ml of 30-mesh quartz in a 450 × 25 mm o.d. Pyrex tube fitted with a central thermocouple well. The catalyst bed was heated to 195° and the rate of flow was then adjusted to keep the temperature inside the catalyst bed below 225°. During about 2.5 hr, 11 g of allene oligomers and about 14 g of unreacted allene were collected. An undetermined amount of tar remained on the catalyst, which gradually became deactivated. Gas chromatographic analysis of the oligomers using a column packed with dimethyl sulfolene on firebrick showed the presence of 30% 1,3 dimer, 8% 1,2 dimer, and 42% trimers, mainly 1,2,4-trimethylenecyclohexane. These were separated by preparative gas chromatography and characterized as follows.

1,3-Dimethylenecyclobutane: ir (gas phase) 3040 (=CH), 2920 (CH), 1660 (C=C), and 880 (=CH_2) cm^{-1}; nmr (neat) δ 3.27 (m, 4, J = 2.5 Hz, CH_2) and 4.85 (m, 4, J = 2.5 Hz, =CH_2).

1,2-Dimethylenecyclobutane: ir (gas phase) 3120 (C=CH), 3280 (CH), 1670 (C=C), and 880 (=CH_2) cm^{-1}.

1,2,4-Trimethylenecyclohexane: ir (neat) 3120 (C=CH), 3280 (CH), 1640 (C=C), and 880 (=CH_2) cm^{-1}

Liquid Phase Cyclization of Allene with Catalyst I.—A mixture of 40 g of allene, 50 ml of tetrahydrofuran, and 0.5 g of catalyst I was heated in a 400-ml Hasteloy C bomb for 8.5 hr at 100–124°. The reaction mixture was filtered and the filtrate was distilled to obtain 13 g of product, bp 80–100° (0.1 mm), and 15.9 g of higher boiling residue. Redistillation gave 3 g of tetramethylenecyclooctane,[4] bp 52° (2 mm), and 10 g of pentamer, bp 90° (2 mm): mass spectrum, m/e (rel intensity), 200 (7), 185 (35), 172 (67), 157 (87), 143 (97), and 129 (100); ir (cm^{-1}) 3100, 2990, 2920, 2860, 1650, 1600, 890; uv max (C_2H_5OH) 235 mμ (ε 5140); near-ir (CCl_4) 6120 cm^{-1} (intensity indicates one =CH_2 per 37–44 mol wt).

Registry No.—Allene, 463-49-0; 1,3-dimethylenecyclobutane, 2045-78-5; 1,2-dimethylenecyclobutane, 14296-80-1; 1,2,4-trimethylenecyclohexane, 14296-81-2; **8a**, 20628-85-7; **8b**, 20628-86-8.

(5) For recent reviews of allene oligomerizations, see (a) B. Weinstein and A. H. Fenselau, *J. Chem. Soc., C*, 368 (1967). and (b) B. Weinstein and A. H. Fenselau, *J. Org. Chem.*, **32**, 2278 (1967).

(6) F. N. Jones and R. V. Lindsey, Jr., *ibid.*, **33**, 3838 (1968).

(7) While our manuscript was in preparation, S. Otsuka, A. Nakamura, K. Tani, and S. Ueda [*Tetrahedron Lett.*, 297 (1969)] reported two new allene pentamers. One of these, which was obtained with a nickel catalyst, was assigned structure **8a** (1,2,4,6,9-pentamethylenecyclodecane). The properties of our pentamer are in quite close agreement with those reported.

(8) Infrared spectra (linear in wavelength) were recorded using a Perkin-Elmer Model 21 spectrophotometer with sodium chloride prism. Nmr spectra were determined with tetramethylsilane as internal standard using a Varian A-60 instrument.

(9) D. L. Herring, *J. Org. Chem.*, **26**, 3998 (1961).

The Synthesis of Olefins from β-Hydroxyphosphonamides. Stereochemistry and Extension to the Formation of Conjugated Dienes

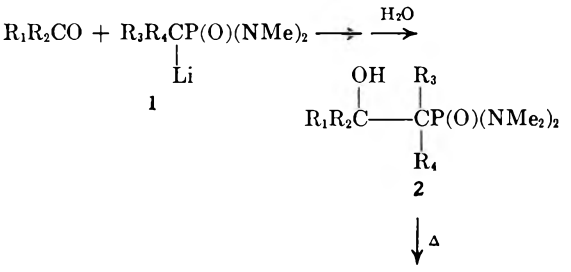
E. J. COREY AND DAVID E. CANE

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received December 17, 1968

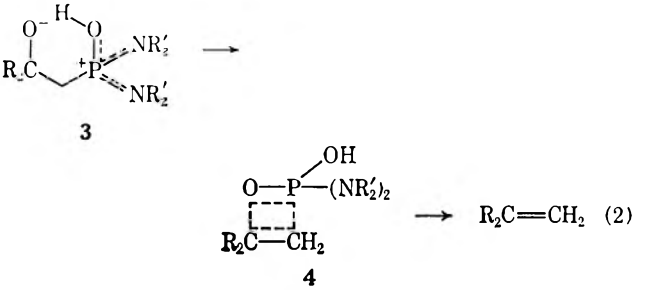
The thermal decomposition of β-hydroxyphosphonamides to olefins has been shown to involve preferential *cis* elimination. The phosphonamide route to olefins has also been extended to conjugated dienes using a modified phosphonamide **13** in which the bulk of the diamide is minimized so as to allow α attack on the corresponding anion by unhindered ketones and aldehydes. The resulting adducts are converted into dienes by thermal decomposition at 80–120°.

β-Hydroxyphosphonamides, available by reaction of α-lithiophosphonamide derivatives with aldehydes or ketones or by reduction of β-ketophosphonamides, undergo decomposition to olefins stereospecifically upon heating in refluxing benzene or toluene[1] (eq 1). We



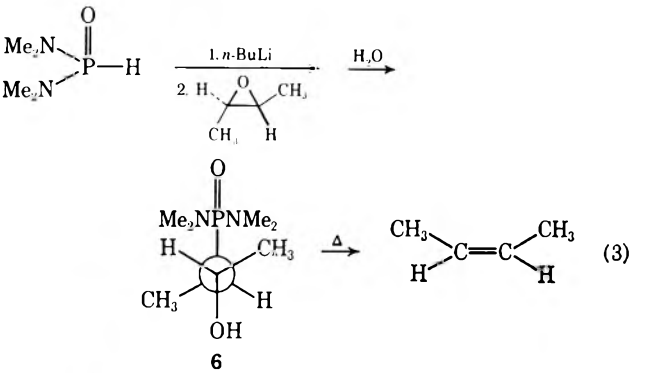
$$(Me_2N)_2PO_2H + R_1R_2C{=}CR_3R_4 \quad (1)$$

have now demonstrated that the decomposition reaction is a *cis* elimination and that the phosphonamide reaction may be extended to the synthesis of dienes. If the decomposition of β-hydroxyphosphonamides to form olefins were to proceed *via* betaines of type **3**, which should be susceptible to cycloelimination of the sort already established for the Wittig reaction itself and also for the related betaines from β-hydroxysulfinamides,[2] a *cis*-elimination pathway would be expected (eq 2)

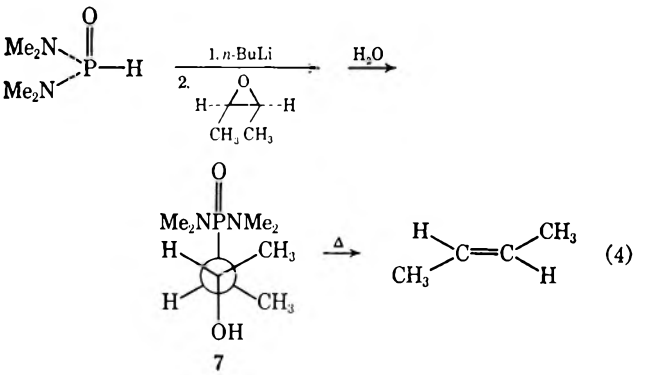


$$\rightarrow R_2C{=}CH_2 \quad (2)$$

As a first step in these studies, we undertook the synthesis of two diastereomeric β-hydroxyphosphonamides of known geometrical configuration which by thermal decomposition would generate isomeric olefins of known stereochemistry. The report by Normant[3] that the diamidophosphite anion (**5**) reacts with a number of alkyl halides to give the corresponding alkylphosphonodiamides, the products of P alkylation, suggested that such an anion might react with a suitable epoxide to produce a β-hydroxyphosphonamide, stereochemically pure and of unambiguous configuration. *cis*- and *trans*-2,3-oxidobutanes were chosen as the substrates. Both are readily available in high purity from the corresponding olefins and are sufficiently unhindered to allow attack by bulky nucleophiles. As illustrated below, when lithium diamidophosphite, generated in tetrahydrofuran by addition of *n*-butyllithium to a solution of bis(dimethylamino)phosphorous acid, was allowed to react with the *trans*- and *cis*-2,3-oxidobutanes, the diastereomeric displacement products **6** and **7**, respectively, were formed (eq 3 and 4). These diastereomers are readily distinguishable by nmr spectroscopy.[4]



(3)



(4)

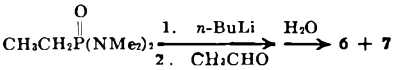
The stereochemistry of olefin formation from **6** and **7** was easily demonstrated. Thermal decomposition of **7** gave a product which was shown by vapor phase

(1) (a) E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5652, 5653 (1966); (b) E. J. Corey and G. T. Kwiatkowski, *ibid.*, **90**, 6816 (1968); (c) E. J. Corey *Pure Appl. Chem.*, **14**, 19 (1967).

(2) E. J. Corey and T. Durst, *J. Amer. Chem. Soc.*, **90**, 5553 (1968).

(3) H. Normant, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1050 (1967).

(4) Generation of a mixture of **6** and **7** by an alternative, nonstereospecific method gave rise to an nmr spectrum which was completely equivalent to a superposition of the spectra of **6** and **7**.

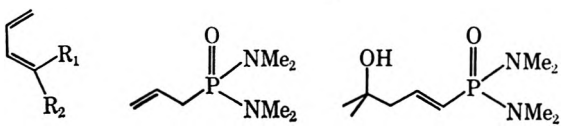


chromatography (vpc) to be greater than 99% *trans*-2-butene, while similar thermolysis of **6** gave 96% *cis*- plus 4% *trans*-2-butene. These reactions were carried out at 80° in toluene in the presence of calcium carbonate–silica gel, necessary to neutralize the acidic phosphoric amide as it is formed and prevent isomerization of the olefinic products. These data clearly indicate a strong preference for *cis* elimination.

As a further test of the *cis*-elimination pathway, *trans*-2-hydroxy bis(dimethylamino)phosphonylcyclohexane (**8**) was synthesized from cyclohexene oxide. Elimination by a *cis* mechanism would now be extremely unfavorable, since it would lead to at least transient formation of the unknown and highly strained *trans*-cyclohexene. On the other hand, a *trans* elimination, if it were to take place at all, would lead directly to *cis*-cyclohexene. In accord with prediction, thermolysis of **8** at 100° for 72 hr, conditions more than sufficient to bring about olefin formation in acyclic β-hydroxyphosphonamides, yielded less than 0.01% cyclohexene. Under drastic conditions (170° for 20 hr) the thermolysis of **8** led to cyclohexene in 25% yield. This result could mean that *trans* elimination can occur at sufficiently high temperatures or that high temperatures cause isomerization of **8** to the *cis* isomer, *e.g.*, by cleavage of the α,β bond (reverse Wittig) and recyclization.

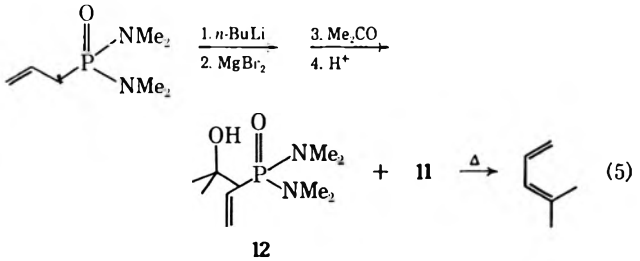
Diene Synthesis.—In order to probe further the generality and limitations of the phosphonamide olefin synthesis, we turned our attention to the possibility of synthesizing 1,1-disubstituted butadienes of type **9** by means of allylphosphonamides.

N,N,N′,N′-Tetramethylallylphosphonodiamide (**10**), when treated with *n*-butyllithium followed by acetone, gave exclusively the product of carbon attachment γ to the phosphorus atom, **11**. This product was stable to thermolysis under the standard conditions for olefin synthesis.



9 **10** **11**

An attempt was made to control the position of electrophilic attack by the addition of Lewis acids so as to force the incoming carbonyl group to become attached selectively to the carbon α to the phosphorus. Formation of the organozinc or organocadmium reagents, by the addition of zinc chloride or cadmium iodide, respectively, to the lithio derivative of **10**, led only to the product of γ attack, **11**, upon reaction with acetone. Reaction of the Grignard reagent, formed from magnesium bromide and the anion of **10**, with acetone gave, under optimum conditions, a product consisting of a 3:1 mixture of α/γ adduct (eq 5), based

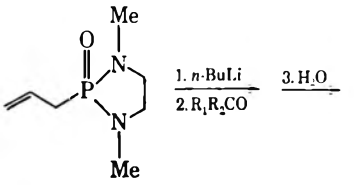


12 (5)

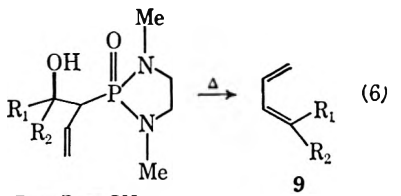
on nmr analysis of the N-methyl resonances. The two components, **12** and **11**, could be separated by preparative tlc or, with more difficulty and in lower yield, by recrystallization. Thermal decomposition of **12** gave a 50% yield of 4-methyl-1,3-pentadiene.

When the sodio derivative, generated by reaction of **10** with phenylsodium, was treated with acetone, only **11** was obtained.

Modification of the phosphonamide so as to reduce the bulk of the amide was more successful. Reaction of symmetrical dimethylethylenediamine with allylphosphonyl dichloride gave a good yield of N,N′-dimethyl-2-allyl-1,3,2-diazaphospholidine 2-oxide (**13**). When **13** was treated with *n*-butyllithium followed by acetone, α adduct **14a** was formed in high yield, essentially uncontaminated by γ-addition product. Thermolysis under vacuum of crude **14a** in mineral oil in the presence of calcium carbonate, added to preserve the neutrality of the reaction mixture, produced the butadiene in 75% yield (eq 6).



13



(6)

14a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = CH_3CH_2$
c, $R_1 = (CH_3)_3C$; $R_2 = H$
d, $R_1 = C_6H_5$; $R_2 = H$
e, $R_1R_2 = (CH_2)_5$

Methyl ethyl ketone added to the α carbon of the anion of **13** to give **14b** as a mixture of diastereomers. Thermal decomposition of **14b** resulted in the formation of a mixture of the isomeric butadienes **9a** (R_1 = CH_3CH_2; R_2 = CH_3) and **9b** (R_1 = CH_3; R_2 = CH_3CH_2) in a ratio of 3:5. The minor component was identified as **9a** by comparison with an authentic sample prepared by reaction of the homoallylic tosylate **15** with potassium *t*-butoxide. All attempts to separate the diastereomers of **14b** by recrystallization or tlc and thus allow generation of isomerically pure **9a** or **9b** were unsuccessful.

Reaction of pivalaldehyde with the anion of **13** gave a mixture of **14c** and **16a** in about equal amounts. Pinacolone and benzophenone each attacked exclusively the γ carbon of **13**. The adducts **16b** and **16c** were stable to heating under the normal conditions for olefin synthesis.

The yields of adducts **14** and of the butadienes resulting from the thermolysis of these adducts are summarized in Table I.

In summary, the controlling factor in the cases examined governing the ratio of α to γ addition seems to be steric. If the greatest degree of negative charge resides on the carbon α to the phosphorus atom, then, all other things being equal, addition should be

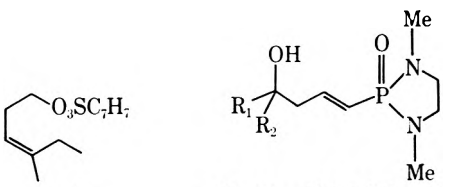
Table I

Conversion $R_1R_2C{=}O \longrightarrow R_1R_2C{=}CHCH{=}CH_2$ *via* Allyldiazaphospholidine Adducts

Carbonyl compound	Yield of adduct, %	Yield of diene, %[a,b]
Acetone	75	75
Methyl ethyl ketone	80	90
Pivalaldehyde	30[c]	50[c,d]
Benzaldehyde	85	60[e]
Cyclohexanone	90	90

[a] Thermolysis of adduct in mineral oil in the presence of calcium carbonate. [b] Yield of isolated product. [c] Corrected for presence of 16a. [d] Yield as determined by vpc. [e] Elimination carried out in benzene at reflux and in the presence of triethylamine to prevent polymerization of the product.

at the α carbon. If the position α to the phosphorus atom is hindered, however, as in the bis(dimethylamide) **10**, or when the carbonyl compound contains bulky groups, then condensation takes place at an alternative site to give the γ-substituted adduct. Only when both the α position and the carbonyl are unhindered will there be selective addition to the α site.[5]



15

16a, $R_1 = (CH_3)_3C$; $R_2 = H$
b, $R_1 = (CH_3)_3C$; $R_2 = CH_3$
c, $R_1 = R_2 = C_6H_5$

For suitable cases the phosphonamide reaction may thus be modified allowing an extension to the synthesis of dienes, although stereochemical control has not been achieved. Work is now in progress with phosphonamide reagents bearing electron-withdrawing functional groups.

Experimental Section

Infrared spectra were taken using a Perkin-Elmer Model 137 Infracord, and nmr data were obtained using Varian Associates Models A-60, T-60, or HA-100 spectrometers. Nmr shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on an AEI-MS-9 double focusing spectrometer. Vpc analyses were performed on F & M Models 300 or 810, and preparative vpc, on an Aerograph Autoprep. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and A. Bernhardt Mülheim, Germany.

Reagents.—The following reagents were used: *n*-butyllithium (Foote Mineral Co.), 1.6 *M* hexane or pentane solution, untitrated; tetrahydrofuran, distilled from lithium aluminum hydride, stored under argon; benzene and toluene dried over sodium wire.

Bis(dimethylamino)phosphorous Acid.[6,7]—Phosphorous acid (7.55 g, 0.092 mol) was added slowly to 30.06 g (0.184 mol) of hexamethylphosphorustriamide. The reaction mixture was stirred for 1 hr at 60°, then overnight at room temperature. The crude reaction mixture was vacuum distilled, the pot temperature being maintained below 80° to prevent thermal decomposition, yielding 11.47 g of bis(dimethylamino)phosphorous acid: bp 67° (0.4 mm); $n^{25}D$ 1.4506 (lit.[7] $n^{21}D$ 1.4518); nmr ($CDCl_3$), δ 2.65 (d, J = 11 Hz, NCH_3, 12 H), 4.82 (d, J = 579 Hz, PH, 1 H); ir λ_{max}^{neat} 4.30, 10.4 μ.

trans-**2-Bis(dimethylamino)phosphonylcyclohexanol (8).**—To a solution of 0.591 g (4.35 mmol) of bis(dimethylamino)phosphorous acid in 10 ml of tetrahyrofuran was added 2.90 ml (4.64 mmol) of 1.6 *M* *n*-butyllithium with stirring at −78° under argon. The reaction mixture was allowed to warm to room temperature during an hour, following which 0.465 g (4.78 mmol) of cyclohexene oxide was added. After 44 hr a Gilman test[8] indicated the disappearance of all lithium diamidophosphite. Water (5 ml) was then added, the tetrahydrofuran was evaporated, and the residue was extracted with three 100-ml portions of methylene chloride. After the mixture was dried over magnesium sulfate evaporation of the solvent and purification by preparative tlc (silica gel; chloroform–methanol, 19:1) gave 0.210 g of **8** as a slightly yellow oil: nmr ($CDCl_3$), δ 1.0–2.4 (m, 9 H), 2.65 (d, J = 14 Hz), and 2.73 (d, J = 11.5 Hz), (NCH_3, 12 H), 3.50–3.95 (m, CHOH, 1 H), 6.0 (s, OH, 1 H); ir λ_{max}^{neat} 3.03 μ.

A sample of **8** was prepared for analysis by bulb-to-bulb distillation [oven temperature, 100° (0.005 mm)].

Anal. Calcd for $C_{10}H_{23}N_2O_2P$: C, 51.27; H, 9.90; N, 11.96. Found: C, 51.34; H, 9.54; N, 11.76.

Attempted Thermal Decomposition of 8.—A mixture of **8** (0.274 g, 1.15 mmol) and 0.75 g of 1:4 (w/w) calcium carbonate–silica gel was heated for 72 hr at 100° in a sealed tube under argon. The tube was cooled and opened, and the volatile products were collected in a trap at −196°, then dissolved in pentane along with 0.25 mmol of *n*-octane as an internal vpc standard. Analysis by vpc, which was capable of detecting a 0.01% yield of cyclohexene, showed no cyclohexene.

Pyrolysis of 8.—A mixture of **8** (0.540 g, 2.3 mmol) and 1.5 g of 1:4 (w/w) calcium carbonate–silica gel was heated for 20 hr at 170° in a sealed tube under argon. The tube was cooled and opened, and the volatile products were collected in a trap at −196°, then dissolved in pentane along with 0.5 mmol of *n*-octane. Analysis by vpc (15 ft × 0.125 in. 10% TCEP on Chromosorb, 60°) showed the presence of cyclohexene in 25% yield.

Reaction of Lithium Diamidophosphite with *cis*-2,3-Oxidobutane.—To a solution of 5.143 g (37.8 mmol) of bis(dimethylamino)phosphorous acid in 75 ml of tetrahydrofuran was added 24.5 ml (39.2 mmol) of 1.6 *M* *n*-butyllithium with stirring at −78° under argon. The reaction mixture was allowed to warm to room temperature during an hour, following which 3.0 g (42 mmol) of *cis*-2,3-oxidobutane, prepared by the method of Pasto and Cumbo,[9] was added. After 72 hr of stirring, saturated ammonium chloride solution was added, the tetrahydrofuran was evaporated, and the residue was extracted with several portions of methylene chloride. The solvent was dried over magnesium sulfate and evaporated to yield 1.88 g of crude solid **7** which could be used without further purification. Alternatively, 1.8 g of **7** was purified by recrystallization from *n*-butyl acetate to yield 0.7 g of white solid: mp 76–80°; nmr ($CDCl_3$), δ 1.06 (d × d, J_{HH} = 8 Hz, J_{PH} = 18 Hz, CCH_3, 3 H), 1.24 (d, J = 6 Hz, $HOCCH_3$, 3 H), 2.0–2.5 (m, PCH, 1 H), 2.65 (d), and 2.75 (d, J = 11 Hz, NCH_3, 12 H), 3.75–4.25 (m, CHOH, 1 H), 5.0 (s, OH, 1 H); ir λ_{max}^{neat} 3.0, 10.3 μ.

An analytical sample of **7** was prepared by sublimation at 45° (0.005 mm).

Anal. Calcd for $C_8H_{21}N_2O_2P$: C, 46.14; H, 10.16; N, 13.45. Found: C, 46.00; H, 10.19; N, 13.13.

Reaction of Lithium Diamidophosphite with *trans*-2,3-Oxidobutane.—Lithium diamidophosphite (0.07 mmol), generated in the usual manner, was stirred for 5 days in 125 ml of tetrahydrofuran with 5.75 g (0.08 mmol) of *trans*-2,3-oxidobutane.[9] Saturated ammonium chloride solution was added to the reaction mixture, and the product was isolated as before to yield 1.97 g of oil which was purified by preparative tlc (silica gel; chloroform–methanol, 19:1) to give 1.18 g of **6**: nmr ($CDCl_3$), δ 1.11 (d × d, J_{HH} = 8 Hz, J_{PH} = 18 Hz, CCH_3) and 1.20 (d, J = 7 Hz, $HOCCH_3$) (total 6 H), 2.0–2.5 (m, PCH, 1 H), 2.68 (d, J = 11 Hz, NCH_3, 12 H), 3.6–4.6 (m, CHOH, 1 H), 5.0 (s, OH, 1 H); ir λ_{max}^{neat} 3.0, 10.3 μ.

The trimethylsilyl ether of **6**, prepared by the reaction of **6** with bis(trimethylsilyl)acetamide, had *m/e* 280.1740 (calcd for $C_{11}H_{29}N_2O_2PSi$: 280.1736).

N,N,N′,N′-Tetramethyl-2-hydroxy-1-methylpropylphosphono-

(5) Ramirez has recently demonstrated a difference in steric hindrance involving bis(dimethylamino) and *s*-dimethylethylenediamino groups attached to phosphorus. See. F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 6276 (1967).

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diamide (6 and 7).—To a solution of 1.074 g (6.55 mmol) of N,N,N′,N′-tetramethylethylphosphonodiamide[1] in 15 ml of tetrahydrofuran was added 4.3 ml (6.88 mmol) of 1.6 *M* *n*-butyllithium at −78° under argon. The solution was stirred for 1 hr at −78° and 2 hr at −20°, whereupon 0.5 ml (9 mmol) of acetaldehyde was added and stirring was continued for 3 hr at −78°. Addition of 5 ml of half-saturated ammonium chloride solution, extraction with methylene chloride, drying over magnesium sulfate, and evaporation of solvent yielded 1.5 g of oil, shown by nmr analysis to be a mixture of *ca.* 2:1 6 and 7.

Thermal Decomposition of 7.—A mixture of 0.137 g of 7 and 0.45 g of 1:4 (w/w) calcium carbonate–silica gel was stirred in a closed system at 80° in 1.5 ml of toluene. The volatile butene was trapped at −78°. After 20 hr a small amount of solvent was added to the liquid in the trap, along with a measured volume of *n*-pentane. The mixture was then analyzed by vpc on a 45 ft × 0.125 in. 15% dimethylsulfolane on Chromosorb P column. The mixture contained greater than 99% *trans*- and only a trace of *cis*-2-butene. The yield, based on the internal standard, *n*-pentane, was about 20%.

Thermal Decomposition of 6.—In exactly the same manner as described above, 6 was heated for 18 hr. Vpc analysis of the product showed 96% *cis*- and 4% *trans*-2-butene, in 20% yield based on the internal standard.

In a control experiment the olefinic product was analyzed after 8- and 32-hr reaction time. No variation in product composition was observed.

Allylphosphonic Dichloride.[10]—Aluminum chloride (60 g, 0.5 mol) was added to 137 g (1.0 mol) of phosphorus trichloride and the mixture was stirred vigorously at 45° under inert atmosphere while 19 g (0.25 mol) of 3-chloropropene was added over 30 min. The reaction mixture was then stirred an additional 20 min until all of the aluminum chloride had dissolved, whereupon excess phosphorus trichloride was removed on the rotary evaporator and the residue was dissolved in 300 ml of methylene chloride and cooled to −20°. Water (81 ml) was added slowly *via* syringe with vigorous stirring. The solid precipitate was filtered and washed with methylene chloride and the filtrate was dried over magnesium sulfate and concentrated *in vacuo*. Distillation under reduced pressure gave 22.28 g (56%) of clear liquid, bp 79–79.5° (15 mm).

N,N,N′,N′-Tetramethylallylphosphonodiamide (10).—Dimethylamine (56 ml, 36 g, 0.84 mol) in 500 ml of ether was cooled and stirred at 0° under argon while 22.3 g (0.14 mol) of allylphosphonic dichloride was added over 10 min. Stirring was continued for 1 hr at 0° and 3 hr at room temperature. The solution was then filtered, calcium oxide was added to the filtrate, the mixture was refiltered, and the solvent was removed. The residue was distilled from calcium hydride to give 20.03 g of a clear liquid, bp 61° (0.03 mm), which solidified upon standing: nmr ($CDCl_3$), δ 2.6 (m, PCH_2) and 2.63 (d, J = 9.5 Hz, NCH_3) (total 14 H), 4.9–6.3 (m, $CH{=}CH_2$, 3 H); ir $\lambda_{max}^{CCl_4}$ 6.12, 10.1, 10.3, 10.95 μ.

N,N′-Dimethyl-2-allyl-1,3,2-diazaphospholidine 2-Oxide (13).—To a solution of 2.527 g (28.7 mmol) of *s*-dimethylethylenediamine in 200 ml of ether and 50 ml of triethylamine was added 4.574 g (28.8 mmol) of allylphosphonic dichloride in ether with stirring at 0° under argon. The solution was stirred for 1.5 hr at 0° and overnight at room temperature. Methylene chloride (50 ml) was then added, the solution was filtered, and the solvent was evaporated. Distillation from calcium hydride through a 6-in. Vigreux column gave 2.575 g (51%) of a clear liquid, bp 98.5–100.5° (0.40–0.45 mm), which solidified on standing: nmr ($CDCl_3$), δ 2.67 (d, J = 9 Hz NCH_3) and 2.6 (m, PCH_2) (total 8 H), 3.1 (m, NCH_2, 4 H), 4.8–6.0 (m, $CH{=}CH_2$, 3 H); ir $\lambda_{max}^{CCl_4}$ 6.11 μ; mass spectrum, *m/e* 174, 133, 90, 42.

Anal. Calcd for $C_7H_{15}N_2OP$: C, 48.27; H, 8.68; N, 16.08. Found: C, 48.31; H, 8.87; N, 16.39.

Generation of the Anion of 10. Reaction with Acetone.—To a stirred solution of 0.829 g (4.71 mmol) of 10 in 15 ml of tetrahydrofuran was added 2.95 ml (4.71 mmol) of 1.6 *M* *n*-butyllithium at −70° under argon. The solution was stirred for 0.5 hr and 0.292 g (5.04 mmol) of acetone was added. After stirring for 20 min at −70°, the solution was allowed to warm to room temperature, following which 5 ml of half-saturated sodium bicarbonate solution was added, and the reaction mixture was extracted with ether. Drying of the ether layers and evaporation of solvent left 0.723 g of 11 as a yellow oil: nmr ($CDCl_3$), δ 1.23 (s, CCH_3, 6 H), 2.6 (m, $=CCH_2$) and 2.62 (d, J = 10 Hz, NCH_3) (total 14 H), 4.7 (s, OH, 1 H), 5.73 (d × d, J_{HH} = 17 Hz, J_{PH} = 22 Hz, PCH, 1 H), 6.2–7.2 (m, =CH, 1 H); ir $\lambda_{max}^{CHCl_3}$ 6.13, 10.2, 11.0 μ

Addition of the Anion of 10 to Cadmium Iodide. Reaction with Acetone.—To a stirred solution of 0.387 g (2.22 mmol) of 10 in 8 ml of tetrahydrofuran was added 1.45 ml (2.32 mmol) of 1.6 *M* *n*-butyllithium at −78° under argon. After the solution was stirred for 0.5 hr, 22.2 ml (4.44 mmol) of 0.2 *M* cadmium iodide in tetrahydrofuran was added, and the mixture was stirred for 0.5 hr at −78° and 45 min at −20°. Acetone (0.13 g, 2.22 mmol) was then added, and the reaction mixture was stirred for 1 hr at −78° and 3.5 hr at 0°. Half-saturated ammonium chloride solution (15 ml) was then added, the tetrahydrofuran was removed under reduced pressure, and the residue was extracted with methylene chloride. After the extracts were dried, the solvent was evaporated, leaving 0.588 g of red-yellow oil. A sample (0.2 g) of this oil was purified by preparative tlc (silica gel; chloroform–methanol, 9:1) to give 0.1 g of a clear oil whose nmr and ir spectra were identical with those of independently prepared 11.

Reaction of the Magnesium Salt of 10 with Acetone.—To a stirred solution of 0.359 g (2.06 mmol) of 10 in 8 ml of tetrahydrofuran was added 1.35 ml (2.16 mmol) of 1.6 *M* *n*-butyllithium at −78° under argon. After 0.5 hr, 1.7 ml (4.33 mmol) of 2.6 *M* magnesium bromide etherate was added, and the resulting mixture was stirred for 15 min at −78° and 45 min at −20°. Acetone (0.120 g, 2.06 mmol) was then added, and the solution was stirred for 1 hr at −78° and 3.5 hr at −20°. Following addition of half-saturated ammonium chloride solution (15 ml), the tetrahydrofuran was evaporated, and the residue was extracted with methylene chloride. Drying and evaporation of the extracts led to recovery of 0.494 g of crude product. The nmr spectrum of this material showed it to be roughly a 3:1 mixture of 12 and 11.

Recrystallization at −20° from pentane containing a trace of ether gave a white solid, mp 54–55°. The mother liquor was concentrated and cooled to yield additional material, mp 53.5–54.5°. The total recovery from both crops was 0.16 g.

Preparative tlc (silica gel; chloroform–methanol, 9:1) of 0.3 g of similarly prepared crude product gave 38 mg of oil, R_f 0.4, identified as 11 by ir and nmr, and 108 mg of white solid, R_f 0.6, mp 52–56°, identified as 12: nmr (12) ($CDCl_3$), δ 1.25 (d, CCH_3, 6 H), 2.69 (d, J = 8 Hz) and 2.68 (d, J = 10 Hz, NCH_3, 12 H), 3.06 (d × d, J_{HH} = 13 Hz, J_{PH} = 10 Hz, PCH, 1 H), 4.9–6.2 (m, $CH{=}CH_2$ and OH, 4 H); ir $\lambda_{max}^{CHCl_3}$ 6.12, 10.0, 10.2, 10.82 μ.

Generation of the Sodio Derivative of 10. Reaction with Acetone.—A suspension of phenylsodium in toluene (2.486 g, 2.68 mmol) was added to a tared flask and mixed with 3 ml of dry *n*-pentane followed by 0.467 g (2.68 mmol) of 10 in 2 ml of *n*-pentane. The reaction mixture was stirred for 2 hr at 0°, after which 15 ml of tetrahydrofuran was introduced. The mixture was stirred for 15 min, and 0.4 ml (5.4 mmol) of acetone was added at 0°. After 10 min, ammonium chloride was added and the product was isolated in the usual fashion to yield 0.724 g of 11.

Generation of the Lithio Derivative of 13. Reaction with Acetone.—To a stirred solution of 0.423 g (2.43 mmol) of 13 in 10 ml of tetrahydrofuran was added 1.6 ml (2.56 mmol) of 1.6 *M* *n*-butyllithium at −78° under argon. After 30 min, 0.35 ml (4.8 mmol) of acetone was added, and the solution was stirred an additional 15 min at −78° and 5 min at −20°. Water (0.2 ml) was added, followed by 100 ml of methylene chloride. The reaction mixture was filtered through a sintered-glass filter or glass wool plug, and the solution was dried over sodium sulfate and refiltered. Evaporation of the solvent yielded 0.565 g of a sticky yellow syrup, 14a (this material contained a residual amount of methylene chloride which could not be removed without thermal decomposition of the adduct: nmr (14a) ($CDCl_3$), δ 1.22 (d, CCH_3, 6 H), 2.71 (d, J = 9.5 Hz), 2.66 (d, J = 9 Hz) (NCH_3), and 2.8–3.4 (m, NCH_2 and PCH) (total area 11 H), 4.8–6.0 (m, $CH{=}CH_2$ and OH, 4 H); ir $\lambda_{max}^{CHCl_3}$ 3.0, 6.15, 10.1, 10.9 μ.

Reaction of the Lithio Derivative of 13 with Methyl Ethyl Ketone.—To a stirred solution of 0.628 g (3.61 mmol) of 13 in 10 ml of tetrahydrofuran was added 2.4 ml (3.84 mmol) of 1.6 *M* *n*-butyllithium at −78° under argon. After 0.5 hr, 0.285 g (4.18 mmol) of methyl ethyl ketone was added. Water (0.2 ml) was added after an additional 10 min, and the solution was allowed to warm to room temperature, whereupon the reaction mixture was diluted with 100 ml of methylene chloride and filtered through a glass wool plug. The solution was dried over sodium

(10) A. M. Kinnear and E. A. Perren, *J. Chem. Soc.*, 3437 (1952).

sulfate and refiltered, and the solvent was evaporated under vacuum at room temperature to yield 0.816 g of a sticky yellow syrup containing some residual methylene chloride: nmr ($CDCl_3$) δ 0.7–2.0 (m, 8 H), 2.68 (d) and 2.74 (d, J = 9 Hz, NCH_3) superimposed on 2.5–2.9 (m, PCH) (total 7 H), 3.0–3.3 (m, NCH_2, 4 H), 4.8–6.0 (m, $CH{=}CH_2$ and OH, 4 H); ir $\lambda_{max}^{CHCl_3}$ 2.95, 6.12, 10.10, 10.9 μ.

Reaction of the Lithio Derivative of 13 with Benzophenone.—To 2.24 mmol of the anion of **13**, generated in the manner described above, was added 0.425 g (2.34 mmol) of benzophenone. The solution was stirred for 15 min at −78° and 15 min at −20°. Water (0.2 ml) was added, followed by 100 ml of methylene chloride, and the product was isolated as above to yield 0.732 g of a crude solid, mp 134–137° (remains cloudy until *ca.* 150°). Two recrystallizations of 0.54 g of this solid from chloroform–hexane gave 0.29 g of **16c**: mp 157–157.5°; nmr ($CDCl_3$), δ 2.29 (d, J = 10 Hz, NCH_3, 6 H), 3.0 (m, NCH_2 and $=CCH_2$, 6 H), 4.2 (s, OH, 1 H), 5.39 (d × d, J_{HH} = 17 Hz, J_{PH} = 22 Hz, PCH, 1 H), 6.1–7.0 (m, $=CH$, 1 H), 7.3 (m, aromatic, 10 H); ir $\lambda_{max}^{CHCl_3}$ 2.75, 10.25 μ.

Anal. Calcd for $C_{20}H_{25}N_2O_2P$: C, 67.40; H, 7.07; N, 7.86. Found: C, 67.57; H, 7.20; N, 7.78.

Reaction of the Lithio Derivative of 13 with Pinacolone.—To 2.03 mmol of the anion of **13**, generated in the manner described above, was added 0.220 g (2.20 mmol) of pinacolone. The solution was stirred for 10 min at −78°. Water (0.2 ml) was added and the solution was allowed to warm to room temperature. Addition of 100 ml of methylene chloride and isolation of the product as above gave 0.472 g of an oil which slowly crystallized. A portion of this solid (0.3 g) was twice recrystallized from ethyl acetate to yield 0.1 g of **16b**: mp 126–128°; nmr ($CDCl_3$), δ 0.97 (s, CCH_3, 9 H), 1.13 (s, CH_3, 3 H), 2.59 (d, J = 10 Hz, NCH_3) on 2.3–2.8 (m, $=CCH_2$ and OH) (total 9 H), 2.9–3.4 (m, NCH_2, 4 H), 5.52 (d × d, J_{HH} = 17 Hz, J_{PH} = 22 Hz, PCH, 1 H), 6.3–7.3 (m, $=CH$, 1 H); ir $\lambda_{max}^{CHCl_3}$ 2.95, 6.15, 10.15 μ.

Anal. Calcd for $C_{13}H_{27}N_2O_2P$: C, 56.90; H, 9.92; N, 10.21. Found: C, 56.61; H, 9.94; N, 10.16.

Generation of 4-Methyl-1,3-pentadiene from 12.—A dry flask containing 0.111 g (0.84 mmol) of **12** was heated to 110° and the volatile products swept with argon (flow rate, 100 ml/min) into a trap held at −78°. Within 0.5 hr gas began to evolve from the melt. The thermolysis was allowed to continue overnight (16 hr). At the conclusion of the reaction the trap contained 20 mg (50%) of a clear liquid contaminated with *ca.* 1 mg of water. The infrared spectrum and vpc retention time (10-ft 10% TCEP on Chromosorb P, 50°) of the product were identical with those of an authentic sample of 4-methyl-1,3-pentadiene.

Formation of 1,1-Disubstituted 1,3-Butadienes by Thermolysis of Allyldiazaphospholidine Adducts. General Procedure Illustrated by Generation of 4-Methyl-1,3-pentadiene from 14a.—A suspension of 0.123 g (0.53 mmol) of **14a** (containing some methylene chloride) in 1 ml of Nujol along with 100 mg of anhydrous calcium carbonate was degassed and then heated to 110–120° for 4 hr under vacuum, the volatile products being condensed in a trap held at −196°. At the conclusion of the reaction the trapped material was distilled into a tared flask to yield 43 mg of liquid. Vpc analysis (10-ft 10% TCEP on Chromosorb, 50°) showed the product to be a mixture of 4-methyl-1,3-pentadiene and methylene chloride, the former in 75% yield. Comparison of the infrared spectrum of the product with that of an authentic sample confirmed the identification of the diene.

Generation of *cis*-and *trans*-4-Methyl-1,3-hexadiene from 14b.—A suspension of 0.389 g (1.58 mmol) of **14b** (containing some methylene chloride) in 0.5 ml of Nujol along with 0.4 g of anhydrous calcium carbonate was degassed and then heated to 133° for 2 hr under vacuum, the volatile products being collected in a trap held at −196°. At the conclusion of the reaction the trapped material was distilled into a tared flask to yield 0.175 g of liquid. Vpc analysis (10-ft 10% TCEP on Chromosorb P, 60°) showed the presence of two components in addition to methylene chloride: **9a** (retention time 7.9 min, relative area 3) and **9b** (retention time 8.9 min, relative area 5). Correcting for methylene chloride in the starting material and product, the over-all yield of diene was 90%. **9a** and **9b** were separated by preparative vpc (16 ft × 0.375 in. 15% β,β'-oxydipropionitrile on 60–80 kg, 70°). The spectra of **9a** follow: nmr (CCl_4), δ 0.97 (t, J = 7.5 Hz, CH_3, 3 H), 1.72 (s, $=CCH_3$, 3H), 2.12 (q, J = 7.5 Hz, CH_2, 2 H), 4.7–6.7 (m, vinyl, 4 H); ir $\lambda_{max}^{CCl_4}$ 6.1, 6.25, 10.15 μ; mass spectrum, *m/e* 96, 81, 55, 53, 44, 41, 39. The spectra of **9b** follow: nmr (CCl_4), δ 0.95 (t, J = 7 Hz, CH_3, 3 H), 1.65 (s, $=CCH_3$, 3 H), 1.98 (q, J = 7 Hz, CH_2, 2 H), 4.6–5.1 (m, vinyl, 2 H), 5.5–5.8 (m, vinyl, 1 H), 6.1–6.8 (m, vinyl, 1 H); ir $\lambda_{max}^{CCl_4}$ 6.03, 6.24, 10.13, 11.1 μ; mass spectrum, *m/e* 96, 81, 55, 53, 44, 41, 39.

***cis*-4-Methyl-1,3-hexadiene from *cis*-4-Methyl-3-hexenyl Tosylate.**—To 0.150 g (1.1 mmol) of 80% potassium *t*-butoxide in dry hexamethylphosphoramide was added 0.229 g (0.88 mmol) of *cis*-4-methyl-3-hexenyl tosylate (**15**)[11] with stirring at 0°. The solution instantly turned deep green. After 1 hr at 0° the system was evacuated and the volatile products were collected in a trap held at −196°, then distilled into a tared flask to give 31 mg of liquid which was shown by nmr and vpc analysis on two columns to be identical with compound **9a** obtained from the thermal decomposition of **14b**.

Generation of 5,5-Dimethyl-1,3-hexadiene from 14c.[12]—A sample of the crude **14c**–**16a** mixture was heated for 2 hr at 105° in mineral oil in the presence of $CaCO_3$ and the volatile products were isolated in the usual fashion. The yield of diene, after correction for **16a** in the initial adduct mixture, was 50%: nmr (CCl_4), δ 1.04 (s, CH_3, 9 H), 4.7–5.3 (m, vinyl, 3 H), 5.6–5.9 (m, vinyl, 2 H); ir $\lambda_{max}^{CCl_4}$ 6.05, 6.24, 10.49 μ.

Generation of Allylidene cyclohexane from 14e.[13]—Thermolysis of **14e** in the usual manner led to isolation of allylidenecyclohexane in 80% yield: nmr (CCl_4), δ 1.6 (m, 6 H), 1.9–2.35 (m, allyl, 4 H), 4.7–5.2 (m, vinyl, 2 H), 5.55–5.85 (m, vinyl, 1 H), 6.2–6.7 (m, vinyl, 1 H); ir $\lambda_{max}^{CCl_4}$ 6.03, 6.24 μ.

Generation of 1-Phenyl-1,3-butadiene from 14d.[14]—Benzene (4 ml) containing 0.321 g (1.15 mmol) of **14d** and 1 ml of triethylamine was stirred and refluxed for 3 hr. At the completion of the reaction, pentane was added, and the solvent was evaporated. The residue was washed with additional pentane and filtered to remove the ammonium phosphodiamidate salts, and the solvent was re-evaporated. Bulb-to-bulb distillation, employing anhydrous potassium carbonate to suppress polymerization, gave 1-phenyl-1,3-butadiene as a clear liquid (89 mg, 60%): nmr (CCl_4), δ 4.9–5.5 (m, vinyl 2 H), 6.1–6.7 (m, vinyl, 3 H), 7.0–7.35 (m, aromatic, 5 H); ir λ_{max}^{neat} 6.11, 6.24, 10.56 μ.

Attempted Thermolysis of 16c.—A benzene or toluene solution of **16c** was refluxed in the presence of silica gel. Filtration and washing of the silica gel with methylene chloride led to recovery of unchanged starting material.

Registry No.—**6**, 20628-39-1; **7**, 20628-40-4; **8**, 20628-82-4; **9a**, 20628-83-5; **9b**, 20628-84-6; **10**, 17070-81-4; **11**, 20628-88-0; **12**, 20628-89-1; **13**, 20628-90-4; **14a**, 20628-91-5; **16b**, 20628-92-8; **16c**, 20628-93-7; bis(dimethylamino)phosphorous acid, 5843-26-5; 5,5-dimethyl-1,3-hexadiene, 1515-79-3; allylidenecyclohexane, 5664-10-8; 1-phenyl-1,3-butadiene, 1515-78-2.

Acknowledgment.—We are grateful to the National Science Foundation and the National Institutes of Health for financial assistance.

(11) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.*, **90**, 5618 (1968).

(12) *Cf.* F. Bohlmann, *Chem. Ber.*, **86**, 657 (1953).

(13) *Cf.* H. Booker, L. K. Evans, and A. E. Gillam, *J. Chem. Soc.*, 1462 (1940).

(14) *Cf.* O. Grummitt and E. I. Becker, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 771; O. Grummitt and F. J. Christoph, *J. Amer. Chem. Soc.*, **71**, 4157 (1949).

Nonplanar Cyclobutane. Steric Product Control in the Deamination of *cis*- and *trans*-3-Methylcyclobutylamine

I. LILLIEN AND L. HANDLOSER

Department of Chemistry, Marshall University, Huntington, West Virginia 25701

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Deamination of the title compounds reveals a significant difference in ratios for the four major products: methylallylcarbinol (*cis*, 18%; *trans*, 59%); cyclopropylmethylcarbinol (*cis*, 60%; *trans*, 20%); *cis*-(2-methylcyclopropyl)carbinol (*cis*, 18%; *trans*, 0%); and *trans*-(2-methylcyclopropyl)carbinol (*cis*, 2%; *trans*, 21%). As in the case of the 3-isopropylcyclobutylamines, stereospecificity in formation of the latter two products is explained in terms of concertion which is conformationally more facile for the *trans*-cyclobutyldiazonium intermediate. The comparatively smaller preponderance of *trans*-(2-methylcyclopropyl)carbinol in the *trans* case, the occurrence of an almost equivalent amount of *cis*-carbinol for the *cis*-amine, and the larger fractions of homoallylic alcohol stand in contrast to the behavior of the isopropyl amines, however. Both the present product ratios and their divergence from those observed in the isopropyl case may be consistently explained in terms of substituent steric effect on orbital opening modes in the parent cyclobutyldiazonium ions and the key 2-alkylcyclopropylcarbinyl cation intermediates.

Within recent years, it has become increasingly apparent that carbonium ion reactivities of substituted cyclobutanes, which have been rationalized by a schema of common bicyclobutonium ion intermediates,[1,2] may require for their more adequate comprehension consideration of competing processes dependent on stereochemical orientation in predominantly puckered[3-10] rings. The solvolysis data of Wiberg and coworkers[8] on fused small ring compounds, and of Dolby[9] and Wilcox[10] and coworkers on polymethylcyclobutyl derivatives, have clearly demonstrated discrete steric requirements for participation in compounds containing the cyclobutane ring. However, such participation appears to show little, if any, relation to the electrical stability factors previously suggested for preferential bicyclobutonium ion stabilization.[11] Moreover, serious doubt has been cast on the viability of the bicyclobutonium ion intermediate as a result of study of cyclopropylcarbinyl reactivity,[12-15] which has implied an essentially unrearranged intermediate. Brown has previously argued in favor of the classical cyclobutane carbonium ion.[16] While recent arguments in support of a symmetrical bicyclobutonium ion have been advanced[17] in consequence of isotope scrambling experiments,[18] the cyclobutyl–cyclopropylcarbinyl cationic rearrangement has been shown to proceed with no positional scrambing in the absence of equilibration in at least one case.[19] Thus, the major support for the bicyclobutonium ion as the intermediate link in the cyclobutyl–cyclopropylcarbinyl rearrangements remains conjectural.

We have recently reported the results of deamination of the isomeric 3-isopropylcyclobutylamines.[20,21] The differences in *cis* and *trans* product ratios are compatible with steric control of an initial orbital overlap process which is concerted with loss of nitrogen in the respective cyclobutyldiazonium intermediates. Pivotal product 2-isopropylcyclopropylcarbinyl cation is formed stereospecifically by suprafacial overlap of C-3 and C-1 orbitals; this is sterically facile in the *trans*-cyclobutyl intermediate. An analogous process is opposed by developing repulsions in the transition state for the *cis*-cyclobutyl intermediate. This factor also appears responsible for *trans* rate preference in solvolysis of the corresponding alcohol brosylates.[22] Wiberg and coworkers have profferred a similar rationale for solvolytic behavior of fused-ring cyclobutanes.[23]

In our work, neither the product distribution nor the rate data were found to be readily reconcilable with bicyclobutonium ion intermediates. As a logical extension of these findings, it appeared of interest to investigate the deamination of the isomeric 3-methylcyclobutylamines to ascertain what effect, if any, the change in substituent would have on relative product distribution. This amine is conveniently available *via* well-known synthetic routes.[11a]

Deamination of 3-methylcyclobutylamine was carried out by Roberts and coworkers several years ago, but on an isomeric mixture.[11a] Major products, methylallylcarbinol, cyclopropylmethylcarbinol, and 2-methylcyclopropylcarbinol, were explained in terms of interconverting bicyclobutonium ions **1** and **2**, with the driving force for formation of **2** being ascribed to greater localization of charge on the carbon bearing the methyl

(1) *Cf.* K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 1331 (1965), for preceding references; in particular, R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959); and J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509, 3542 (1951).

(2) S. Winstein and E. Kosower, *ibid.*, **81**, 4399 (1959).

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(9) L. J. Dolby and C. Wilkins, *ibid.*, 2379 (1964).

(10) C. F. Wilcox, Jr., and D. L. Nealy, *J. Org. Chem.*, **28**, 3450 (1963); C. F. Wilcox, Jr., and R. J. Engen, *Tetrahedron Lett.*, 2759 (1966).

(11) (a) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 3671 (1961); (b) E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *ibid.*, **83**, 2719 (1961).

(12) M. Vogel and J. D. Roberts, *ibid.*, **88**, 2262 (1966).

(13) H. G. Richey, Jr., and J. M. Richey, *ibid.*, **88**, 4971 (1966).

(14) P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966).

(15) H. L. Goering and K. E. Rubinstein, Abstracts, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, p 11k.

(16) H. C. Brown, "The Transition State," Spec. Pub. No. 16, The Chemical Society, London, 1962, p 140.

(17) J. E. Baldwin and W. D. Foglesong, *J. Amer. Chem. Soc.*, **90**, 4311 (1968).

(18) J. E. Baldwin and W. D. Foglesong, *ibid.*, **90**, 4303 (1968).

(19) Deamination of 3-isopropylcyclobutylamine-1-*d* leads to specifically deuterated cyclopropylcarbinols: I. Lillien and L. Handloser, *Tetrahedron Lett.*, 1035 (1969).

(20) I. Lillien and R. A. Doughty, *ibid.*, 3953 (1967).

(21) I. Lillien and R. A. Doughty, *J. Org. Chem.*, **33**, 3841 (1968).

(22) I. Lillien, G. F. Reynolds, and L. Handloser, *Tetrahedron Lett.*, 3475 (1968).

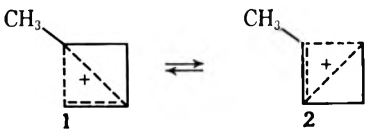
(23) K. B. Wiberg and J. G. Pfeiffer, *J. Amer. Chem. Soc.*, **90**, 5324 (1968).

TABLE I

PER CENT PRODUCT DISTRIBUTION IN THE AQUEOUS DEAMINATION OF ISOMERIC 3-METHYLCYCLOBUTYLAMINES (AVERAGE OF TWO RUNS)[a,b]

Amine	3	4	5[c]	6[c]	7[c]	8[c]
cis[c]	18.3	59.4	17.7	1.8[d]	2.0	0.8
trans[c]	58.8	19.2	0	21.1	0.7	0.2

[a] Percentages are corrected for isomeric amine contamination, which was minor. [b] Small amounts of unidentified material totaling 2–3% for each isomer were observed, with retention time similar to that of known products. [c] Assignment from nmr data. [d] Probably results from thermal inversion of *cis*-cyclopropylcarbonium intermediate: K. B. Wiberg, and G. Szeimies, *J. Amer. Chem. Soc.*, **90**, 4195 (1968).



1 2

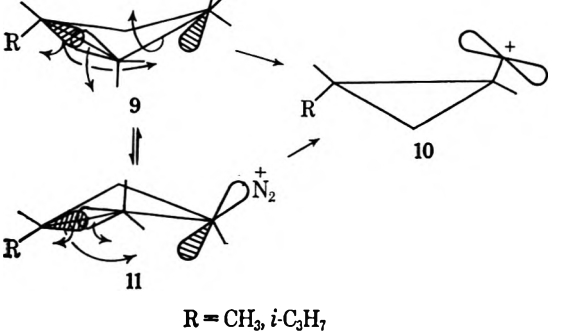
group. An important problem in this rationale lies in the fact that, while **2** may explain the large fraction (47%) of cyclopropylmethylcarbinol obtained, **1** must simultaneously acount for the small proportion (9%) of 2-methylcyclopropylcarbinol and the large proportion (39%) of allylmethylcarbinol. However, the former carbonium ion is more stable thermodynamically,[24] and the reverse was observed for the isopropyl case.[21] These facts argue against such a common progenitor for both of these products. Other objections to this general scheme have been cited,[21] and recent results militate against the likelihood of a **1**–**2** interconversion in this system.[19] In consequence of the foregoing considerations, we consider it of interest to report our observations in the deamination of the individual isomers.

Results and Discussion

Separation of the individual amine isomers was readily achieved by preparative vpc, employing a 30-ft Carbowax–KOH column. Isomeric assignment was made on the basis of nmr; the proton geminal to the NH_2 is further downfield (3.52 ppm) in the *trans* than in the *cis* isomer (3.15 ppm).[25] Results of two runs agreed closely, and are shown in Table I.

Stereospecificity in formation of 2-methylcyclopropylcarbinol is evidenced as in the isopropyl case, and as is demanded by orbital symmetry considerations.[26] However, in contrast to the isopropyl case, the present yields of **5** and **6** are almost equivalent.[27] Conversely, the proportion of **6** produced for *trans*-amine is substantially less than in the isopropyl case (where it is 55%). This difference corresponds to only a small change in the free energy of activation (*i.e.*, *ca.* 0.6 kcal/mol), which falls in the same range as the small magnitudes of conformational free-energy differences which prevail in this system.[5–7] Perhaps the most singular datum in the present results is the quite high proportion of **3** observed for the *trans*-amine, in contrast to the corresponding 3-isopropylamine, in which the homoallylic alcohol was a minor product.

The suggestion was previously made that products may arise directly from the cyclobutyldiazonium ion.[21] However, it now appears more likely that the common precursor is the 2-alkylcyclopropylcarbinyl cation or ion pair formed by initial rate-determining rearrangement of the cyclobutyldiazonium ion. A concerted, suprafacial overlap pathway from *trans*-diazonium intermediate **9** or **11** to *trans*-cyclopropylcarbinyl cation **10** (large arrows) subsequent to disrotatory C-2–C-3 bond opening[23] (small arrows) appears facile for both R = CH_3 and R = *i*-C_3H_7, since the transition state involves a net reduction in nonbonded interactions. It is difficult to make an *a priori* decision as to whether **9** or **11** more correctly represents the actual intermediate. Both can undergo the disrotatory orbital process preceding formation of **10** with comparative ease, although ensuing overlap is more direct for **11**. A simple conformational first approximation would tend to favor **9** on the basis that axial diazonium is more readily accommodated than axial alkyl. However, this may be a naive assumption, since it neglects the small differences which separate the conformational free energies of pseudoaxial and pseudoequatorial substituents in flexible cyclobutanes,[5–7] as well as the possibility that bulky solvation of the charged group may tip the delicate conformational balance. Wiberg and coworkers have argued, on the basis of calculations,[28] that cross-ring σ-bond stabilization is more effective for an equatorial leaving group. When this conclusion is accepted, it



9 10 11

R = CH_3, *i*-C_3H_7

(24) M. Hanack and H.-J. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **6**, 666 (1967).

(25) *Cf.* for analogy I. Lillien and R. A. Doughty, *J. Amer. Chem. Soc.*, **89**, 155 (1967).

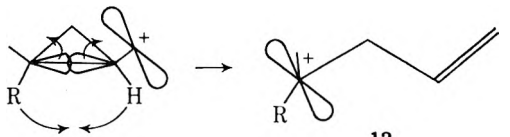
(26) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

(27) Repetition of the deamination reported in ref 20 and 21 has revealed that cis-3-isopropylcyclobutylamine does yield some *cis*-(2-isopropylcyclopropyl)carbinol. This product escaped prior detection, as under the vpc conditions then employed, it was not separated from *cis*-3-isopropylcyclobutanol. The adjusted product percentages for the *cis*-amine follow: *cis*-(2-isopropylcyclopropyl)carbinol, 11.1%; *cis*-3-isopropylcyclobutanol, 7.6%; *trans*-3-isopropylcyclobutanol, 1.2%. No *cis*-(2-isopropylcyclopropyl)carbinol was found for the *trans*-amine. The presence of this product for the *cis*-amine, however, does not vitiate the accompanying rationale, which is based in large part on the greater preponderance of the *trans*-cyclopropylcarbinol for the *trans*-3-isopropylcyclobutylamine.

(28) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).

becomes evident that the differing yields of the carbinols corresponding to **10** cannot be attributed to a difference in the conformational effects of isopropyl and methyl on the stability of **11**. Axial methyl should favor this route as opposed to axial isopropyl, but the converse appears to be reflected in the respective yields of these carbinols. Thus it seems most likely that an explanation of *trans*-product variation when the substituents isopropyl and methyl are compared must be sought in the differing effects of these groups on the collapse of the 2-alkylcyclopropylcarbinyl cation intermediate **10**.

Consideration of the path from **10** to **3** carbonium ion reveals that disrotatory orbital opening of the C-1–C-2 bond is required for conservation of maximum bonding during rearrangement.[26] It is seen that this process will engender R–H repulsive interactions. One may therefore anticipate that in the close proximity of the ensuing transition state, such motion will be energeti-

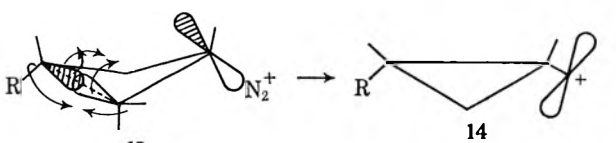


10 12

cally less restricted when R = CH_3 than when R = *i*-C_3H_7.[29] Thus, the much larger proportion of homoallylic alcohol obtained for the *trans*-3-methyl deamination (as opposed to the *trans*-3-isopropyl case) becomes readily intelligible in terms of the same kind of steric factors as govern the initial cyclobutyl rearrangement (*i.e.*, **11** → **10** *vs.* **13** → **14**). One might be tempted to cite the differing electrical capabilities of methyl and isopropyl to stabilize the homoallylic carbonium ion as a significant factor in this context. This might in part account for the greater yield of homoallyl alcohol for the *cis*-3-methylcyclobutyl as opposed to the *cis*-3-isopropylcyclobutyl case. However, the large *trans/cis* homoallylic yield ratio for the methylcyclobutyl isomers (*ca.* 3) clearly implicates a steric factor.

Where the route to homoallyl alcohol, *via* its precursor carbonium ion, is more favorable, it may successfully compete with unrearranged solvolysis. Thus, the smaller proportion of **6** observed, as opposed to its isopropyl counterpart, probably reflects better competitive diversion of **10** to **3** for the reasons given above, rather than abrupt change in mechanism.

A similar course of reasoning can account for the *cis*-amine product distribution. The CH_3–H interactions in the developing transition state for conversion of *cis*-diazonium intermediate **13** to *cis*-cyclopropylcarbinyl



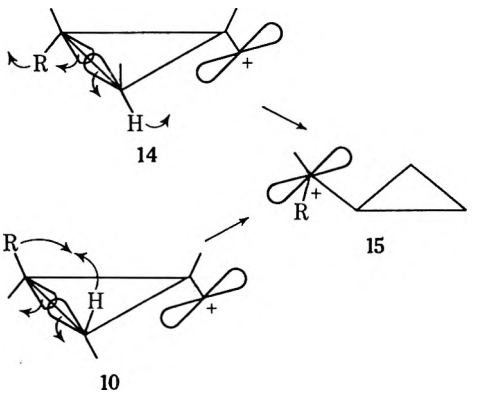
13 14

R = CH_3, *i*-C_3H_7.

(29) It has been shown [N. L. Allinger and L. A. Freiberg, *J. Org. Chem.*, **31**, 894 (1966)] that the conformational free energies of methyl and isopropyl in cyclohexanes (ΔG_{CH_3} = 1.8, $\Delta G_{i\text{-}C_3H_7}$ = 2.1) are similar because isopropyl can adopt a conformation in which its methyl groups are rotated away from a hydrogen atom in axial opposition ("*meso*"). However, in the closer proximity of the smaller ring systems under present consideration, increased restriction of rotational degrees of freedom may be expected to result in a greater loss of entropy, and thus in increased energy of activation, for transition states involving such isopropyl interactions.

cation **14** (large arrows), subsequent to disrotatory orbital opening (small arrows), are less than those for the analogous isopropyl-H interactions. This is therefore an energetically more favorable process. Indeed, the relative proportions of the *cis* and *trans* isomers of this carbinol are almost equivalent. The small amount of *trans*-carbinol obtained from *cis*-amine may simply reflect an energetically advantageous consumption of some **14** by thermal inversion[30] to **10** prior to conversion to carbinol.[31]

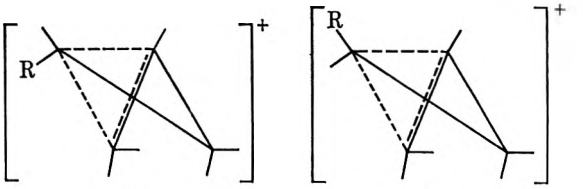
Major *cis*-amine product **4**, as well as its isopropyl homolog, is formed[19] *via* the process indicated below from **14**, again assuming disrotatory orbital opening of



R = CH_3, *i*-C_3H_7

the C-2–C-3 bond. For the *cis* precursor **14**, no steric difficulties are expected. However, for the *trans* process from **10**, R–H oppositions arise, resulting in a smaller yield of **4**, even though **15** may be expected to be more stable than either **14** or **10**.[24]

Any attempt to rationalize these results through a scheme of bicyclobutonium ion *intermediates* meets with several serious objections. The difficulty of trying to relate the two ions **16** and **17**, derivable from *cis*- and *trans*-amines, respectively, to differential product dis-



16 17

tribution has been pointed out for the isopropyl case,[21] and is equally evident in the present instance. Moreover, there is an immediate dilemma inherent in attempting to account for the quite different homoallyl alcohol/*trans*-(2-alkylcyclopropyl)carbinol ratios, 0.1 for the *trans*-isopropylamine, but 2.8 for the *trans*-methylamine. This reflects a change in relative rates by a factor of about thirty; yet, in both cases, both products would ostensibly ensue from the same ion **17**.

Finally, the interconversion of ions **1** and **2** previously called on[11a] to rationalize product formation in the deamination of 3-methylcyclobutylamine may be *specifically excluded* by the results of deamination of the analogous 3-isopropylcyclobutylamine-1-*d*.[19]

(30) *Cf.* Wiberg and Szeimies, footnote *d*, Table I.

(31) A similar result was noted in the solvolysis of *cis*-3-isopropylcyclobutyl brosylate; *cf.* ref 22. Indeed, solvolysis of *trans*-(2-isopropylcyclopropyl)carbinyl 3,5-dinitrobenzoate yields no *cis*-carbinol, whereas the *cis* ester gives a substantial yield of *trans*-carbinol (I. Lillien, unpublished work).

The present results provide further support for a picture of conformationally dependent, classical processes functioning in carbonium ion reactivity of substituted cyclobutanes, and contribute to an increasing mass of evidence which impugns the concept of nonclassical bicyclobutonium ion intermediates.

Experimental Section

3-Methylenecyclobutanecarbonitrile was prepared from a bomb reaction of allene and acrylonitrile as described.[32] However, a run of 2 mol (80 g) of allene, 8 mol (424 g) of acrylonitrile, and 4 g of hydroquinone in the presence of 100 ml of dry benzene diluent, in a 2-l. bomb under autogenous pressure at 196° for 14 hr, produced a yield of 155 g (1.62 mol, 81%) of material with n^{23}D 1.4596 (lit. n^{25}D 1.4590). This represents a considerable improvement over the *ca.* 60% reported in the absence of diluent, and in a smaller vessel for a shorter time.[32] Conversion to 3-methylcyclobutylamine was carried out as reported.[11a] Isomers were separated by freezing the effluent vapors from a 30 ft × 0.25 in., 5% KOH–20% Carbowax 20M on Chromosorb W column maintained at 70° with a helium flow rate of *ca.* 35 ml/min. Under these conditions, the retention times of the *cis* and *trans* isomers were 13.07 and 14.53 min, respectively.

Deamination was carried out on the individual isomers and the mixture as previously described.[11a] The deamination mixture was analyzed on a 30 ft × 0.25 in., 5% CO-990 on Chromosorb W column. Components were obtained by isolation of effluent vapors from a mixed amine deamination. With the CO-990 column operated at 100° and a helium flow rate of 40 ml/min., retention times were as follows:

Inadequate separation of *trans*-(2-methylcyclopropyl)carbinol and *cis*-3-methylcyclobutanol resulted in isolation of mixtures. However, content could be assayed by nmr integration and comparison with authentic material.

(32) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 32 (1962).

Table II

Product	Retention time, min
4-Penten-2-ol	7.70
Cyclopropylmethylcarbinol	9.63
trans-(2-Methylcyclopropyl)carbinol	12.61
cis-3-Methylcyclobutanol	12.70
trans-3-Methylcyclobutanol	13.46
cis-(2-Methylcyclopropyl)carbinol	15.00

Authentic 4-penten-2-ol was synthesized from allylmagnesium bromide and acetaldehyde. Its retention time was found to differ widely from its isomers 1-penten-3-ol and 3-penten-2-ol under these conditions. Cyclopropylmethylcarbinol was prepared by lithium aluminum hydride reduction of commercial cyclopropyl methyl ketone. *cis*- and *trans*-(2-methylcyclopropyl)carbinol were prepared by a Simmons–Smith reaction[33] with commercial crotyl alcohol, whose *cis*/*trans* ratio was about 3:1, and were isolated by freezing of effluent vapors from the CO-990 column. Isomeric configuration was assigned on the bssis of retention time (*cis* longer) and nmr, as has been discussed[34] and also observed for the homologous 2-isopropylcyclopropylcarbinols.[21] The methylene protons were at higher field for the *trans* isomer, and were seen as a ABX multiplet for the *cis* carbinol, and an A_2X doublet for the *trans*. 3-Methylcyclobutanol was prepared as described,[11a] and the isomers were separated by preparative vpc on the CO-990 column. Configuration was assigned by analogy with the 3-isopropylcyclobutanols.[25] The proton geminal to hydroxy was centered at 3.9 ppm for the *cis* and 4.4 ppm for the *trans* isomer.

Registry No.—*cis*-3-Methylcyclobutylamine, 20826-76-0; *trans*-3-methylcyclobutylamine, 20826-77-1.

(33) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1019.

(34) G. W. Van Dine, Ph.D. Thesis, Princeton University, Princeton, N. J., 1967, p 152.

Ring-Cleavage Reactions of 2-Bicyclo[2.1.1]hexyl Grignard Reagents[1]

E. Alexander Hill,[2a] Robert J. Theissen,[2b] and Kathleen Taucher[2c]

Departments of Chemistry, University of Minnesota, Minneapolis, Minnesota, and University of Wisconsin-Milwaukee, Milwaukee, Wisconsin

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Ring-cleavage reactions of 2-bicyclo[2.1.1]hexyl Grignard reagents have been investigated. Preparation of the chloride or bromide from β-5,5-dimethylbicyclo[2.1.1]hexan-2-ol (**1**) leads to a mixture of halides including α- and β-2-halo-5,5-dimethylbicyclo[2.1.1]hexanes (**2** and **3**) and 2-halo-3,3-dimethylbicyclo[2.1.1]hexane (**4**) as major products. The Grignard reagents from these halides rearrange on heating to the Grignard reagent derivable from 4-halomethyl-3,3-dimethylcyclopentene (**5**). In the preparation of the halide, **5** is also a minor product, which is postulated to form by nucleophilic attack of halide ion on an intermediate ester or carbonium ion. During formation of the Grignard reagent, an alternative cleavage occurs yielding eventually 4-isopropylcyclopentene and 4-isopropenylcyclopentene. A radical process is believed responsible for these latter products. The Grignard reagent from 2-chlorobicyclo[2.1.1]hexane rearranges cleanly to the reagent derivable from 4-chloromethylcyclopentene. The ring cleavages observed are all slower than the analogous cleavage of the Grignard reagents from α-cyclobutylethyl halides, despite substantially greater relief of ring strain in the bicyclic system. These results are in agreement with predictions from a concerted four-center mechanism for the ring-cleavage reactions. However, hybridization effects, the *gem*-dimethyl effect, and overlap control, the magnitude of which are difficult to assess, may contribute to the slowness of the observed cleavages.

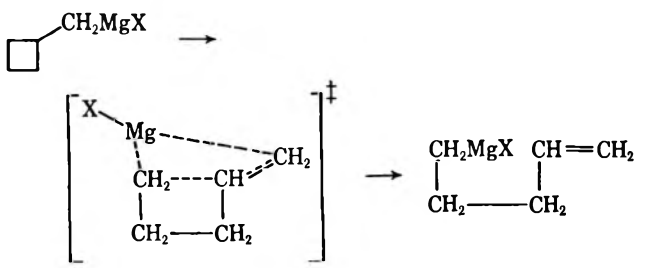
A kinetic and mechanistic study of the ring cleavage of cyclobutylmethyl organomagnesium compounds has been reported previously.[3,4] A concerted four-center process was considered to be more consistent with observed solvent, α-deuterium, and methyl substituent effects than were alternative radical and carbanionic mechanisms. The proposed mechanism, in which transfer of the magnesium is synchronous with bonding

(1) (a) Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research, and to the National Science Foundation and the Shell Oil Co. for summer and academic year fellowships, respectively, for R. J. T. (b) Presented in part at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, p 19-K.

(2) (a) To whom inquiries should be addressed: University of Wisconsin-Milwaukee, Milwaukee, Wis. 53201. (b) Taken in part from the Ph.D. Thesis of R. J. Theissen, University of Minnesota, 1966. (c) National Science Foundation Undergraduate Research Participant, University of Wisconsin-Milwaukee, 1967.

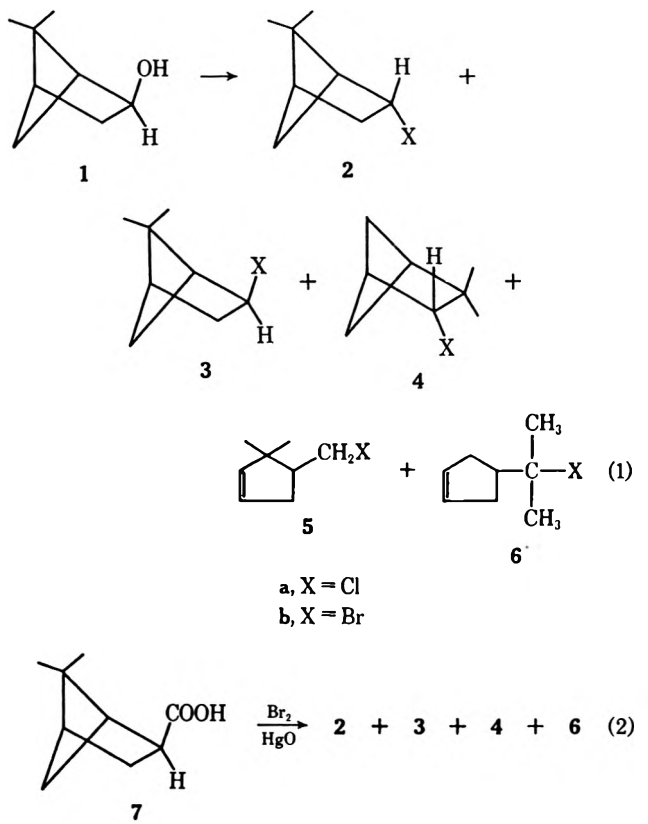
(3) E. A. Hill and J. A. Davidson, *J. Amer. Chem. Soc.*, **88**, 4663 (1964).

(4) Analogous cleavages of other cyclobutylmethyl and cyclopropylmethyl organometallic compounds are known: M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *ibid.*, **82**, 2646 (1960); P. T. Lansbury, *ibid.*, **85**, 1886 (1963); H. G. Richey, Jr., and E. A. Hill, *J. Org. Chem.*, **29**, 421 (1964).



changes in the carbon skeleton, has a further consequence. The rate of ring cleavage should be quite sensitive to geometric restrictions on the conformation of the starting and transition states, which might be achieved by incorporating the cyclobutylalkyl system into a rigid bicyclic skeleton. In the present paper, we report a study of the preparation and cleavage of Grignard reagents derived from one such bicyclic skeleton, 2-substituted bicyclo[2.1.1]hexyl. Most of the work now reported deals with compounds with 5,5- or 3,3-dimethyl substitution, although some work is included on the unsubstituted 2-bicyclo[2.1.1]hexyl Grignard reagent.

Preparation of Halides.—The bicyclo[2.1.1]hexyl skeleton was synthesized by previously published routes. 5,5-Dimethylbicyclo[2.1.1]hexan-2-ol (**1**) was prepared from β-pinene by the synthesis developed by Meinwald and Gassman.[5] The chloride and bromide were obtained by treating **1** with thionyl chloride and the triphenylphosphine–bromine reagent,[6] respectively (eq 1). The bromide was also made in low yield from 5,5-dimethylbicyclo[2.1.1]hexane-2-carboxylic acid (**7**) by the modified Hunsdiecker procedure of Cristol and Firth[7] (eq 2).



a, X = Cl
b, X = Br

(5) (a) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 2857 (1960); (b) *ibid.*, **82**, 5445 (1960).

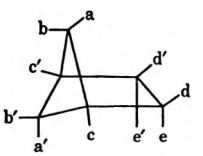
(6) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *ibid.*, **86**, 964 (1964).

(7) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

In all cases, the product was shown by nmr and gas chromatography to be a mixture of up to five isomeric halides. Unfortunately, separation by gas chromatography was incomplete, and, furthermore, isomerization was found to occur during chromatography. Therefore, it was necessary to carry the halide mixtures through the Grignard studies. For this reason, care was taken to characterize the halide mixtures as fully as possible by partial gas chromatographic separation and nmr.[8] Approximate product distributions for the three halide preparations are listed in Table I which is shown on p 3064.

Assignments of structure were based primarily on the methyl and CHX resonances, which are also in Table I. For the former, assignments were facilitated by published data[9-13] and spectra of compounds with known structure.[14] The CHX resonances of the α and β isomers of 5,5-dimethylbicyclo[2.1.1]hexan-2-ol and the corresponding halides are similar in position and overlap in mixtures. The CHX spectrum of the α-bromide could be observed with minimum interference and may be interpreted as a first-order multiplet with apparent coupling constants of 7.1, 2.5, 1.6, and 1.6 Hz. The most obvious interpretation would assign the first two coupling constants to the *cis*- and *trans*-vicinal couplings and the latter two to the near bridgehead hydrogen (J_{cd}) and remote *exo* hydrogen ($J_{bd'}$). Long-range couplings of the latter type fit approximately to a "W" arrangement of intervening bonds and have been suggested previously.[13] Observation of the CHBr resonance with simultaneous irradiation in the vicinity of δ (ppm) 1.9 and 2.48 eliminated the 2.5- and 7.1-Hz coupling, respectively. By double irradiation at low

(8) For discussion of nmr spectra, we will follow the lettering scheme of Wiberg, Lowry, and Nist,[9] in slightly modified form as shown. In keeping



with nomenclature suggested by Meinwald and Gassman,[5] isomeric positions on the ethylene bridge of the 5,5-dimethyl isomers are designated α or β if they are *cis* to the methylene or isopropylidine bridges, respectively. A substituent on the one-carbon bridges is *endo* in the a or a′ positions, and *exo* in b or b′.

(9) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

(10) T. Gibson and W. F. Erman, *J. Org. Chem.*, **31**, 3028 (1966).

(11) R. C. Cookson, J. Hudec, S. A. Knight, and B. R. D. Whitear, *Tetrahedron*, **19**, 1995 (1963).

(12) (a) J. Meinwald and A. Lewis, *J. Amer. Chem. Soc.*, **83**, 2769 (1961); (b) K. Ebisu, L. B. Batty, M. Higaki, and H. O. Larson, *ibid.*, **88**, 1995 (1966); (c) R. S. H. Liu and G. S. Hammond, *ibid.*, **86**, 1892 (1964); (d) R. Srinivasan and F. I. Sonntag, *ibid.*, **89**, 407 (1967); (e) J. Meinwald and J. K. Crandall, *ibid.*, **88**, 1292 (1966).

(13) A. Cairncross and E. P. Blanchard, Jr., *ibid.*, **88**, 496 (1966).

(14) Some characteristic features are summarized.

Compd	δ (*endo*-5-CH_3)	δ (*exo*-5-CH_3)	δ (*endo*-6-H)
12	0.75	1.25	0.72
α **1**	0.73	1.22	
β **1**	1.07	1.29	0.73
β **1** benzoate	1.11	1.28	0.74
7	0.79	1.33	0.89

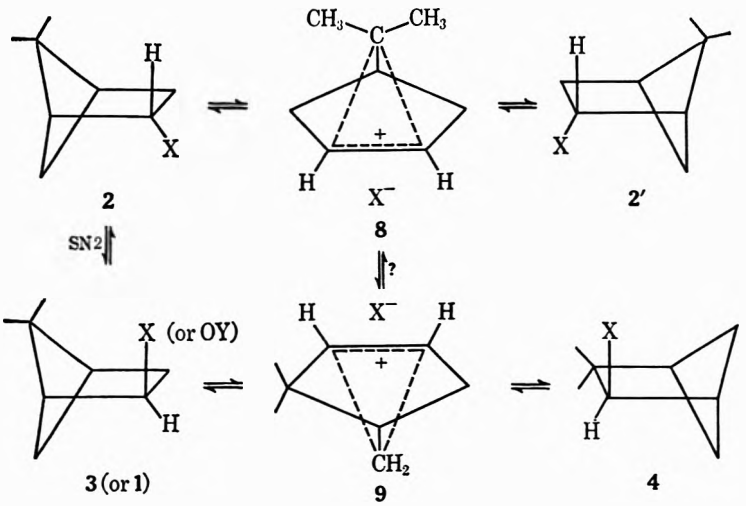
The *endo*-6 hydrogen of α **1**, and the *endo*-5 and *endo*-6 hydrogens of 3,3-dimethylbicyclo[2..11]hexane were apparently shifted downfield by a *syn* substituent on the two-carbon bridge, and were not seen. The *endo*-5-methyl group of **7** is apparently shifted upfield by the magnetic anisotropy of the carboxy group. Examples of a previously reported [R. S. Liu, *Tetrahedron Lett.*, 2159 (1966)] long-range coupling, $J_{cc'}$, of 8 Hz was observed in compounds **4a** and **13**.

power levels,[15a] the sign of the coupling constant between the resonances at δ 1.9 and 2.48 was shown to be opposite their coupling to the CHBr proton.[16] The α-chloride was apparently similar, although only part of it could be seen clearly. For the β isomers, the spectral appearance was substantially different and could not be cleanly interpreted as a first-order pattern. Some simplification which resulted from double irradiation indicated that the CHCl proton was probably coupled to more than one proton in the vicinity of δ 2.1 to 2.2. For the rearranged 2-halo-3,3-dimethylbicyclo[2.1.1]hexanes **4**, the CHX absorption was a triplet with J = 1.5 Hz. One of the coupled protons is undoubtedly the adjacent bridgehead hydrogen. The other most probably results from bd′ coupling.

In addition to the bicyclic isomers, olefinic nmr absorption indicated that some ring cleavage had occurred during the halide preparations. The 4-halomethyl-3,3-dimethylcyclopentenes were isolated by gas chromatography in reasonably pure form and characterized by their nmr spectra. The methyls of the *gem*-dimethyl group are nonequivalent, owing to *cis* and *trans* relationship to the halomethyl group. The CH_2X appears at higher field than CHX resonances of the bicyclic compounds and exhibits a coupling pattern which may be analyzed as the AB portion of an ABX spectrum.[15b] Parameters obtained at 100 MHz are shown in Table II. Nonequivalence of the methylene protons is reasonable, since the halomethyl group is bonded to an asymmetric carbon atom, and additionally, the adjacent *gem*-dimethyl group might be expected to produce some rotational restriction. To help to confirm the structure of the primary halide, a Grignard reagent was prepared from a sample of the bromide which had been partially separated by gas chromatography. The bromide used was about 50% **4b** and 50% **5b**, based on integration of the nmr spectrum. Hydrolysis of the Grignard reagent yielded a mixture of hydrocarbons which was 50% 3,3,4-trimethylcyclopentene and 50% 2,2-dimethylbicyclo[2.1.1]hexane.

Additional weak olefinic signals were present in distilled samples of the halides, but did not appear in the gas chromatographed fractions. It is likely that tertiary halide **6** might be formed during synthesis of the halides, but not survive gas chromatography. The analogous alcohol has been isolated in solvolytic studies.[17] If the tertiary halide is held responsible for the additional signals, a reevaluation of the product distributions in Table I would show it to comprise 0.7% of the chloride product and 1.5 and 6% of the product in the two bromide preparations. Substantial amounts of the corresponding hydrocarbons, 4-isopropylcyclopentene and 4-isopropenylcyclopentene, were isolated from Grignard reactions, but, in large measure, they were apparently derived from the other halides.

The variation in composition of the halide mixtures is of some interest. Had the thionyl chloride and triphenylphospine–bromine reactions proceeded with clean SN2 inversion of configuration, pure **2** would have been formed (eq 3). Wagner–Meerwein rearrangement of



(3)

this halide by a stereospecific nonclassical carbonium ion-pair mechanism leads only to racemization. The other bicyclic halides **3** and **4** are related to each other by such a stereospecific rearrangement, but a "crossover" is required for interconversion with **2**.[18] An "SNi" carbonium ion process in competition with SN2 would explain the bicyclic isomers. The larger amount of simple inversion product **2** in the triphenylphosphine–bromine reaction is consistent with the demonstrated tendency[6] of that reagent to react by direct displacement and with the greater nucleophilicity of bromide. Formation of isomer **4** could occur by rearrangement in the "SNi" ion pair or by Wagner–Meerwein rearrangement of **3** to **4**. The increased proportion of **4** in the bromide is consistent with the latter possibility, because of the greater lability of alkyl bromides. In the Hunsdiecker reaction, the probable free-radical intermediate would not be expected to rearrange. The absence of **3b** and presence of **4b** in that reaction is most satisfactorily explained by mercuric salt catalysis of the Wagner–Meerwein rearrangement of **3** to **4**.

(15) (a) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1966: (a) p 468; (b) pp 357–364.

(16) A similar result has been reported for norbornanes and norbornenes: J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); F. A. L. Anet, H. H. Lee, and J. L. Sudmeier, *J. Amer. Chem. Soc.*, **87**, 4431 (1967).

(17) J. Meinwald, P. G. Gassman, and J. J. Hurst, *ibid.*, **84**, 3722 (1962); J. Meinwald and P. G. Gassman, *ibid.*, **85**, 57 (1963).

(18) In eq 3, the nonclassical formalism is used for convenience and in recognition of the solvolysis results of J. Meinwald, P. G. Gassman, and J. J. Hurst.[17] Formation of all products *via* rearranging classical ions might also be considered. A "crossover" between the two nonclassical systems **8** and **9** is suggested in the solvolysis studies[17] and by our finding that **2b** and **3b** both appear to be converted into **4** during gas chromatography.

TABLE I

COMPOSITION AND NMR SPECTRA OF PRODUCTS IN 2-HALODIMETHYLBICYCLO[2.1.1]HEXANE PREPARATIONS

Component	% of product Cl[a]	% of product Br[b]	% of product Br[c]	Nmr, δ, ppm: Methyl Cl	Methyl Br	CHX Cl	CHX Br
2	10	44	40	0.76	0.78	4.38	4.43
				1.27	1.31		
3[d]	47	8	0	1.12	1.16	4.30	4.29
				1.30	1.32		
4[e]	39	33	60	1.12	1.17	3.98	4.09
				1.14	1.20		
5[f,g]	4	15	0	0.90	0.89	3.49	3.37
				1.14	1.16		

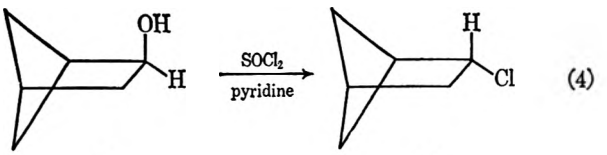
[a] From alcohol and $SOCl_2$–C_5H_5N. [b] From alcohol and P-$(C_6H_5)_3$–Br_2. [c] From acid and HgO–Br_2. [d] Nmr doublet at δ 0.82 from *endo*-6 hydrogen of chloride. Corresponding absorption in bromide was obscured by methyl group of mixture. [e] Additional prominent nmr absorptions: δ 1.6 (m, 4), 2.05 (pair of triplets, 1, J 8.0, 2.5, and 2.5 Hz), 2.50 (broadened doublet, 1, J = 8.0 Hz) in chloride. [f] Olefinic absorption at δ 5.47 (chloride) and 5.49 (bromide). [g] Additional olefinic absorptions at δ 5.59, 5.71, and 5.8 in the three reactions might be assigned to halides **6a** and **6b**.

TABLE II

Parameter	Hz: Chloride	Hz: Bromide
$\lvert J_{AB} \rvert$	10.5	9.4
$\lvert J_{AX} \rvert$	8.6	9.4
$\lvert J_{BX} \rvert$	6.0	5.2
$\lvert \nu_A - \nu_B \rvert$	17.7	18.7

The primary ring-opened halide **5** is an unexpected reaction product. It seems unlikely that either a classical or a nonclassical ion would be likely to cleave directly to a primary carbonium ion, and indeed no such products were detected in solvolysis and deamination studies.[17] The most probable explanation would seem to be that the phosphorus or chlorosulfite ester intermediate either undergoes a fragmentation concerted with nucleophilic attack on the primary carbon by chloride or bromide, or, more likely, the bridging methylene of nonclassical cation **9** is attacked by halide. In either case, steric hindrance to more normal substitution might enhance this unusual reaction pathway. In any event, nucleophilic participation by halide seems necessary. Absence of the primary halide from the Hunsdiecker reaction is consistent with the expectation that cleavage to a primary radical would not occur. Either radical or cationic cleavage to yield the tertiary halide **6** would be reasonable.

In addition to the methyl-substituted bicyclohexyl chlorides, the unsubstituted 2-chlorobicyclo[2.1.1]hexane (**11**)[19] was prepared from the corresponding alcohol (**10**). In this instance, the conversion into halide was quite clean (eq 4).

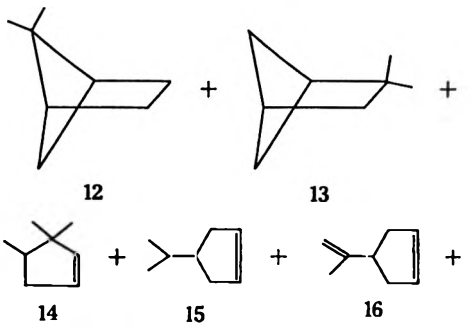


(4)

10 **11**

Formation and Cleavage of Grignard Reagents.—Grignard reagents were prepared in ether and in tetrahydrofuran from the chloride and bromide mixtures derived from **1** (eq 5). After reaction of the halide with magnesium, solvent and any hydrocarbons generated during formation of the reagent were pumped to a cold trap under high vacuum, and new solvent was added. Hydrolysis of the residual Grignard reagent yielded a mixture of four hydrocarbons (eq 6), which were separated by preparative gas chromatography and identified by ir and nmr spectra. The hydrocarbons found were 5,5-dimethylbicyclo[2.1.1]hexane (**12**), 2,2-dimethylbicyclo[2.1.1]hexane (**13**), 3,3,4-trimethylcyclopentene (**14**), and 4-isopropylcyclopentene (**15**). The hydrocarbons in the solvent pumped from the preparation of the Grignard reagent contained, in addition, 4-isopropenylcyclopentene (**16**) and small amounts of some unidentified components of longer retention time.

"bicyclohexyl halide mixture" $\xrightarrow[\text{ether or tetrahydrofuran}]{\text{Mg}}$



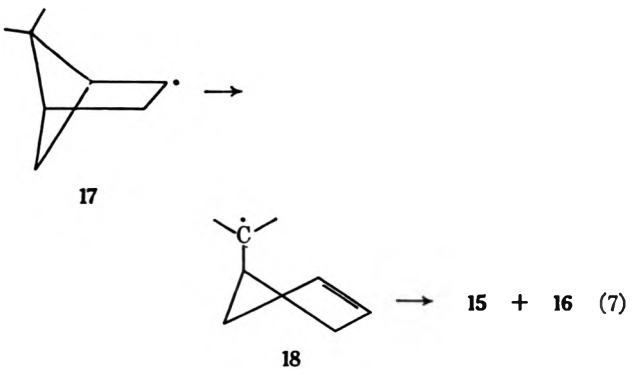
Grignard reagent (5)

Grignard reagent $\xrightarrow{H_2O}$ **12** + **13** + **14** + **15** (6)

The Grignard reagent from the chloride was formed in a yield of 60–80%, based on acid titer and semiquantitative analysis of the hydrocarbon fractions. However, the Grignard reagent from the bromide was apparently formed in only about 15% yield. The major side reaction appears to be a disproportionation, in which isopropenylcyclopentene is the major product formed by hydrogen loss. In both preparations, the amount of halide eventually appearing with isopropyl- or isopropenylcyclopentene skeleton far exceeds the 1–3% of this skeleton in the original halide mixture. For instance, in the Grignard reagent from the bromide mixture, the hydrocarbons pumped from the Grignard reagent (about 75% of the total product) contained 37% of this skeleton. While the unrearranged 5,5-dimethylbicyclo[2.1.1]hexyl bromides had comprised 51% of the halide mixture, the corresponding hydrocarbon made up only 24% of the hydrocarbons pumped from the Grignard, and 47% of the hydrocarbons from hydrolysis of the Grignard reagent. It appears likely that a free radical **17** generated during reaction of the

(19) Preparation of the same chloride by chlorination of the hydrocarbon has been reported previously.[12d] Nmr spectra agree. Nmr data on **10** are in good agreement with other generalizations of bicyclo[2.1.1]hexane spectra. The spectrum was run at 100 MHz and decoupled to help clarify the spin–spin coupling pattern. The ring proton of the CHOH group is a broad doublet. By double irradiation, it was shown to be coupled to multiplets at δ 1.94 (J = 7.5 Hz) and 1.24 (J = 2.0 Hz), which were in turn coupled with each other (J = 11.5 Hz), as expected for the methylene group at C_3. There was weak coupling to the bridgehead (δ 2.39) and possibly to a proton of the three-hydrogen multiplet at δ 1.34–1.70, which presumably includes the two *exo* protons and one of the *endo* protons. The other *endo* proton appears as a quartet at δ 0.90, with coupling constants of about 7 and 9 Hz to protons within the same three-proton multiplet and is apparently coupled to no other protons in the molecule.

halide with magnesium cleaves to tertiary radical **18**, which leads eventually to much of the disproportionation product (eq 7). Alternatively, it is possible that



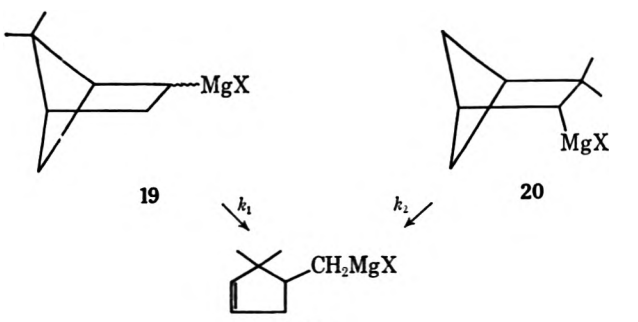
17 **18**

15 + 16 (7)

some cationic ring cleavage of the bromide may occur under the influence of Lewis-acidic magnesium compounds. To test the possibility, a small sample of bromide mixture containing no **6b** was refluxed for 0.5 hr in 0.8 *M* ethereal ethylmagnesium bromide solution. The recovered bromide was very slightly altered in composition. A new weak olefinic absorption appeared at δ 5.59, which could correspond to no more than 4% **6b**. (This resonance differs somewhat in position from that observed in the halide mixtures previously.) A new methyl signal of undetermined origin was also observed at δ 1.26.

As discussed earlier, small amounts of the bromide mixture were partially separated by preparative gas chromatography. Small-scale Grignard reagents were made from fractions containing (1) 50% **5** and 50% **4**; (2) 15% **5**, 46% **4**, and 39% **2** and **3**; (3) 4% **5**, 19% **4**, and 77% **2** and **3**. In fraction 1, the only products isolated from immediate hydrolysis of the mixture were the corresponding hydrocarbons **14** and **13**, but, in the other two reactions, 10 and 16%, respectively, of the total hydrocarbons were of the isopropenyl- or isopropylcyclopentene skeleton, while other hydrocarbons compared roughly with the amounts of the corresponding halides in the mixtures.

When the Grignard reagent mixture was heated in either ether or tetrahydrofuran for several hours at 100–125°, the hydrocarbon mixture formed on hydrolysis changed in composition, with the trimethylcyclopentene increasing at the expense of the bicyclic hydrocarbons. The isopropylcyclopentene (present in significant amount only in the Grignard reagent from the chloride) underwent little or no change. There was very little (<10%) loss of organometallic owing to attack on solvent or hydrolysis by adventitious proton sources. The principal processes occurring on heating are thus ring cleavage of the two bicyclic Grignard

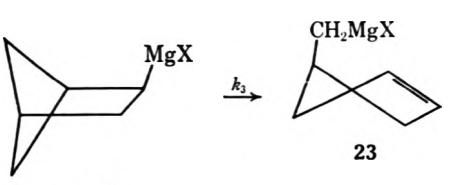


19 **20** **21**

reagents. From qualitative inspection of chromatograms, it is apparent that $k_2 > k_1$.

Nmr spectra of Grignard reagent mixtures confirmed the nature of the reaction which was occurring. The original reagent from the chloride in ether showed absorption at δ 0.33, with apparent coupling constants of 2.6, 7.2, and 7.2 Hz, and at 0.01, about 4 Hz in width, with a hint of splitting with a coupling constant of about 2 Hz. These are reasonably assigned to Grignard reagents **19** and **20**, respectively. (The α isomer of **19** would be preferred on steric grounds.) The apparently identical 7.2-Hz vicinal coupling constants in the spectrum of **19** could be attributed to a "deceptively simple" situation in which this is the average of *cis* and *trans* coupling;[20] the long-range coupling found with the halide isomers appears to be small (<1 Hz) in both Grignard reagents. The olefinic region of the original Grignard spectrum had two minor peaks, presumably due to a small amount of Grignard reagent **21** and olefins **14**, **15**, and **16**, which were not pumped off before taking the nmr sample. The spectrum in tetrahydrofuran was similar, but with the α-H multiplets at δ 0.10 and −0.15. On heating, a higher field multiplet appeared at δ −0.48 (−0.66 in THF), which could be analyzed as the AB portion of the ABX spectrum of the CH_2MgX group in **21**. Parameters derived were $|J_{AB}| = 11.5$ Hz, $|J_{AX}| = 11.0$ Hz, $|J_{BX}| = 4.5$ Hz, and $|\Delta\nu_{AB}| = 19.5$ Hz, showing a reasonable similarity to the spectra reported for halides **5**. Simultaneously, a strong olefinic singlet appeared at δ 5.53. In the tetrahydrofuran spectrum two major peaks remained in the methyl region at δ 0.69 and 0.90 after heating. The rate of change of the nmr patterns was roughly comparable with that derived from gas chromatographic analysis of the hydrolyzed Grignard reagent.

2-Chlorobicyclo[2.1.1]hexane was converted into a Grignard reagent without complication and in high yield. Immediate hydrolysis yielded a single hydrocarbon (>99.5%) identified spectroscopically as bicyclo[2.1.1]hexane. Hydrolysis after 18 hr at 90° produced a new hydrocarbon (95% yield), identified as 4-methylcyclopentene. The nmr spectrum of the initial ethereal Grignard solution showed a multiplet at δ 0.01 with apparent coupling constants of 2.6, 7.8, and 7.8 Hz, similar to that observed for the 5,5-dimethyl homolog. Less well-defined absorptions apparently also attributable to Grignard reagent **22** were at δ 0.9, 1.8, and 2.6. On heating, new high-field doublet absorption appeared at δ −0.22 (J = 8.1 Hz) and olefinic absorption at 5.59, attributed to primary Grignard **23**. Absorption from **22** decreased in intensity.



22 **23**

Rates of ring-cleavage reactions of the dimethylbicyclohexyl Grignard reagents were determined from gas chromatographs of hydrocarbons obtained on hydrolysis of heated samples of the reagents. For comparison, rates of ring cleavage were also determined for α-cyclo-

(20) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

butylethylmagnesium bromide and chloride. Values of rate constants extrapolated to 100° are summarized in Table III. Also listed is a rough estimate of the rate constant for the 2-bicyclohexyl Grignard estimated from nmr spectra.

Discussion

From earlier kinetic studies, it was concluded that the most acceptable mechanism for ring cleavage of the cyclobutylmethyl Grignard reagent is a concerted four-center process. On the basis of the small effect of α-deuterium or α-methyl substitution and insensitivity to solvent polarity, alternative free-radical and carbanion mechanisms were considered less likely.[3] In the present study, the preference for kinetically controlled cleavage of the 5,5-dimethylbicyclo[2.1.1]hexyl Grignard reagent to a primary rather than a tertiary organometallic likewise argues against a radical mechanism and suggests that the carbon to which the magnesium migrates has appreciable organometallic character in the transition state.

An expected consequence of a cyclic mechanism is sensitivity to geometric restriction in a rigid bicyclic system. It may be calculated for the 2-bicyclo[2.1.1]-hexyl skeleton[21] that the magnesium and the carbon to which it will become attached are separated by 3.3 Å, as opposed to a minimum 2.9 Å in a simple cyclobutylmethyl derivative.[22] In the bicyclic compound, the dihedral angle between the carbon–magnesium bond and the cleaving carbon–carbon bond is 73°; in the cyclobutylmethyl system, free rotation allows any dihedral angle. It thus seems reasonable that the rigidity of the bicyclic system might make it more difficult to attain optimum transition state geometry.

On the other hand, the bicyclo[2.1.1]hexyl skeleton should be substantially more strained than a simple cyclobutyl ring. It is reasonable that a part of this additional strain should be relieved in the transition state, resulting in a rate acceleration. For instance, Srinivasan has found that thermal cleavage of bicyclo-[2.1.1]hexane to 1,5-hexadiene has an activation energy 6.8 kcal lower than that for analogous cleavages of simple disubstituted cyclobutanes.[23] It is apparent also that cationic and probably radical cleavages are facilitated by the high ring strain. Unfortunately, no thermochemical data appear to be available for bicyclo-[2.1.1]hexane. Therefore, an attempt was made to estimate the strain of this molecule on the basis of the geometry calculated by Wilcox.[21] While there are substantial uncertainties in such an estimate, it appears likely that bicyclo[2.1.1]hexane is between 10 and 16 kcal more highly strained than cyclobutane.[24] Coupled with 4 kcal of ring strain in the product,[32] cleavage of the 2-bicyclo[2.1.1]hexyl Grignard reagent should be 6 to 12 kcal more exothermic than cleavage of the α-cyclobutylethyl Grignard.

It is then significant to find that the methyl-substituted bicyclohexyl Grignard reagents cleave much less rapidly than the simple cyclobutylethyl Grignard and that the unsubstituted bicyclohexyl reagent is also slower. The observed result is thus consistent with a sizable rate deceleration owing to geometric restrictions on a cyclic transition state.

A closely related factor which should result in a decrease in cleavage rate by any mechanism (including carbanion or radical) is steric restriction of π-orbital

(21) Calculations were made on the geometrical model of C. F. Wilcox, Jr., *J. Amer. Chem. Soc.*, **82**, 414 (1960).

(22) Calculations were based on the geometry of bromocyclobutane, as determined by W. G. Rothchild and B. P. Dailey, *J. Chem. Phys.*, **36**, 2931 (1962).

(23) R. Srinivasan and A. A. Levi, *ibid.*, **88**, 3363 (1963).

(24) One approach is to calculate contributions to the strain energy from angle bending, torsion, and van der Waals repulsions. This approach is complicated by the known fact that the simple quadratic dependence of energy upon angle distortion is invalid for large distortions. Wiberg[25] and Allinger[26] have independently suggested the use of an empirical sigmoid bond angle–strain energy relationship, which presumably also incorporates any contributions from 1,3 carbon–carbon van der Waals interactions as bond angles are decreased and any bond-stretching necessary to accommodate such repulsions in a strained ring. These curves were normalized to fit cyclobutane; so it is likely that they should provide reasonable strain energies for the angles of the cyclobutane ring in bicyclo[2.1.1]hexane. However, they differ substantially in the vicinity of 100°, leading to total bond-bending strain energies of 32.0 (Wiberg) and 23.9 (Allinger) kcal/mol. A similar discrepancy is noted for calculations on norbornane.[27] (Some objection might be raised to using a markedly different potential function for energy calculations from that used in predicting the geometry, but Wilcox[21] noted that variation of the parameters had remarkably little effect on calculated geometry.) Torsional energy (ignoring the possibility of a decrease in torsional strain due to exocyclic bond spreading in small-ring systems) was calculated in the conventional manner to contribute 6.6 kcal/mol. Average torsional angles at the bridgehead were used. van der Waals repulsions, aside from those possibly implicit in bond bending and torsional contributions, were presumed small. The resulting estimate of total strain energy is then 38.6 or 30.5 kcal/mol (*vs.* the experimental value of 26 kcal for cyclobutane[28]). The latter estimate is probably low.[27] A calculation using the customary quadratic relation for bond bending yields a strain estimate of at least 65 kcal/mol.

An alternate approach to torsional and van der Waals strain has been presented by Simmons.[29] In this treatment, torsional energy is treated as a manifestation of hydrogen–hydrogen van der Waals repulsions, using a "hard" potential function. This procedure appears to be invalid in the present instance, as it predicts torsional and H–H repulsion strain energy in cyclohexane to be no less than in norbornane or bicyclohexane.

An additional estimate of strain energy for bicyclo[2.1.1]hexane treats the molecule as a modified cyclobutane. The increased folding (42°) of the cyclobutane ring due to bridging is estimated to increase strain by 1.2 kcal/mol over that of cyclobutane.[25] Torsional and bond-angle strain in the two-carbon bridge should contribute an additional 2.8 and 3.3 (Wiberg) or 1.1 (Allinger) kcal/mol. Finally, distortion of the two bonds on the cyclobutane ring to the proper angle to bond to the two-carbon bridge requires a decrease in a total of four C–C–C angles to 97.2°. This should contribute about 10 (Wiberg) or 5 (Allinger) kcal/mol more. Estimates of total strain energy add up to 43 (Wiberg) or 36 (Allinger) kcal/mol.

(25) K. B. Wiberg and G. M. Lampman, *J. Amer. Chem. Soc.*, **88**, 4429 (1966).

(26) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. Tyminski, and F. A. Van Catledge, *ibid.*, **90**, 199 (1968).

(27) Norbornane appears to be a reasonable proving ground for strain energy calculations in a bicyclic system, since there exists in the literature a strain energy value of 18.5 kcal/mol derived from the heat of combustion.[30] However, the exact magnitude of this strain energy rests on an assumed heat of fusion of 4 kcal/mol, which was presented with no justification, and might be somewhat in error. The situation is further confused by an estimated heat of vaporization of only 2.2 kcal, used by Allinger.[26] A more reasonable estimate would seem to be closer to 8.5 kcal, based on Trouton's rule. With the probably erroneous heat of vaporization, use of the methods of Franklin or Klages[31] to estimate gas phase heats of formation for the unstrained molecule leads to a strain energy of only 12 kcal/mol. Allinger and coworkers[26] calculated the contribution of "strain terms" to norbornane as 12.01 kcal/mol. It is not certain whether calculations on norbornane were used to help establish their empirical strain energy–bond angle curve, but it does appear likely that their curve may not be soundly based vicinity of 10–15° bond angle distortions. Calculations similar to those described for bicyclo[2.1.1]hexane lead to total strain energies of 22.75 and 13.85 kcal/mol, based on bond-bending strain curves of Wiberg and Allinger. The result provides no clear choice between the two. Another calculation by Allinger's method has been reported by Wilcox and compared with his electron diffraction results.[32]

(28) S. Kaarsemaker and J. Coops, *Rec. Trav. Chim.*, **71**, 261 (1952).

(29) H. E. Simmons and J. K. Williams, *J. Amer. Chem. Soc.*, **86**, 261 (1964).

(30) A. Bedford, A. E. Beezer, C. T. Mortimer, and H. D. Springall, *J. Chem. Soc.*, 3823 (1963).

(31) G. J. Janz, "Thermodynamic Properties of Organic Compounds," Academic Press, Inc., New York, N. Y., 1967, pp 58–85.

(32) J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *J. Amer. Chem. Soc.*, **90**, 3149 (1968).

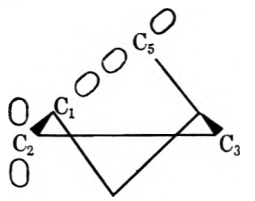
(33) (a) R. B. Turner, "Kekule Symposium," Butterworth and Co., Ltd., London, 1959, p 67; (b) R. B. Turner, P. Goebel, W. von E. Doering, and J. F. Coburn, Jr., *Tetrahedron Lett.*, 997 (1965).

Table III
Rates of Ring Cleavage of 2-Bicyclo[2.1.1]hexyl Grignard Reagents in Ether[a]

Grignard	X	Concn, M[b]	T, °C	$k \times 10^7$[c]	$\Delta H^{\ddagger}$[c]	$\Delta S^{\ddagger}$	k_{rel} (100°)
19[d]	Cl	0.16	102.7	7.64 ± 0.39	32.1 ± 1.3	−1.4	0.0016
		0.16	118.7	49.6 ± 4.2			
		0.16	125.7	96.6 ± 5.8			
19	Br	0.03[e]	102.7	31.7 ± 1.9	30.6 ± 1.1	−1.2	0.0070
		0.03	114.6	122 ± 6			
		0.046	114.6	134 ± 6			
		0.03	125.7	367 ± 9			
20[f]	Cl	0.16	102.7	44.0 ± 3.2	33.4 ± 2.0	5.3	0.0085
		0.16	118.7	269 ± 21			
		0.16	125.7	653 ± 75			
20	Br	0.03[e]	102.7	322 ± 32	28.2 ± 1.9	−4.6	0.0681
		0.03	114.6	970 ± 83			
		0.04	114.6	1100 ± 51			
		0.03	125.7	2960 ± 140			
22[g]	Cl	1.2	88.0	100			0.1
Cyclobutylethyl	Cl	0.145	66.0	169 ± 15	25.7	−5.8	1.68
			80.0	803 ± 92			
Cyclobutylethyl	Br	0.06	66.0	53.1 ± 0.9	31.9 ± 0.7	11.1	1.00
			80.0	355 ± 4			
			94.0	1880 ± 45			

[a] Water content of solvent 1.2×10^{-3} M or less. [b] Metal-bound alkyl group concentration as determined by acid titration or gas chromatography. [c] 50% confidence limits. [d] 5,5-Dimethylbicyclo[2.1.1]hexane-2-magnesium halide. [e] Low concentration of reagent due to large amounts of disproportionation. [f] 3,3-Dimethylbicyclo[2.1.1]hexane-2-magnesium halide. [g] Bicyclo[2.1.1]hexane-2-magnesium halide.

overlap in the forming double bond. As the bond between carbon atoms 1 and 5 begins to break, the hybrid orbital on carbon atom 1 evolves into a p orbital, and π bonding between this orbital and the orbital on carbon atom 2 develops. Most probably, the transition state occurs at some intermediate stage in this transformation. However, at such an intermediate stage, the geometry of the molecule prevents parallel orientation of the axes of the orbitals on C_1 and C_2, diminishing



their overlap and hence the stabilization which the transition state may derive from their bonding. Expressed somewhat differently, the forming π bond is twisted, so that the relief of strain in the transition state is less than in a more mobile system of comparable initial strain. There seems to be little basis in experiment for evaluating the magnitude of this effect, but experiments are currently under way in these laboratories to determine its importance in free-radical cleavage reactions. It might be noted that, in the rearrangements of the bornyl radical studied by Berson, cleavage to the primary radical, which might be geometrically preferred, does compete with cleavage to the tertiary radical, although the latter predominates.[34]

Several other factors, with a potential influence on the rate, make the above interpretation less certain. The two-carbon bridge of the bicyclohexyl system possesses substantial angle strain, with a bond angle of 100°.[22] It is expected that a carbon atom in a strained ring would use increased s character in its other bonds, which should lead to stabilization of a carbon–metal bond. To the extent that equilibrium data of Applequist[35] and Dessy[36] may be taken to reflect the stability of polar carbon–metal bonds, this prediction is verified. Stabilization of the starting state by such an effect should produce a decrease in rate, but it is premature to attempt an evaluation of the magnitude of this effect.

An additional factor may be important with the methyl-substituted systems. The "*gem*-dimethyl effect"[37] is expected to stabilize the strained-ring system relative to the transition state for its cleavage. This effect may account for much of the difference in rate between the methylated and unmethylated bicyclo[2.1.1]hexylmagnesium chlorides. In addition, it is possible that the attachment of an alkyl group (the two-carbon bridge) to the 3 position on the cyclobutane ring may have a sizable rate effect. No information is available now to evaluate alkyl group effects at that position, but a 2-alkyl group slows the rate of ring cleavage of cyclobutylmethylmagnesium chloride by a factor of about 0.3,[38] slightly more than the statistical factor of 0.5 (since ring cleavage occurs mainly to the side away from the methyl group).

Another factor, which is particularly important with the dimethylbicyclohexylmagnesium bromide is the large amount of magnesium halide produced by disproportionation in the Grignard preparation. It had

(34) J. A. Berson, C. J. Olsen, and J. S. Walia, *J. Amer. Chem. Soc.*, **84**, 3337 (1962).

(35) D. E. Applequist and D. F. O'Brien, *ibid.*, **85**, 743 (1963).

(36) R. E. Dessy, W. Kitching, T. Psarras, R. Salinger, A. Chen, and T. Chivers, *ibid.*, **88**, 460 (1966).

(37) See T. C. Bruice and W. C. Bradbury, *ibid.*, **90**, 3808 (1968); F. G. Bordwell, C. E. Osborne, and R. D. Chapman, *ibid.*, **81**, 2698 (1959), and references therein. Heats of formation calculated by Allinger and coworkers[39] for methyl-substituted cycloalkanes predict that alkyl group substitution on a cyclobutane ring produces a substantially greater degree of stabilization than the corresponding substitution in a cyclopentane or cyclohexane.

(38) E. A. Hill and R. A. Doughty, unpublished data.

been found previously that addition of magnesium chloride to cyclobutylmethylmagnesium chloride decreased the rate of ring cleavage. In an attempt to remove the excess of magnesium bromide, one preparation of the bromo Grignard was treated with a slight excess of dioxane. However, the net effect appeared to be to decrease the Grignard concentration (0.05 to 0.02 *M*), while still leaving an excess of bromide in solution (0.05 *M*). The rate of ring cleavage *decreased* by a factor of about 5. A curious difference may be noted in the bicyclic system, in that the bromo Grignard reacts more rapidly than the chloro Grignard while the opposite is true with both cyclobutylmethyl and α-cyclobutylethyl reagents. With the unsubstituted bicyclohexyl Grignard, formation of the Grignard reagent appeared to occur very cleanly, and so no complications are present owing to an excess of magnesium chloride.

Experimental Section

Infrared spectra were obtained on Beckman IR-5 and IR-8 spectrometers and on a Unicam SP500. Nuclear Magnetic resonance spectra were obtained with Varian A-60 and HA-100 spectrometers at ambient temperature with tetramethylsilane as internal standard. (Nmr spectra of Grignard solutions were compared with the high field solvent signal, which, in turn, was referenced to tetramethylsilane in several Grignard solutions.) Microanalyses were performed at the University of Minnesota by Mrs. O. Hamerston and T. S. Prokopov. Boiling points are uncorrected; melting points are calibrated. Gas chromatograms were run on an Aerograph Model A-90-P gas chromatograph, using the following columns: A, 17% Apiezon J on Chromosorb P, 10 ft × 1/2 in.; B, 25% Carbowax 400 on Chromosorb P, 10 ft × 1/4 in.; C, 25% Ucon Polar on Chromosorb P, 10 ft × 1/4 in. and 10 ft × 1/2 in.; D, 20% Carbowax 20M on Chromosorb P, 10 ft × 1/4 in.; E, 25% tricresyl phosphate on Chromosorb P, 10 ft × 1/4 in.; F, 20% Dow Hi-Vac grease on Chromosorb W, 10 ft × 1/4 in.

β-5,5-Dimethylbicyclo[2.1.1]hexan-2-ol (1) was prepared by lithium aluminum hydride reduction of the corresponding ketone as described by Meinwald and Gassman:[5] bp 91–92° (25 mm); n^{24}D 1.4758 [lit.[5] bp 90–92° (24 mm); n^{23}D 1.4757]; ir (neat) 3370 (OH), 1013 cm^{-1} (CO); nmr (CCl_4) δ 0.73 (*d*, 1, J = 8 Hz, *endo* C_6H), 1.07 (s, 3, *endo* C_5CH_3), 1.29 (s, 3, *exo* C_5CH_3), 1.5–2.3 (m, 5), 3.30 (s, broad, 1, OH), 4.33 (q, broad, 1, J = 7.5, 3.5 Hz, CHOH). Its benzoate was obtained as an oil: ir (neat) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 0.84 (d, 1, J = 8 Hz), 1.11 (s, 3, CH_3), 1.28 (s, 3, CH_3), 1.5–2.5 (m, 5), 5.34 (m, 1, CHOH), 7.44 (m, 3, aryl), 8.07 (m, 2, aryl).

Reduction of 5,5-dimethylbicyclo[2.1.1]hexan-2-one with sodium and alcohol was carried out as described previously.[5] The nmr spectrum of the mixture so obtained showed methyl bands of the β isomer at δ 1.08 and 1.28, as well as new stronger methyl groups at 0.75 and 1.25 due to the α epimer. Only one complex multiplet was observed in the CHOH region at δ 4.32.

Reaction of 5,5-Dimethylbicyclo[2.1.1]hexan-2-ol with Thionyl Chloride.—Over a period of 0.5 hr, 9.95 g (0.083 mol) of thionyl chloride was added to a stirred mixture of 10.5 g (0.083 mol) of 5,5-dimethylbicyclo[2.1.1]hexan-2-ol and 6.6 g (0.083 mol) of dry pyridine cooled to 0°. The reaction mixture was stirred for 2 hr at 90–100°. Salt that crystallized on cooling was removed by filtration and washed with ether. The organic phase was washed with dilute hydrochloric acid and sodium bicarbonate solutions and water, dried ($MgSO_4$), and distilled to yield crude chloride. After passage in pentane solution over a column of alumina to remove traces of alcohol, 6.6 g (55%) of chloride product was obtained by distillation: bp 72–73° (30 mm); n^{24}D 1.4760; ir (neat) 2970, 1468, 1391 and 1373 [$C(CH_3)_2$], 1290, 1265, 915, 720 cm^{-1}.

Anal. Calcd for $C_8H_{13}Cl$: C, 66.43; H, 9.05. Found: C, 66.72; H, 9.31.

The nmr spectrum suggested a mixture, and gas chromatography (column C) showed three partially overlapping peaks with relative areas 5, 42, and 53% in order of increasing retention time. The three peaks were partially separated on a preparative scale (154°), and components in the fractions were identified by nmr absorptions. Nmr spectra of the chromatographic fractions indicated the following compositions: (1) 90% 4-chloromethyl-3,3-dimethylcyclopentene (**5a**) and 10% 2-chloro-3,3-dimethylbicyclo[2.1.1]hexane (**4a**); (2) 5% **5a** and 95% **4a**; (3) 10% **4a**, 22% α-2-chloro-5,5-dimethylbicyclo[2.1.1]hexane (**2a**), and 68% β-2-chloro-5,5-dimethylbicyclo[2.1.1]hexane (**3a**). Prominent nmr features are summarized in Table I.

An attempted rechromatogram of the third fraction brought about an increase in the percentage of **4a**, apparently primarily at the expense of **3a**. Other evidence of instability of the products to chromatographic conditions was to be found in minor, ill-formed early peaks in the repeated chromatograms.

The nmr of the total product mixture contained an additional weak resonance at δ 5.59, tentatively assigned to **6a**. The product distribution as derived from the nmr spectrum is listed in Table I.

Reaction of 5,5-Dimethylbicyclo[2.1.1]hexan-2-ol with Triphenylphosphine and Bromine.—Over a period of 25 min, 8.8 g (0.055 mol) of bromine was added to a solution of 6.9 g (0.055 mol) of 5,5-dimethylbicyclo[2.1.1]hexan-2-ol and 15.45 g (0.059 mol) of triphenylphosphine in 40 ml of dry dimethylformamide at 50–55°. After stirring at 55° for 2 hr, the mixture was distilled at 0.8 mm, up to a temperature of 85°. The distillate was diluted with 50 ml of saturated aqueous sodium chloride and extracted with three 25-ml portions of 30–60° petroleum ether. The solution was dried (Na_2SO_4), passed through a short column of alumina, and distilled, yielding 5.85 g (57%) of bromide: bp 68–70° (9 mm); n^{21}D 1.5011; ir (neat) 2970, 1462, 1390 and 1370 [$C(CH_3)_2$], 1230, 901, 685 cm^{-1}.

Anal. Calcd for $C_8H_{13}Br$: C, 50.81; H, 6.93. Found: C, 50.55; H, 6.81.

The nmr spectrum indicated a mixture, and gas chromatography (column D, 140°) showed three overlapping peaks, the last of which had a pronounced shoulder. Relative areas of four components were estimated as 14, 34, 44, and 8%, in order of increasing retention time. A preparative partial separation was carried out, and the three fractions collected were characterized by their nmr spectra. The following compositions were indicated: (1) 50% 4-bromomethyl-3,3-dimethylcyclopentene (**5b**) and 50% 2-bromo-3,3-dimethylbicyclo[2.1.1]hexane (**4b**); (2) 17% **5b**, 45% **4b**, 28% α-2-bromo-5,5-dimethylbicyclo[2.1.1]hexane (**2b**), and 10% β-2-bromo-5,5-dimethylbicyclo[2.1.1]hexane (**3b**); (3) 4% **5b**, 20% **4b**, 55% **2b**, and 21% **3b**. Rechromatography of fraction 1 yielded **5b** in about 90% purity. Prominent nmr features are summarized in Table I. An additional nmr absorption at δ 5.71 in the product mixture was tentatively assigned to the olefinic hydrogens of **6b**.

The integral of the original chloride mixture in the vinyl, CHX, and methyl regions was consistent with a distribution of products **2b**:**3b**:**4b**:**5b**:**6b** of 43:7.5:33:15:1.5. The estimate is approximate, since the result is sensitive to small errors in some of the integrals.

Reaction of β-5,5-Dimethylbicyclo[2.1.1]hexane-2-carboxylic Acid with Bromine and Mercuric Oxide.—Over a period of 25 min, 8.65 g (0.054 mol) of bromine was added to a stirred suspension of 8.30 g (0.054 mol) of β-5,5-dimethylbicyclo[2.1.1]-hexane-2-carboxylic acid and 6.30 g (0.028 mol) of red mercuric oxide in 50 ml of carbon tetrachloride. The reaction was sightly exothermic. After the reaction mixture was heated at 80° for 40 min, cooled, and filtered, the solvent was distilled. The residue was dissolved in ether and extracted with dilute base. Upon acidification of the basic solution, a 48% recovery of starting acid was realized. The ether layer was dried and fractionated, yielding 0.55 g (5%), bp 67–68° (9 mm). The infrared and nmr spectra were similar to those of the product from the previous preparation except that the absorptions ascribed to 4-bromomethyl-3,3-dimethylcyclopentene (**5b**) were missing. From the integration, the mixture appeared to have the composition **2b**:**4b**:**6b** of 38:56:6.

The residue from distillation of the bromide had a strong infrared carbonyl band at 1730 cm^{-1} (neat) suggesting that ester formation had been the predominant reaction path. In an attempted decarboxylation of the carboxylic acid with lead tetraacetate only recovered acid (84%) was obtained.

5,5-Dimethylbicyclo[2.1.1]hexane.—A solution of 5,5-dimethylbicyclo[2.1.1]hexan-2-one (2.0 g, 0.016 mol), 85% potassium hydroxide (2.0 g), and 95% hydrazine (2.5 g, 0.078 mol) in 15 ml of triethylene glycol was stirred in an open flask at 150–160° for 1 hr and then refluxed at 190–200° for 3 hr. Distillation yielded a clear liquid (1.2 g, 68%), which was taken up in pentane, washed with water, dried, and separated by gas chromatog-

raphy (column A). It contained three components in relative amounts of 0.5, 90.5, and 9%. The first of these appeared from its infrared spectrum to be saturated, but was not characterized further owing to the small amount. The second component was 5,5-dimethylbicyclo[2.1.1]hexane: $n^{25}D$ 1.4451; ir (neat) 2960 (CH), 1479 (w), 1479 (s), 1460 (s), 1387 and 1370 [s, $C(CH_3)_2$], 1300 (m) 1274 (s), 1259 (s), 1194 (m), 1185 (m), 1161 (m), 1115 (m), 1083 (m), 920 (m), 821 cm^{-1} (m); nmr (neat), methyl singlets at δ 0.75 and 1.25, an "A_2B_2" pattern centered at 1.61 (ethylene bridge), broad singlet at 2.08 (bridgehead hydrogens), additional absorption which is partially covered, apparently centered ~0.8 and 2.0 accounting for the remaining two hydrogens.

Anal. Calcd for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.23; H, 13.03.

The third fraction was composed of two unsaturated materials present in similar quantities (as shown by further chromatography on column B): ir (neat) 3075 (=CH), 2960, 2870, 1770 (w, $=CH_2$ overtones), 1642 (C=C), 1450, 1380 (CH_3), 986, 958, 888, cm^{-1}; nmr (CCl_4) δ 1.02 (t, J = 7.5 Hz, CH_3), 1.03 (broad singlet), 1.73 (broad singlet), 1.9 (multiplet), 4.69 (broad singlet, $=CH_2$), 5.1–6.4 (multiplet, =CH). These components were not identified further, but are believed to have arisen by pyrolytic cleavage of some component or intermediate in the reaction.

2-Chlorobicyclo[2.1.1]hexane.—Over a period of 30 min, 12.1 g (0.102 mol) of thionyl chloride was added to a solution of 10.0 g (0.102 mol) of bicyclo[2.1.1]hexan-2-ol and 8.0 g (0.102 mol) of dry pyridine maintained at 0°. The reaction mixture was then stirred for 2 hr at 90–100° and overnight at 25°. Pentane (20 ml) was added and the organic solution was filtered from the solid pyridinium salts. The filtrate was washed with dilute hydrochloric acid and saturated sodium bicarbonate, dried ($MgSO_4$), and distilled through a 6-in glass helix packed column, bp 37° (25 mm) [lit.[19] 134–136° (760 mm)]. A trace of alcohol was removed by passage through alumina. The product was greater than 99% pure by gas chromatography: ir (neat) 2900, 1445, 1300, 1280, 1260, 1205, 1147, 1003, 925, 913, 850, 815, and 700 cm^{-1}.

Grignard Reagent from "2-Chlorodimethylbicyclo[2.1.1]hexane."—Sublimed magnesium (0.15 g, 6.14 mg-atoms) was placed in a throughly dried flask with a sealed condenser and flame dried under nitrogen. To the flask was added 0.75 g (5.19 mmol) of chloride mixture in 3.5 ml of dried ether (distilled from lithium aluminum hydride in a stream of prepurified nitrogen). A very small crystal of iodine and 0.01 g of methyl iodine were required to initiate the Grignard reagent formation. After a reflux time of 45 min, a sample was transferred to an nmr tube and sealed. The solvent from the remainder of the solution was pumped under high vacuum to a cold trap (<10 μ for 45 min). The residual Grignard reagent wss dissolved in new dry ether (24 ml), and the resulting clear solution was transferred by syringe under a stream of nitrogen to a set of 36 ampoules, which were sealed under less than an atmosphere of nitrogen for use in kinetics studies. The Grignard concentration was 0.16 M (75%) by acid titration. Several similar preparations of Grignard reagent in ether or tetrahydrofuran were made which varied somewhat in final concentration, yield of reagent (60–80% by acid titration and chromatographic analysis of hydrocarbons), and the efforts needed to initiate reagent formation.

The hydrocarbons removed with the solvent and the hydrocarbons produced by hydrolysis of the Grignard reagent were separatedly analyzed by gas chromatography (column C, 78°, 200 cc/min). Results are presented in Table IV. The components shown were collected and identified as follows, in order of increasing retention time.

(1) 3,3,4-Trimethylcyclopentene (**14**) was obtained with the following spectra: ir (CS_2) 3060 (=CH), 2900, 1650 and 1612 (C=C), 1390, 1377, 1365, 1211, 1100, 1072, 947, 902, 754, 751 (vs, =CH) cm^{-1}; nmr (15% in CS_2) δ 0.81 (s, 3, CH_3), 0.95 (d, 3, J = 7 Hz, CH_3), 1.03 (s, 3, CH_3), 1.7–2.5 (complex multiplet, 3), 5.48 (broadened singlet, 2, =CH); mass spectrum (7 eV) m/e (rel intensity), 110 (7), 96 (8), 95 (100), 93 (6), 79 (5), 77 (7), 66 (26), 55 (17), 53 (9), 44 (6), 41 (16), 39 (11). The spectra require a trimethylcyclopentene with a nonequivalent *gem*-dimethyl group. The 3,3,4 isomer is most consistent with the positions of aliphatic proton resonances and is the only isomer derivable in straightforward fashion from the bicyclic system.

(2) 2,2-Dimethylbicyclo[2.1.1]hexane (**13**) was obtained: ir (neat and gas, 20 mm) 2960 (vs), 1460 (s), 1390 and 1373 [$C(CH_3)_2$], 1306, 1238, 1200, 1068, 938, 848, 800 cm^{-1}; nmr (CCl_4) δ 1.08 [s, 6, $C(CH_3)_2$], 1.37 (m, 6), 2.19 (AB pattern, 2, J = 7 Hz, $\Delta\nu$ = 0.37 ppm, with additional coupling). The bicyclic skeleton is required by the lack of olefinic absorption in the nmr and ir. The single unsplit methyl peak and the coupled bridgehead protons at δ 2.19 allow only the 2,2-dimethyl isomer.

(3) 5,5-Dimethylbicyclo[2.1.1]hexane (**12**) was obtained with ir and nmr identical with those of independently synthesized material.

(4) 4-Isopropylcyclopentene (**15**) was obtained: ir (neat and gas) 3060 (=CH), 2960, 1620 (C=C), 1459, 1391 and 1373 [$C(CH_3)_2$], 1300, 1260, 1180, 937, 686 cm^{-1} (*cis* CH=CH); nmr (CCl_4) δ 0.89 (unsymmetrical doublet, 6, J = 6 Hz, CH_3), 1.4–2.5 (m, 6), 5.60 (broadened singlet, 2, =CH). The infrared spectrum is in agreement with a published spectrum[39] and, in addition, the 4-isopropyl isomer is preferred by the similarity of the aliphatic methylene resonance at about δ 2.1 to that of 4-methylcyclopentene. Two minor unidentified components followed in the hydrocarbon pumped from the chloro-Grignard preparation.

(5) 4-Isopropenylcyclopentene (**16**) was obtained: ir (CS_2) 3060 (=CH), 2940, 1643 and 1617 (C=C), 1378, 890 ($=CH_2$), 675 cm^{-1} (*cis* CH=CH); nmr (CS_2) δ 1.69 (s, 3 $=CCH_3$), 2.0–3.0 (m, 5), 4.60 and 4.68 (2, $=CH_2$), 5.63 (s, 2, CH=CH). The isopropenyl group is indicated by an unsymmetrically disubstituted double bond and unsplit allylic methyl group in the ir and nmr spectra. Orientation relative to the double bond in the cyclopentene ring is indicated by the absence of methylene absorption above δ 2.0.

Table IV

Hydrocarbons from Dimethylbicyclo[2.1.1]hexyl-2-magnesium Halide Preparations

Component[a]	% of C_8 hydrocarbons: Solvent from chloride[b]	Grignard from chloride	Solvent from bromide	Grignard from bromide
14	3	8	9	23
13	13	26	29	30
12	14	58	24	47
15	24	5	8	
16	37	3	30	

[a] In order of retention time, 25% Ucon Polar on Chromosorb P. [b] Two minor components between **15** and **16** were present in about 3% each, but were not identified owing to small quantities.

Sealed ampoules of the Grignard solution were heated in an oil bath and analyzed in the following manner. The ampoules were broken open under a nitrogen atmosphere, the solvent and volatile materials were pumped to a cold trap (30 min at <5 μ), nitrogen was readmitted to the system, and the residual Grignard reagent was hydrolyzed with ice-cold 3 M H_2SO_4 after addition of ~0.5 ml of ether. The hydrocarbons in the ether solution were analyzed gas chromatographically. It was possible from such analyses to determine separate rate constants for disappearance of the bicyclic components **12** and **13**.

Grignard Reagent from "2-Bromodimethylbicyclo[2.1.1]-hexane" Mixture.—A reaction flask containing 0.316 g (13 mg-atoms) of sublimed magnesium was flame dried under high vacuum, and about 5 ml of ether (over lithium aluminum hydride) was distilled into the flask on a vacuum line. Under a stream of dry nitrogen, 1.5 g (7.93 mmol) of bromide mixture was added by syringe. The flask was warmed to initiate reaction and refluxed for 50 min under nitrogen. After removal of an nmr sample, solvent and volatiles were pumped to a cold trap under vacuum (<5 μ). Fresh ether (40 ml) was distilled into the flask, and the resulting clear solution was transferred by syringe to ampoules and sealed under nitrogen. Titration for base and bromide ion gave concentrations of 0.03 and 0.18 M, respectively. Analysis of the Grignard solutions was carried out in a manner similar to that for the chloride. Compositions of the hydrocarbon mixtures are shown in Table IV. In another preparation of Grignard reagent, base concentration was 0.05 M and bromide concentration 0.2 M. An amount of dioxane equivalent to the bromide was added, the sample was sealed, shaken for 3 days, and centrifuged, and the clear supernatant solution was withdrawn. Base and bromide concentrations were 0.02 and 0.05 M, respectively.

(39) W. Hückel and R. Bross, *Ann.*, **664**, 1 (1963).

Grignard Reagent from 2-Chlorobicyclo[2.1.1]hexane.—Sublimed magnesium (0.156 g, 6.5 mg-atoms) was placed in a dried flask with a sealed condenser and flamed out under nitrogen. To this was added 0.69 g (5.9 mmol) of 2-chlorobicyclo[2.1.1]-hexane in 4 ml of ether (distilled from lithium aluminum hydride). About 0.01 g of methyl iodide was used to initiate formation of the Grignard, and reflux was continued for 3 hr. Most of the reagent was transferred by syringe to two ampoules and an nmr tube and sealed under nitrogen, and the remaining reagent was hydrolyzed with water. Gas chromatography (column A) showed one hydrocarbon component comprising at least 99.5% of the total, which was isolated by preparative chromatography: ir (gas) 2930 (vs), 1460, 1292, 1203, 1123, 1078, 1018, 898, 829 cm^{-1}; nmr identical with reported spectra of bicyclo[2.1.1]-hexane.[9,40]

The sealed tubes were heated for 18 hr at 90°, opened, hydrolyzed, and analyzed in a similar fashion. The major component (~95%) was isolated by preparative gas chromatography: ir identical with the published spectrum[41] of 4-methylcyclopentene; nmr (CCl_4) δ 1.10 (d, 3, CH_3), 1.95 (m, 2) 2.45 (m, 3), 5.58 (s, 2, olefinic).

α-Cyclobutylethyl chloride was prepared by adding α-cyclobutylethanol (5.0 g, 0.050 mol) to a solution of preformed triphenylphosphine dichloride[42] (0.055 mol) in dry dimethylformamide (50 ml) at 35–40°. Work-up as in previous halide preparations gave a 25% yield of chloride: bp 127–128°; $n^{23}D$ 1.4408 (lit.[3] bp 122–127.5°); ir (neat) 2970 (vs), 2860 (m), 1450 (s), 1380 (m), 1252 (s,) 1050 (m), 670 cm^{-1}; nmr (neat) δ 1.34 (d, 3, J = 6.6 Hz), 3.87 (m, 1, coupling constants of 6.6 Hz to three hydrogens and 7.6 Hz to a lone hydrogen, CHCl). A small amount (*ca.* 11%) of isomeric impurity was probably responsible for a broad absorption at δ 4.24. Gas chromatography showed two components (about 12%) in addition to the major product. In a previous sysnthesis using thionyl chloride, about 56% of the product consisted of rearranged isomers with a cyclopentane ring.[3]

α-Cyclobutylethyl Bromide.—Bromine (12.95 g, 0.08 mol) was added to a stirred solution of α-cyclobutylethanol (8.0 g, 0.080 mol) and triphenylphosphine (22.0 g, 0.084 mol) in dry dimethylformamide (50 ml) at 55°. Work-up as in the case of α-cyclobutylethyl chloride gave the product bromide (5.2 g, 40%): bp 62–64° (30 mm); $n^{27}D$ 1.4730; ir (neat) 1380 (s), 1240 (s), 1181 (s), 1161 (s), 1040 (m) cm^{-1}; nmr (neat) δ 1.54 (d, 3, J = 6.7 Hz), 1.84 (m, 7), 4.00 (doublet of quartets, 1, J = 8.0, 6.7 Hz, CHBr). In addition, three broad resonances at *ca.* δ 3.50, 3.65, and 4.40 from isomeric impurities amounted to about 0.1 proton. Gas chromatography showed three minor components in addition to the major product.

Anal. Calcd for $C_6H_{11}Br$: C, 44.19; H, 6.80. Found: C, 44.17; H, 6.94.

Grignard reagents from α-cyclobutylethyl bromide and chloride were prepared in ether in a manner similar to that described for previous Grignard preparations. Immediate hydrolysis of the Grignard reagent from the chloride produced a mixture of hydrocarbons consisting of 68% ethylcyclobutane, 19% 2-hexene (almost exclusively *cis*), and 13% methylcyclopentane. After the mixture was heated, hydrolysis of the Grignard reagent yielded hydrocarbon mixtures with an equal mixture of *cis*- and *trans*-2-hexenes increasing at the expense of the ethylcyclobutane. The methylcyclopentane remained as a constant fraction of the total. Similar results were obtained from the bromide.

Registry No.—**2a**, 20826-69-1; **2b**, 20826-70-4; **3a**, 20826-71-5; **3b**, 20826-72-6; **4a**, 20826-95-3; **4b**, 20826-96-4; **5a**, 20826-97-5; **5b**, 20826-98-6; **13**, 20858-75-7; **14**, 20826-99-7; **16**, 20827-00-3; **19** (X = Cl), 20827-01-4; **19** (X = Br), 20827-02-5; **20** (X = Cl), 20858-76-8; **20** (X = Br), 20827-03-6; **22** (X = Cl), 20827-04-7; cyclobutylethyl-2-magnesium chloride, 20858-77-9; cyclobutylethyl-2-magnesium bromide, 20826-73-7; 5,5-dimethylbicyclo[2.1.1]hexane, 20826-74-8; α-cyclobutylethyl bromide, 20826-75-9.

(40) R. Srinivasan, *J. Amer. Chem. Soc.*, **83**, 4923 (1961).

(41) K. Kochloefl, V. Bazant, and F. Šorm, *Collect. Czech. Chem. Commun.*, **22**, 1895 (1957).

(42) D. G. Coe, R. S. Landauer, and H. W. Rydon, *J. Chem. Soc.*, 2281 (1954).

The Stereochemistry of Methylation of Lithium Enolates of 2-Methyl-4-*t*-butylcyclohexanone[1a]

BYRON J. L. HUFF,[1b,c] F. NORMAN TULLER,[1d] AND DRURY CAINE

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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The reaction of the lithium enolate of 4-*t*-butylcyclohexanone and the three lithium enolates derived from *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanone with methyl iodide or methyl-d_3 iodide in 1,2-dimethoxyethane has been investigated. In all cases, mixtures of stereoisomeric methylation products were obtained. The results have been interpreted by considering that the geometry of the transition state for the alkylation reaction closely resembles the reactants.

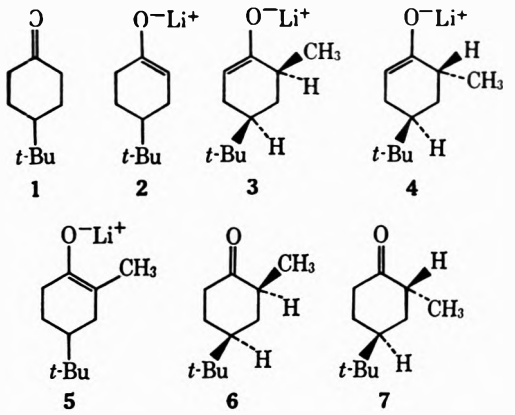
Alkylation reactions of a number of systems involving trapping of specific lithium enolates of unsymmetrical ketones have demonstrated that these species, in contrast to other alkali metal enolates, undergo slow proton-transfer reactions with derived alkylation products.[2] This unique property makes lithium enolates particularly valuable in studies on the stereochemistry of alkylation of simple enolate systems, since kinetically formed alkylation products having epimerizable centers α to the carbonyl group should be isolable under appropriate conditions.

We have studied the stereochemistry of methylation of the lithium enolate **2** derived from 4-*t*-butycyclohexanone (**1**). In addition, we have determined the stereochemistry of methylation of the enolates **3**, **4**, and **5**, derived from *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanone, **6** and **7**, respectively, by treating enolate mixtures composed largely of each of these species with methyl iodide or methyl-d_3 iodide in 1,2-dimethoxyethane (DME). Enolate **2** was formed by titration of a solution of trityl lithium in DME at room temperature with **1** until the equivalence point was reached, and then excess methyl iodide was added rapidly. Vpc

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This work was presented in part at the Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967. (b) Abstracted in part from the Ph.D. Dissertation of B. J. L. Huff, Georgia Institute of Institute of Technology, May 1968. (c) NASA Fellow, 1965–1967. (d) NDEA Fellow, 1966–present.

(2) (a) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem. Soc.*, **83**, 2965 (1961); G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965); (b) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965); (c) D. Caine, *ibid.*, **29**, 1868 (1964); (d) D. Caine B. J. L. Huff, *Tetrahedron Lett.*, 4695 (1966).

analysis[3] of the alkylation mixture showed that **6** and **7** were produced in a 55:45 ratio. These alkylation results are in complete agreement with those of House and coworkers,[4] who treated **2** with excess triethyloxonium tetrafluoroborate in methylene chloride and excess ethyl iodide in DME using a short reaction period. Thus, in methylations and ethylations of **2**, the C-2 alkyl group is introduced *cis* and *trans* to the *t*-butyl group with about equal facility.



Before undertaking alkylation of the 2-methyl-4-*t*-butylcyclohexanone enolates, the composition of kinetic and equilibrium lithium enolate mixtures obtained by treating *cis*-2-methyl-4-*t*-butylcyclohexanone[5a] (**6**) and mixtures of *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanone containing largely the *trans* isomer[6] (**7**) with tritylllithium in DME at room temperature were determined by the acetic anhydride quenching method.[7] The kinetic runs involved addition of a DME solution of the ketone to excess tritylllithium in DME, while under equilibrium conditions an excess of the ketone was employed and the enolate solution was heated at reflux for 3 hr. The results are recorded in Table I. As expected, the ratios of the less to the more substituted enolates obtained by treating **6** with tritylllithium in DME were similar to those reported earlier for 2-methylcyclohexanone.[2d] For both ketones, there is a 6–7 to 1 preference for proton removal from the less substituted 6 position by tritylllithium in DME at room temperature. The exclusive conversion of **7** into **4** under kinetic conditions apparently results from the usual kinetic preference coupled with the importance of stereoelectronic control in the enolization process.[8,9]

TABLE I

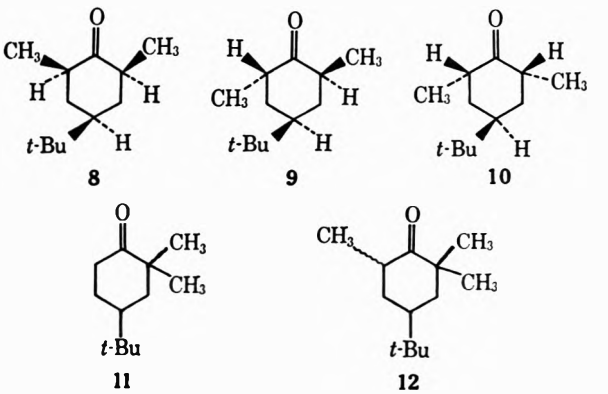
COMPOSITION OF THERMODYNAMIC AND KINETIC MIXTURES OF LITHIUM ENOLATES OF *cis*- AND *trans*-2-METHYL-4-*t*-BUTYLCYCLOHEXANONE GENERATED WITH TRITYLLITHIUM IN DME[a]

Ketone	Conditions	Enolate composition, % $\Delta^{1,6}$	Enolate composition, % $\Delta^{1,1}$
6[b]	Kinetic	86[c]	14[c]
6[b]	Thermodynamic	11[c]	89[c]
23% 6 + 77% 7[d]	Kinetic	97 (20% **3**, 77% **4**)[e]	3

[a] The enolate compositions were determined by the acetic anhydride quenching method (ref 7); see the Experimental Section for details. [b] The presence of *ca.* 6% **7** along with **6** was neglected. [c] Percentages are averages of two or more runs. [d] Average of two runs using 25:75 and 20:80 mixtures of **6** and **7**. [e] Spectroscopic evidence indicated that ketone **7** is converted exclusively into the $\Delta^{1,6}$-enolate with tritylllithium in DME (see Experimental Section).

As with other cyclic ketones, the more substituted lithium enolate is the more stable and enolate mixtures containing mainly **5** were produced under thermodynamic conditions.[2b-d]

For the methylation runs, solutions of the kinetic and equilibrium lithium enolate mixtures derived from **6** and **7** were prepared as described for the acetic anhydride quenching experiments and then treated with excess methyl iodide at room temperature. The relative amounts of starting ketones, the four possible monoalkylation products **8**, **9**, **10**, **11**, and the dialkylation product **12**, were determined by vpc[3] and are recorded in Table II. Each of the alkylation products, with the exception of **10**, was isolated by preparative vpc[3] and exhibited nmr and mass spectral properties consistent with its structure. The structure of **10** was assigned on the basis of its behavior on vpc and by the fact that refluxing the methylation product mixture containing **10** with 10% hydrochloric acid gave the equilibrium mixture of 2,6-dimethyl-4-*t*-butylcyclohexanones (85% **8** and 15% **9** by vpc[3]) and **11** and **12** only. This 85:15 *cis*/*trans* ratio corresponds closely to that reported by Conia and Briet[10] for several 2-alkyl-6-methyl-4-*t*-butylcyclohexanones.



The data in Table II allow the determination of the stereochemistry of methylation of the enolates **3** and **4**. In the methylation of **3**, the products derived from the introduction of the new group *cis* and *trans* to the *t*-butyl group, *i.e.*, **8** and **9**, respectively, were formed in a ratio of 1:1.8. Only a small amount of the dimethyla-

(3) A 10 ft × 0.25 in. column containing 15% 4-methyl-4-nitropimelonitrile on 60/80 firebrick that had been acid washed and neutralized was employed for the analysis.

(4) H. O. House, B. A. Tefertiller, and H. O. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

(5) (a) Actually, the equilibrium mixture of **6** and **7**, which contains about 6% **7**, was employed.[5b] It was felt that the presence of this small amount of **7** in the mixture would not significantly influence the enolate composition and alkylation data. (b) N. L. Allinger, *et al.*, *J. Amer. Chem. Soc.*, **88**, 2999 (1966).

(6) The mixture was prepared by kinetic hydrolysis of the enamine prepared from **6** and pyrrolidine; see S. K. Malhotra and F. Johnson, *Tetrahedron Lett.*, 4027 (1965); F. Johnson and A. Whitehead, *ibid.*, 3825 (1964). We wish to thank Dr. Malhotra for making the experimental details for the hydrolysis procedure available to us.

(7) (a) H. J. Ringold and S. K. Malhotra, *J. Amer. Chem. Soc.*, **84**, 3402 (1962) (b) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(8) Under kinetic conditions, **6** is converted into a 70:30 mixture of enolates analogous to **3** and **5** using trityl potassium in DME. This base is thus less selective than tritylllithium in forming the less substituted metal enolate. However, it was observed that tritylpotassium as well as trityl lithium converts **7** exclusively into the $\Delta^{1,6}$-enolate.

(9) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 151 ff.

(10) J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881, 3888 (1966).

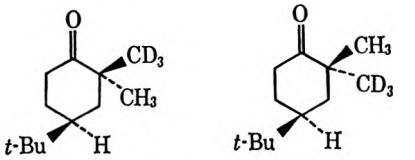
TABLE II
PRODUCTS OF REACTION OF LITHIUM ENOLATE MIXTURES DERIVED FROM *cis*- AND *trans*-2-METHYL-4-*t*-BUTYLCYCLOHEXANONE WITH METHYL IODIDE IN DME[a]

Enolate mixture	Composition of ketone mixtures, %[a] 6	7	8	9	10	11	12
86% 3, 14% 5	..	..	28	52	..	14	6
11% 3, 89% 5	26[b]	2[b]	5	..	..	53	13
20% 3, 77% 4, 3% 5	..	..	9	55	19	3	14

[a] See Experimental Section. [b] Excess ketone (25%) employed for equilibration of the enolates.

tion product **12** was produced in this run; thus, dialkylation did not significantly influence the **8** to **9** ratio. To establish that the ratio of **8** to **9** represented the kinetic product ratio, an experiment similar to that described by House and coworkers[4] was employed in order to demonstrate that equilibration between these ketones was insignificant during reaction and work-up. A mixture containing equal amounts of **6** and its 2,6,6-trideuterio derivative was treated under kinetic conditions with tritylllithium in DME. The mixture was alkylated with methyl iodide as described above, and then worked up in the usual way. The mass spectrum of the dialkylation products revealed the presence of d_0 and d_2 species, but no significant amount of d_1 species. Since all of the alkylation experiments reported herein were conducted under the same conditions as above, significant equilibration among kinetic alkylation products in any of the runs is unlikely. In the alkylation of **4**, after correcting for the presence of **3** (see Table II) in the enolate mixture, the ratio of **9** (new methyl group *cis* to the *t*-butyl group) to **10** (new methyl group *trans* to the *t*-butyl group) is *ca.* 2:1. The dimethylation product **12** accounted for about 14% of the alkylation mixture in this case. Ketones **8** and **9**, having axial hydrogen atoms α to the carbonyl group, should be more readily converted to their enolate anions[7b] than **10**, so that the **9** to **10** ratio may actually be slightly larger than 2:1.

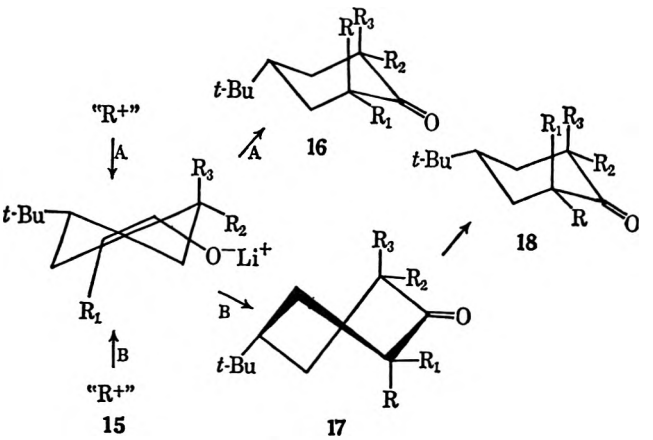
Reaction of the enolate mixture composed largely of **5** with methyl-d_3 iodide gave a mixture of 2-methyl-2-methyl-d_3-4-*t*-butylcyclohexanones, *i.e.*, **13** and **14**, which was isolated by preparative vpc.[3] Ketone **11** exhibits low ($\delta_{TMS}^{CCl_4}$ 1.13 ppm) and high field ($\delta_{TMS}^{CCl_4}$ 1.00 ppm) singlets in carbon tetrachloride solution, and these absorptions are moved upfield and downfield, respectively, when the solvent is changed to benzene.[10] This solvent shift behavior is characteristic of axial and equatorial methyl substituents.[11] The methyl absorptions of ketones **7** and **6** occur at low and high field, respectively, in deuteriochloroform[12] and carbon tetrachloride solution, and each of these absorptions show solvent shifts similar to those of **11** in benzene solution. Assuming a chair conformation for the ring in **11**, it appears that the 1.13-ppm absorption can be assigned to the axial C-2 methyl group *trans* to the *t*-butyl group and the 1.00-ppm absorption to the equatorial C-2 methyl group *cis* to the *t*-butyl group. Integration of the methyl region of the nmr spectrum of the mixture of **13** and **14** showed that the ratio of the low to high field singlets was 3:7. Thus, we have tentatively concluded that **14** is the major product of trideuteriomethylation of **5**.



13 **14**

Conia and Briet[10] have carried out alkylations of the sodium enolate analogous to **5** and related species derived from several 2-alkyl-4-*t*-butylcyclohexanones in benzene, and, on the basis of chemical evidence, originally assigned configurations to the 2-alkyl-2-methyl products which indicated that there was a slight preference for the introduction of the new group *cis* to the *t*-butyl group.[13] However, Conia has recently pointed out that the chemical evidence for the original assignments is not unequivocal and that probably the assignments should be reversed.[14]

The above results on the methylation of the lithium enolates **2**, **3**, **4**, and **5**, those of House and coworkers[4] on the ethylation of **2**, and those of Conia and Briet[10] on the alkylation of sodium enolates analogous to **5** clearly demonstrate that there is a low degree of stereoselectively involved in these reactions. Considering the half-chair conformation **15**, energetically favorable perpendicular attack by the alkylating agent can occur from either of two directions, *i.e.*, path A or path B.[15] Path A attack would lead to the chair conformation **16** having the new group axial to the ring and *trans* to the *t*-butyl group. Path B attack would lead initially to the twist-boat conformation **17** which could undergo conformational change to the chair form **18** having the new group equatorial to the ring and *cis* to the *t*-butyl group.



a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_3 = H$; $R_2 = CH_3$
d, $R_1 = CH_3$, $R_2 = R_3 = H$

(11) M. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., Calif., 1964, p 159 ff.

(12) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

(13) Apparently, the nature of the metal cation and solvent does not materially influence the alkylation stereochemistry in this system, as we obtained essentially the same ratio of products as that reported by Conia and Briet[10] on reaction of **5** with isobutyl iodide in DME.

(14) J. M. Conia, personal communication.

(15) See L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965), and references therein.

As pointed out by House and coworkers,[4] it has been generally assumed that chair-axial attack (path A) would be the more favorable reaction pathway, so that a predominance of products such as **16** would be predicted. However, such an argument requires that the formation of the new C–C bond be relatively far advanced in the transition state for the alkylation reaction.[16]

Our recent finding on the rates of alkylation of alkali metal enolates of 2,2- and 2,6-dimethylcyclohexanone appeared to be best interpreted by considering that the transition state for the enolate alkylation reaction has a geometry close to that of the reactants.[17] This interpretation has also been invoked by House and coworkers[4] and appears to provide the best explanation for the stereochemical results of the alkylation of the enolates of 4-*t*-butylcyclohexanone and derivatives as well as other systems.[4,10,18] This would mean that steric factors within the metal enolate would be the major factor controlling the stereochemistry of the alkylation reaction. The 1:1 product ratio in the alkylation of **2** suggests that the steric interactions involved for either mode of attack on the enolate **15a** (**2**) are about equal. For both **3** and **4**, attack from the side of the enolate opposite to the C-6 methyl group is favored by about 2:1. Considering enolate **15b** (**4**), the 1,3 interaction between the quasiaxial C-6 methyl group and the approaching alkylating agent that would be involved in path A attack is apparent from models. In **15c**, the quasiequatorial methyl group at C-6 does not appear to offer significant hindrance to approach of the alkylating agent from the same side of the enolate anion. However, in this species there is a sizable solvent shell–quasiequatorial methyl group interaction[19] which could be relieved to some extent if the enolate undergoes a change in conformation toward the half-boat form. Such a change would bring the C-6 methyl group into a position in which it could exert hindrance to the approach of the alkylating agent *via* path B.

The apparent slight preference for path A attack in alkylation of **15d** (**5**) as compared with **15a** (**2**) is difficult to explain. This suggests that the transition state for alkylation may have somewhat more product character in the former case. As enolate mixture composition studies on cyclohexanone derivatives show, more substituted lithium enolates are more stable than less substituted ones, and **5** should be of lower energy than **2**. Thus, a lower degree of reactivity for **5** with resultant increase in the extent of bonding in the alkylation reaction transition state might be expected. Another possibility is that the transition state for alkylation of **5**, being more sterically hindered than that for **2**, requires closer approach of the alkylating agent. In that case, steric factors within the developing product would play a more important role than in alkylation of the unsubstituted enolate.

The arguments above are probably an oversimplification, since they are not based upon knowledge of the full details of the alkylation reaction mechanism. Kinetic studies on the alkylation of **3** and **5** show that the reaction is first order in metal enolate.[20] This appears to rule out the possibility that the free enolate anion is the reactive species, but it does not establish whether monomeric ion pairs or some higher aggregates are involved in the reaction. If aggregates are involved, the actual structures of these species would be expected to have some bearing on the stereochemistry of the reaction.

Experimental Section[21]

cis-**2-Methyl-4-*t*-butylcyclohexanone** (**6**).—This compound was prepared by the method of Conia and Briet[10] in 23% yield from 4-*t*-butylcyclohexanone. Vpc analysis[3] indicated that a mixture composed of 94% **6** and 6% **7** was obtained. The nmr spectral properties of **6** were identical with those reported.[10]

The trideuterio derivative of **6** was prepared by refluxing the ketone (3.0 g) for 10 hr with 10 ml of deuterium oxide containing 0.10 g of potassium carbonate. The exchange was repeated three times using fresh batches of deuterium oxide and potassium carbonate, and, in a final exchange, 10 ml of dioxane was added along with the deuterium oxide as a cosolvent. After cooling, the mixture was added to 10 ml of deuterium oxide and extracted with three 15-ml portions of ether. The ether solution was dried over sodium sulfate, the solvent was removed under reduced pressure, and the residue was distilled to give 2.0 g of *cis*-2-methyl-4-*t*-butylcyclohexanone-d_3: bp 60–65° (0.4 mm); mass spectrum (70 eV) *m/e* (rel intensity) 171 (77), 170 (4), 115 (100), 69 (63), 57 (93). The parent ion peak ratios showed that the sample contained 5% d_2 species and 95% d_3 species.

trans-**2-Methyl-4-*t*-butylcyclohexanone** (**7**).—A solution of 12.0 g (0.071 mol) of **6** and 12 ml of pyrrolidine (shaken with potassium hydroxide and freshly distilled prior to use) in 60 ml of dry benzene was refluxed under nitrogen for 48 hr using a Dean–Stark water separator. After removal of the solvents under reduced pressure, the mixture was distilled and yielded 10.5 g of the enamine, N-(*trans*-2-methyl-4-*t*-butylcyclohex-6-enyl)pyrrolidine, bp 79–85° (0.1 mm). To a solution of the enamine (10.5 g) in 250 ml of diglyme (refluxed over calcium hydride and freshly distilled prior to use) under nitrogen, 10.0 g of 50% aqueous acetic acid was added dropwise with stirring over 3 min. The mixture was stirred for 10 min and poured into a mixture of 250 ml of water and 250 ml of ether. After shaking, the layers were separated and the aqueous layer was extracted with four 125-ml portions of ether. The combined ethereal extracts were washed with 125 ml of water, 125 ml of saturated aqueous sodium bicarbonate, and 100 ml of brine. The ethereal solution was dried over magnesium sulfate, the solvent was removed under reduced pressure, and the residue was distilled to give 5.6 g (71%) of a mixture of **6** and **7**, bp 60–65° (0.5 mm). Vpc analysis[3] of this mixture showed that it contained 75% **7** and 25% **6**.

Preparative vpc[3] was attempted in an effort to obtain pure **7** and a sample composed of 80% **7** and 20% **6** was obtained. Further purification of a sufficient quantity of this material for subsequent experiments appeared to be impractical and mixtures of **6** and **7** were employed. However, a small sample of **7** of greater than 95% purity was collected[3] and showed nmr (CCl_4) δ 2.7–1.2 (broad absorption, 7), 1.10 (d, 3, J = 7 Hz, C-2 axial $CHCH_3$), and 0.92 ppm [s, 9, $C(CH_3)_3$]; nmr (C_6H_6) δ 1.00 (d, 3, J = 7 Hz, C-2 axial $CHCH_3$) and 0.80 ppm [s, 9, $C(CH_3)_3$].[22]

(16) Although the free-energy differences (*ca.* 3 kcal/mol) between the boat and chair forms of α-alkyl-4-*t*-butylcyclohexanones are considerably smaller than that between the chair and boat forms of cyclohexane[5b] (and perhaps are even smaller for 2,2- and 2,6-dialkyl-4-*t*-butylcyclohexanones), products such as **16** still should be significantly favored if the transition state for the alkylation reaction closely resembled the products.

(17) D. Caine and B. J. L. Huff, *Tetrahedron Lett.*, 3399 (1967).

(18) Reference 9, p 202 ff.

(19) S. K. Malhotra and F. Johnson, *J. Amer. Chem. Soc.*, **87**, 5513 (1965).

(20) B. J. L. Huff, Ph.D. Dissertation, Georgia Institute of Technology, 1968.

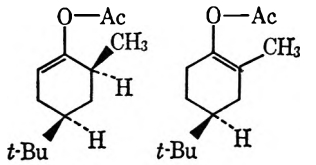
(21) Boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137 or Model 457 infrared spectrophotometer. Nmr spectra were determined at 60 Mc with a Varian A-60 spectrometer. Mass spectra were determined using a Varian M-66 mass spectrometer. Vapor phase chromatography was performed using an Aerograph A-90-P3 with helium as the carrier gas. 1,2-Dimethoxyethane (DME) was distilled through a 6-ft column packed with glass helices and dried by reflux over lithium aluminum hydride and distillation prior to use. Methyl iodide was dried over calcium chloride and distilled prior to use. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(22) See ref 11 for the nmr spectral properties of **7** in deuteriochloroform and pyridine solution.

Determination of the Composition of Thermodynamic and Kinetic Mixtures of Lithium Enolates of *cis*- and *trans*-2-Methyl-4-*t*-butylcyclohexanone by the Acetic Anhydride Quenching Method. General Procedure.—A general procedure for preparing the lithium enolate mixtures with variations to allow for kinetic and thermodynamic control was followed. In a flame-dried apparatus, triphenylmethane was dissolved in dry DME at room temperature under nitrogen, and a solution containing approximately an equivalent amount of phenyllithium in benzene–ether was added. The red solution was stirred for 30–45 min until the disappearance of phenyllithium was indicated by a negative Gilman test.[23]

For formation of the kinetic lithium enolate mixture, 0.9 equiv of ketone (based on tritylllithium) in DME was added to the solution dropwise with stirring; in all cases the red color of the tritylllithium solution persisted after the addition of the ketone was complete. For the thermodynamic enolate mixture, 1.10–1.25 equiv of ketone was added dropwise with stirring and the mixture was allowed to stir for 18 hr at the ambient temperature or for 3 hr at reflux temperature to bring about enolate equilibration. The enolate solution was added dropwise with stirring under nitrogen over 15–30 min to 10 equiv of freshly distilled acetic anhydride at room temperature. The mixture was stirred for 30 min and the excess acetic anhydride was destroyed by addition of the reaction mixture to a stirred mixture of pentane and saturated aqueous sodium bicarbonate (50–75 ml of each per 0.010 mol of ketone) at 0°. The pentane solution was separated, washed with saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled to yield a mixture of enol acetates.

A. *cis*-2-Methyl-4-*t*-butylcyclohexanone (6).[5] Thermodynamic Mixture.—A solution of tritylllithium was prepared from 3.02 g (0.012 mol) of triphenylmethane in 50 ml of DME and 0.0080 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether). After stirring for 1 hr, a solution of 1.56 g (0.0094 mol) of **6**[5] in 10 ml of DME was added dropwise with stirring and the mixture was refluxed for 3 hr. After being cooled to room temperature, the mixture was quenched with acetic anhydride as described above. Distillation gave 0.94 g of a mixture of enol acetates **19** and **20**, bp 70–75° (0.4 mm). The mixture was freed from a trace of **6** by preparative vpc.[24]

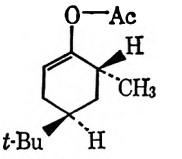


19 **20**

Although several chromatography columns were tested, we were unable to separate mixtures of isomeric enol acetates derived from **6** and **7** by vpc. However, by integration of the nmr spectrum of the above mixture, the composition was found to be *ca.* 90% **20** and *ca.* 10% **19**. An independent run gave a mixture containing 88% **20** and 12% **19**. The infrared spectrum of the mixture showed absorptions at 1750 (ester C=O) and 1710 cm^{-1} (C=C) in carbon tetrachloride. The nmr spectrum (CCl_4) of **20** was deduced from the spectrum of the mixture and was as follows: δ 2.19–1.00 (broad absorption, 7), 2.02 (s, 3, $COCH_3$), 1.47 (s, 3, C=C—CH_3), and 0.88 ppm [s, 9, $C(CH_3)_3$]. Combustion analysis of the mixture of **19** and **20** follows. *Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.51; H, 10.70.

B. *cis*-2-Methyl-4-*t*-butylcyclohexanone (6).[5] Kinetic Mixture.—Ketone **6** [1.00 g (0.0060 mol) in 10 ml of DME] was added dropwise to a tritylllithium solution derived from 2.42 g (0.0099 mol) of triphenylmethane, 50 ml of DME, and 0.0075 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether). The mixture was quenched with acetic anhydride and the product was distilled to give 0.75 g (60%) of a mixture of enol acetates, bp 70–80° (0.5 mm), containing a trace of **6**. After preparative vpc,[24] nmr spectral analysis showed that the mixture contained 86% **19** and 14% **20** (average of two independent runs which agreed within 5%). The nmr spectrum (CCl_4) of **19** was deduced from the spectrum of the mixture and showed the following: δ 5.22 (m, 1, CH=C), 2.2–1.2 (broad absorption, 6), 2.01 (s, 3, $COCH_3$), 0.98 (low field peak of doublet due to $CHCH_3$), and 0.89 ppm [s, $C(CH_3)_3$ plus high field peak of doublet for $CHCH_3$].

C. Mixtures of *cis*- and *trans*-2-Methyl-4-*t*-butylcyclohexanone Containing Mainly the *trans* Isomer. Kinetic Conditions.—A solution of tritylllithium was prepared from 0.484 g (0.002 mol) of triphenylmethane, 10 ml of DME, and 0.0015 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether), and to this was added dropwise 0.200 g (0.0012 mol) of a mixture composed of 80% **7** and 20% **6** in 5 ml of DME. The resulting enolate mixture was quenched with acetic anhydride and after work-up the resulting enol acetate mixture was purified by preparative vpc.[24] Careful integration of the nmr spectrum of the mixture revealed that it contained no more than 3% **19** and 97% a mixture of **20** and the less substituted enol acetate of **7**, *i.e.*, **21**. A rough estimate of the percentages of **20** and **21** could be made by integration of the methyl doublet for **21** (see spectral data below) *vs.* the low-field peak of the methyl doublet for **20**, and this indicated that **21** was produced in an amount equal to the amount of **7** present in the starting ketone; *i.e.*, the mixture contained *ca.* 80% **21** and *ca.* 17% **20**. An independent run was conducted using a 25:75 mixture of **6** and **7**, and nmr spectral data indicated that a mixture of enol acetates containing 3% **19**, 22% **20**, and 75% **21** was produced. Nmr spectral studies on enol acetate mixtures resulting from other runs using ketone mixtures containing 55% **6** and 45% **7** and 40% **6** and 60% **7** also revealed that the amount of **21** formed corresponded to the amount of **7** initially present, while the sum of **19** and **20** corresponded to the amount of **6** initially present. Thus it was clear that **7** was converted essentially exclusively into **4** with tritylllithium in DME under kinetic conditions.



21

The nmr spectrum (CCl_4) of **21** could be deduced from the spectrum of mixtures rich in this component and was as follows: δ 5.27 (m, 1, CH=C), 2.2–1.3 (broad absorption, 6), 2.03 (s, 3, $COCH_3$), 1.02 (d, 3, J = 6 Hz, $CHCH_3$), and 0.89 ppm [s, 9, $C(CH_3)_3$].

Methylation of the Lithium Enolate of 1 and Thermodynamic and Kinetic Mixtures of Lithium Enolates of 6 and 7. General Procedure.—The enolate solutions were prepared in a manner identical with that described above for the acetic anhydride quenching experiments. For the methylation, a sixfold excess of methyl iodide was added in one portion to the stirred enolate solution at room temperature. After stirring for 30 min, the reaction mixture was poured into a mixture of water and ether (50–75 ml of each per 0.01 mol of ketone). The ether layer was separated and the aqueous layer was saturated with sodium chloride and extracted with three 50-ml portions of ether. The combined ethereal extracts were washed with 3% hydrochloric acid (50 ml per 0.010 mol of ketone), saturated sodium bicarbonate, and brine. The ether solution was dried over sodium sulfate, the solvent was removed under reduced pressure, the residue was distilled, and the distillate was analyzed by vpc.[3]

A. Methylation of the Lithium Enolate of 1.—A solution of tritylllithium was prepared as described above from 3.05 g (0.0125 mol) of triphenylmethane, 50 ml of DME, and 0.010 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether). To this solution under nitrogen a solution of 1.54 g (0.010 mol) of **1** in 25 ml of DME was added with stirring. After the addition was complete, the mixture was stirred for 30 min at room temperature and 8.52 g (0.060 mol) of methyl iodide was added in one portion. After stirring for 30 min at room temperature, the reaction mixture was worked up as described above. Distillation gave 1.45 g of a mixture of ketones, bp 60–70° (1.0 mm). Vpc analysis[3] of the mixture showed that it contained 10% **1**, 41% **6**, 34% **7**, and 15% a mixture **8** and **9** (ketones **8** and **9** were identified as described below). The ratio of **6** to **7** was thus 55:45. In two other experiments performed under similar conditions, **6** to **7** ratios which agreed with this value within 5% were obtained.

(23) H. Gilman, "Organic Chemistry," Vol. I, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1943, pp 486–500.

(24) A 5 ft × 0.25 in. column containing 20% SF-96 on Chromosorb W was employed.

B. Methylation of the Kinetic Mixture of Lithium Enolates of 6.[5]—A solution of tritylllithium was prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.009 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether). To this solution 1.45 g (0.0080 mol) of **6**[5] in 10 ml of DME was added dropwise with stirring. After the reaction mixture was stirred for 30 min at room temperature, 8.52 g (0.060 mol) of methyl iodide was added in one portion, and the mixture was stirred for 30 min. After work-up, vpc analysis[3] of the alkylation mixture showed the following: **8** (28%), **9** (52%), **11** (14%), and **12** (6%). Distillation yielded 1.25 g of a mixture of ketones, bp 62–68° (0.4 mm), of the same composition by vpc.[3] Using this mixture, a sample of **9** was collected by vpc[3] and found to exhibit the following spectral properties: ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 2.75–1.25 (broad absorption, 7), 1.13 (d, 3, J = 7.5 Hz, axial $CHCH_3$), 0.97 (d, 3, J = 6.2 Hz, equatorial $CHCH_3$), and 0.90 ppm [s, 9, $C(CH_3)_3$]: mass spectrum (70 eV) m/e (rel intensity) 182 (57), 126 (77), 57 (91), and 41 (100). Exact mass calcd for $C_{12}H_{22}O$: 182.166. Found: 182.166.

The above alkylation mixture (0.80 g) was refluxed overnight with 15 ml of 10% hydrochloric acid and extracted with ether, and the ether solution was washed with aqueous sodium bicarbonate and water and dried over sodium sulfate. After removal of the solvents, the residue was analyzed by vpc[3] and found to contain 68% **8**, 12% **9**, 14% **11**, and 6% **12**.

A sample of **8** was collected from this mixture by vpc[3] and exhibited the following spectral properties: ir (CCl_4) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 2.75–1.25 (broad absorption, 7), 0.96 (d, 6, J = 6 Hz, $CHCH_3$), and 0.91 ppm [s, 9, $C(CH_3)_3$]; nmr (C_6H_6) δ 2.50–1.20 (broad absorption, 7), 1.00 (d, 6, J = 6 Hz, $CHCH_3$), and 0.78 ppm [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV) m/e (rel intensity) 182 (33), 126 (56), 57 (100), and 41 (27). Exact mass calcd for $C_{12}H_{22}O$: 182.166. Found: 182.165.

Compounds **11** and **12** were characterized as described below.

A 50 50 mixture of **6** and its 2,6,6-trideuterio derivative was converted to the kinetic lithium enolate mixture with tritylllithium reacted with methyl iodide, and worked up in a manner identical to that described for the run with **6** alone. After distillation, a mixture of products having the same vpc[3] composition as observed above was obtained. The isomeric mixture of 2,6-dimethyl derivatives of 4-*t*-butylcyclohexanone and 4-*t*-butylcyclohexanone-d_2 was collected by vpc[3] and analyzed by mass spectrometry. Approximately equal-intensity parent-ion peaks for the d_2 and d_0 species were observed, but the presence of a significant amount of d_1 species could not be detected.

C. Methylation of the Kinetic Mixture of Lithium Enolates Derived from Mixtures of 6 and 7 Containing Mainly 7.—To a solution of tritylllithium in DME prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.009 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether) a solution containing 1.45 g (0.008 mol) of a 25:75 mixture of **6** and **7** was added dropwise with stirring. The resulting enolate solution was stirred for 30 min, and 8.42 g (0.060 mol) of methyl iodide was added in one portion. Work-up of the reaction mixture in the usual way and distillation of the resulting ketone mixture gave 1.30 g of material, bp 60–65° (0.4 mm). Vpc analysis[3] of this mixture showed that it contained 4% **11**, 59% **9**, 11% **8**, 10% **12**, and 16% another compound having a different retention time from either of the two starting materials or any of the products. The peak for the new product appeared on the chromatogram as a well-defined shoulder on the trailing edge of the peak for **9**. When the distilled reaction mixture was refluxed overnight with 20 ml of 10% hydrochloric acid and worked up in the usual way, a mixture of products having the following composition by vpc[3] was produced: **11** (4%), **12** (10%), **8** (73%), and **9** (13%). No other volatile compounds were present. This demonstrated that the new compound was converted into the equilibrium mixture of **8** and **9**; thus it must have been the 2,6-dimethylcyclohexanone having the two methyl groups *cis* to each other and *trans* to the *t*-butyl group, *i.e.*, **10**.

A separate run was performed on one-tenth the scale used above and using a ketone mixture containing 20% **6** and 80% **7**. The ketone mixture formed in this run had the following composition by vpc:[3] 2% **11**, 7% **8**, 51% **9**, 22% **10**, and 18% **12**. The average values for these two runs are reported in Table II.

D. Methylation and Trideuteriomethylation of the Equilibrium Mixture of Lithium Enolates from 6.[5]—To a tritylllithium solution prepared from 1.52 g (0.0062 mol) of triphenylmethane, 50 ml of DME, and 0.0050 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether), 0.97 g (0.0062 mol) of **6**[5] was added dropwise with stirring. After the addition, the mixture was heated at reflux for 3 hr and cooled to room temperature, and 4.2 g (0.030 mol) of methyl iodide was added in one portion. After stirring for 30 min, the mixture was worked up in the usual way and distilled to give 0.62 g of a mixture of ketones, bp 78–90° (3.5 mm), which by vpc analysis[3] showed the following composition: 26% **6**, 2% **7**, 53% **11**, 5% **8**, and 13% **12**.

Compound **11** was collected by vpc[3] and exhibited nmr spectral properties identical with those reported Conia and Briet.[10]

Compound **12** was collected and showed the following properties: nmr (CCl_4) δ 2.60–1.00 (broad absorption, *ca.* 6), 1.15 (s, 3), 1.02 (s, 3), 0.99 (d, J = 6.2 Hz, 3), and 0.91 ppm [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV) m/e 196.

For the trideuteriomethylation, a solution of tritylllithium was prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.0090 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether) and 1.81 g (0.010 mol) of **6**[5] was added dropwise with stirring. The solution was refluxed for 3 hr and cooled to room temperature, and 8.42 g (0.058 mol) of methyl-d_3 iodide was added in one portion. Work-up and distillation yielded 1.35 g of a mixture, bp 50–60° (0.1 mm), having the same composition by vpc[3] as that reported above. The mixture of 2-methyl-2-methyl-d_3 products **13** and **14** was collected by vpc[3] and analyzed by nmr spectroscopy. Integration of the spectrum revealed a 3:7 ratio for the singlets at δ (CCl_4) 1.13 and δ (CCl_4) 1.00 ppm. (In benzene solution the ratio of the singlets at δ (C_6H_6) 1.11 and δ (C_6H_6) 0.94 ppm was 7:3).

The mass spectrum (70 eV) of the mixture of **13** and **14** showed the following major peaks: m/e (rel intensity) 185 (69), 129 (88), and 57 (100).

Registry No.—**2**, 20826-82-8; **3**, 20826-60-2; **4**, 20826-61-3; **5**, 20826-83-9; **6**-d_3, 16084-13-2; methyl iodide, 74-88-4; methyl-d_3 iodide, 865-50-9; **8**, 20826-63-5; **9**, 20826-64-6; **12**, 20826-84-0; **19**, 20826-65-7; **20**, 20826-66-8; **21**, 20826-67-9.

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Catalytic Conversion of Benzoic Anhydrides into Fluorenones

JOCHANAN BLUM AND ZEEV LIPSHES

Department of Organic Chemistry, Hebrew University, Jerusalem, Israel

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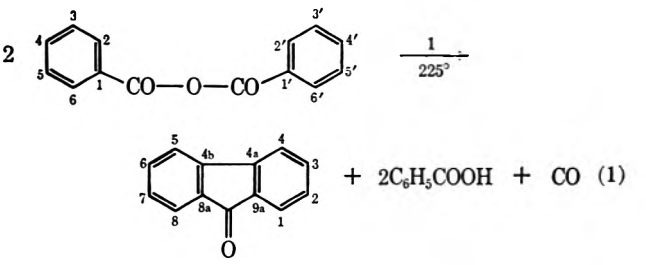
Chlorotris(triphenylphosphine)rhodium (1) has been shown to catalyze the transformation of benzoic anhydride to fluorenone and of substituted benzoic anhydrides to fluorenone derivatives. Benzoic anhydride and 1 react at 140° to give a divalent rhodium complex. A mechanism of the new catalytic reaction and a general pathway for the formation of the fluorenones is suggested.

Chlorotris(triphenylphosphine)rhodium (1), $RhCl(PPh_3)_3$, which has been shown to exhibit outstanding catalytic properties in numerous organic reactions,[1-12] catalyzes the conversion of benzoic anhydride into fluorenone in a novel reaction; if, for example, benzoic anhydride was heated with a catalytic quantity of the rhodium complex 1 at 240° for 4.5 hr, carbon monoxide was evolved. The resulting product consisted of 30% benzoic acid, 36% fluorenone, 6% biphenyl, 3% benzophenone, and *ca.* 25% unidentified tarry material. At 225°, the reaction is more selective, as benzoic acid and fluorenone are the primary products (eq 1). At higher temperatures than 240°, the formation of biphenyl increases, as shown in Table I. As this reaction appears to proceed *via* a different pathway, its study will be reported in a separate publication.



The behavior of substituted benzoic anhydrides, which is summarized in Table II, shows unequivocally that the reaction proceeds so that the carbon atoms 1 and 1′ in an *ortho*-substituted anhydride become atoms 4a and 8a in the fluorenone molecule, respectively, etc. The carbon atom 4b would then have to come from either the 2 or 6 position, and likewise the carbon atom 9a from the 2′ or 6′ position of the starting material. Thus the three *para*-substituted benzoic anhydrides studied (see Table II) gave only 2,6-disubstituted fluorenones on heating with 1. 2,6-Dimethylfluorenone was characterized by reduction (with red phosphorus and hydriodic acid) to the known 2,6-dimethylfluorene,[13] and 2,6-dichlorofluorenone by comparison with an authentic specimen.[14,15] The ketone obtained from *p*-deuteriobenzoic anhydride was assumed to be 2,6-dideuteriofluorenone on the strength of its nmr spectrum which resembles closely those of 2,6-dichloro- and 2,6-dimethylfluorenone (but not the spectrum of the unsubstituted parent compound). Although the mass spectrum indicated the presence of small quantities of nondeuterated and monodeuterated fluorenone in the preparation, these contaminants did not show up in the nmr spectrum.

By the above mechanism a *meta*-substituted benzoic anhydride would have been expected theoretically to yield a mixture of the 1,5-, 3,5-, 1,7-, and 2,6-disubstituted fluorenones. In fact, *m*-toluic anhydride gave only 1,7- and 2,6-dimethylfluorenone in the ratio 2:5. We shall refer to this fact in the further discussion.

The *ortho*-substituted benzoic anhydride studied, *o*-toluic anhydride, afforded the expected 1,5-dimethylfluorenone (identified by its oxidation to fluorenone-1,5-dicarboxylic acid),[16] but only in 5–10% yield.

In an attempt to obtain and identify the intermediates of this catalytic reaction, benzoic anhydride was treated with 1 in *o*-xylene at 140°. An insoluble yellow product resulted to which we assign the structure of chloro(phenyl)bis(triphenylphosphine)rhodium-(II) (5, Ar = C_6H_5) on the basis of the elementary

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(16) G. Charrier and E. Gigbi, *ibid.*, **69**, 2211 (1936).

TABLE I
TRANSFORMATION OF BENZOIC ANHYDRIDE BY 1 AT DIFFERENT TEMPERATURES

Expt	Temp, °C	Yield of neutral products, mol %: Fluorenone	Benzophenone	Biphenyl
1	225	42	Traces	Traces
2	240	36	3.5	5.7
3	270	27	2.8	10.4
4	350	4.8	3.1	36.0

$RhCl(PPh_3)_2(solvent)$ (2) $(ArCO)RhCl(PPh_3)_2$ (3) $ArRhCl(CO)(PPh_3)_2$ (4)

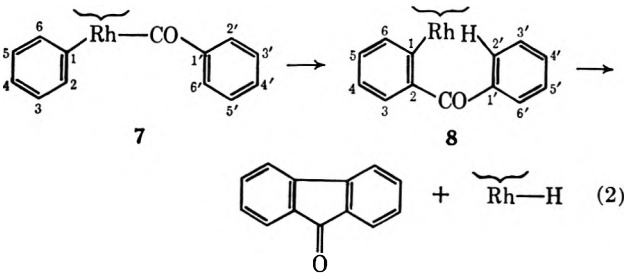
$ArRhCl(PPh_3)_2$ (5) $RhCl(CO)(PPh_3)_2$ (6)

analysis and the infrared spectrum. The presence of a phenyl–rhodium bond is made likely by the observation that the compound, heated above the melting point, gives an almost quantitative yield of biphenyl. Furthermore, by passing carbon monoxide through a suspension of the compound in methylene chloride, a complex mixture resulted that absorbed at 1680 cm^{-1} (ArCO–Rh).

The above formula **5** would indicate that the rhodium is present in the compound in the rare divalent state. Indeed, it has been shown by esr measurements that the compound **5** is paramagnetic even after repeated recrystallizations; it is thus unlikely that the effect is due to a spurious contaminant. The esr spectrum is composed of a large number of strong signals between $g = 2.85$ and 9.85, and their positions are shifted by rotation of the sample in the magnetic field. It should be mentioned that the starting material **1** did not show any resonance lines under the conditions of our measurements.[17a,17,18]

The well-known dissociation of **1** to **2** would open the way to a reaction of the latter with the benzoic anhydride to give a rhodium-containing carboxylate and benzoylchlorobis(triphenylphosphine)rhodium(II) (**3**, Ar = C_6H_5). Whilst such a compound has not been *isolated* in any of our experiments, we have found an indication of its existence by the appearance of a carbonyl absorption at 1685 cm^{-1} when *p*-chlorobenzoic anhydride was heated with **1** in boiling toluene. Compound **3** could isomerize, in a well-known manner, to the rhodium carbonyl derivative **4** which eventually would lose carbon monoxide and thus give **5**.

Whilst in boiling *o*-xylene (bp 140°) **5** is formed, chlorocarbonylbis(triphenylphosphine)rhodium(I) (**6**)[10b] is isolated when **1** and benzoic anhydride are heated in boiling mesitylene (bp 160°).[19] Although the catalytic transformation of benzoic anhydride to fluorenone takes place at even higher temperature at which we have not been able to isolate any defined rhodium complex, we assume that also **6** is a very active catalyst in our reaction.[20] Indeed, the isolated complex **6** is as active in the conversion of benzoic anhydrides into fluorenones as **1**. It could give, with the anhydride, a rhodium complex of type **7** having both an aryl and an aroyl ligand. A subsequent—probably electrophilic—attack of the aroyl group on either positions 2 or 6 of the aryl ligand would give a complex of type **8**,[21,22] which in turn would decompose to fluorenone by abstraction of the hydrogen atom at C-2 by the metal, the latter thus forming a rhodium–hydride complex (eq 2).



(2)

Indeed the formation of such a complex was proven by nmr: the crude reaction mixture (carefully freed from paramagnetic material insoluble in deuteriochloroform) showed a series of peaks centered at τ 27. This rhodium–hydride may be the source of the hydrogen required for the formation of the benzoic acid as the second product in our reaction. This would recall the transformation of phthalic anhydride to benzoic acid by dicobalt octacarbonyl.[23] The sequence of reactions assumed here and partly substantiated, would lead one to expect two steric effects: (a) a substituent located at position 3 of the aryl group in **7** should lower the rate of transformation of **7** to **8**, (b) both blocking of the hydrogen atom attached to C-2′ in compound **8** and the shielding of the Rh–C-1 bond in this complex should impede the eventual formation of a fluorenone. This is indeed in accordance with our observations.

para-Substituted anhydrides, in which the complex **8a** does not exhibit any steric hindrance, give relatively high yields of the 2,6-disubstituted fluorenones. The same applies to *one* of the intermediates, *viz.*, **8b** expected from *m*-toluic anhydride, whilst the formation of **8c** is obstructed by the methyl group at position 3. Thus it is reasonable that 1,7-dimethylfluorenone is formed in lower yield than the 2,6 isomer. In the other possible intermediates, **8d** and **8e**, the hydrogen atom to be abstracted is blocked by the methyl group at position 3′, preventing cyclization to the two possible

(17) D. R. Eaton and S. R. Suart, *J. Amer. Chem. Soc.*, **90**, 4170 (1968).

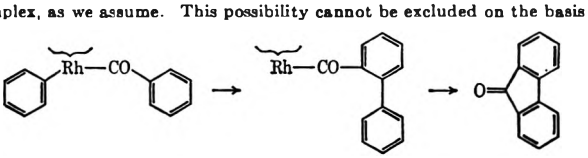
(18) A referee has suggested that the complex **5** may be derived from *tervalent*, not from *divalent* rhodium. As rhodium is low spin in its complexes, it does not seem to us that tervalent rhodium would show paramagnetism. In any event, the proposed mechanism would not appear to be affected by this point. Another referee questioned whether the complex **5** is monomolecular. This, indeed could not be proven, as the compound is not sufficiently soluble in any solvent. It can, however, be recrystallized from a very large amount of xylene.

(19) It is a moot question whether under the conditions of fluorenone formation (230°) **6** decarbonylates to **2** or not. Wilkinson, *et al.*,[10e] claim that the decarbonylation of **6** takes place above 200°, while according to Ohno and Tsuji[10d] the complex is stable at least up to 260°.

(20) It is, of course, difficult to ascribe whether any of the various complexes identified, and, if so, which, is the "true" catalyst in this sequence of reactions.

(21) Obviously, two different rhodium compounds may be formed from **6** and the anhydride, one having an aryl group and one having an aroyl group as ligand; they could react *intermolecularly* to form complex **8**.

(22) One referee suggested an alternative mechanism which assumes that the biphenyl system is formed first, and not from the aroyl–aryl–rhodium complex, as we assume. This possibility cannot be excluded on the basis of



the evidence at hand; however, the steric considerations outlined in the text are the same in both schemes.

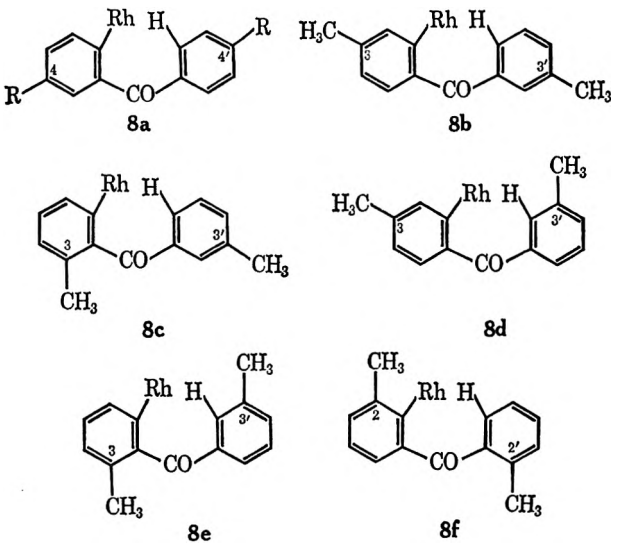
(23) I. Wender, S. Friedman, W. A. Steiner, and R. B. Anderson, *Chem. Ind.* (London), 1694 (1958).

TABLE II

CONVERSION OF BENZOIC ANHYDRIDES INTO FLUORENONES BY 1

Anhydride (g/g of catalyst)	Reaction: Temp, °C	Reaction: Time, hr	Fluorenone formed	Yield,[a] %
Benzoic (4.0/0.2)	240	4.5	Unsubstituted	72
o-Toluic (5.1/0.2)	235	3	1,5-Dimethyl-	5–10
m-Toluic (5.0/0.2)	240	2.5	2,6-Dimethyl-	34
			1,7-Dimethyl-	14
p-Toluic (3.5/0.18)	240	3.5	2,6-Dimethyl-	72
p-Chlorobenzoic (10/0.2)	240	4	2,6-Dichloro-	50
p-Deuteriobenzoic (5.0/0.2)	245	3	2,6-Dideuterio[b]	91

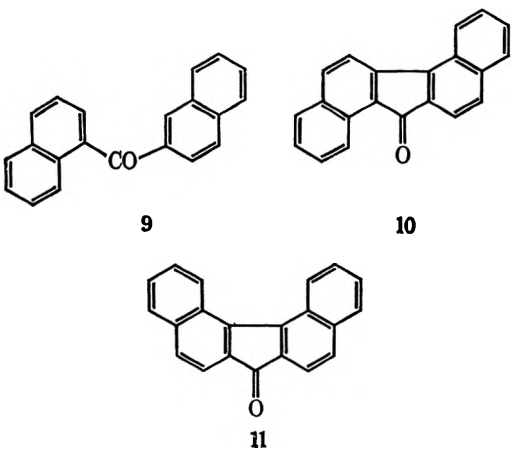
[a] Calculations are based on 2 mol of anhydride leading to 1 mol of fluorenone. [b] Contaminated with some mono- and undeuterated fluorenone.



dimethylfluorenones other than the 2,6 and the 1,7 isomer.

In the complex **8f**, from *o*-toluic anhydride, the Rh–C bond is strongly shielded by the neighboring methyl group; thus the formation of 1,5-dimethylfluorenone in very low yield is not unexpected. The main reaction (34%/mol of anhydride) is the formation of 2,3′-ditolyl ketone, which is accompanied by varying quantities (up to 7%) of a lactone, $C_{16}H_{14}O_2$, the structure of which has not yet been elucidated.

It is not surprising that also α-naphthoic anhydride—being an *ortho*-substituted benzoic anhydride—gives none of the expected 13H-dibenzo[*a*,*g*]fluoren-13-one (**10**). The products formed were α,β-dinaphthyl ketone



(**9**, 14%), small quantities of a lactone, $C_{22}H_{14}O_2$, and surprisingly, a 32% yield of 13H-dibenzo[*a*,*i*]fluoren-13-one (**11**). This would indicate that the cyclization reaction is accompanied (or preceded) by an isomerization to a rhodium derivative of naphthalene in the β position.

It is noteworthy that benzoic *acids* are partially converted into fluorenones when heated with **1**; benzoic acid gives 5.6% fluorenone (for each 2 mol of acid) when heated at 235° for 2 hr with **1** and 28% at 250° for 2 hr. We assume that under these conditions part of the acid, which is not decarboxylated, is first dehydrated to the corresponding anhydride.

Also nonaromatic anhydrides react with **1** (or **6**), although the products are of different nature. One mole of hydrocinnamic anhydride, when treated with 0.01 mol of **1** at 300° for 3 hr, gives 0.15 mol of diphenethyl ketone, 0.35 mol of hydrocinnamic acid, and 0.5 mol of styrene. The formation of styrene is at least formally equivalent to the hydrogen abstraction occurring in **8**.

Experimental Section

The general procedure used for the conversion of aromatic acid anhydrides into derivatives of fluorenone is illustrated by the following example.

Fluorenone from Benzoic Anhydride.—A mixture of 4.0 g of benzoic anhydride and 0.2 g of chlorotris(triphenylphosphine)-rhodium (**1**) was placed in a flask preheated at 250° and connected to a distilling apparatus and a gas collector. After a few minutes, carbon *monoxide* began to be evolved. The bath temperature was lowered by 10° and the heating was continued for 4.5 hr (until the evolution of the gas, which consisted at that time mainly of carbon *dioxide*,[24] had practically ceased). The reaction mixture was cooled and digested with 10% aqueous sodium hydroxide, and the neutral material was taken up in warm benzene or methylene chloride. The *aqueous* layer was acidified and the precipitate was filtered and recrystallized from water to yield 1.3 g (60%)[25] of benzoic acid. The *organic* solution was washed with water, dried, and concentrated and the residue was purified either by column chromatography (on alumina) or by preparative vapor phase chromatography on a 5-ft-long column packed with 10% SE-30 on Chromosorb W at 200°. Thus, 0.155 g (5.7%) of biphenyl, 0.097 g (3%) of benzophenone, and 1.15 g (0.36 mol/mol of anhydride or 72% of the theoretical yield) of fluorenone were obtained. The products were identified by comparison with authentic samples.

When the above experiment was carried out with 0.1 g of *trans*-chlorocarbonylbis(triphenylphosphine)rhodium (**6**) and 2.7 g of benzoic anhydride at 240°, similar results were obtained. In one experiment, in which 2.2% biphenyl and 1.7% benzophenone were formed, the yield of fluorenone exceeded the theoretical value by 4%. Obviously, part of the benzoic acid formed has also been converted into fluorenone under these conditions.

Transformation of Benzoic Acid into Fluorenone.—A mixture of 4.0 g of benzoic acid and 0.2 g of **1**, heated for 4 hr at 230°, as

(24) The catalyst causes decarboxylation of free aromatic acids, though slowly, as we have indicated in previous studies (*cf.* ref 10a).

(25) The yield of acid from the anhydride was calculated, in accordance with eq 1, on the basis of 1 mol of acid from 1 mol of anhydride charged.

described above, yielded 0.3% biphenyl, 5.2% fluorenone (based on 1 mol of ketone from 2 mol of acid), and no benzophenone.

On repetition of the experiment applying direct heating to allow the benzoic acid to reflux vigorously (at 249°) for 2 hr, the yields of biphenyl, benzophenone, and fluorenone rose to 0.9, 0.2, and 28%, respectively. In this process, the rhodium compound was partially reduced to the free metal which precipitated as a mirror.

2,6-Dimethylfluorenone was obtained from *p*-toluic anhydride and 1 or, together with 1,7-dimethylfluorenone, from *m*-toluic anhydride (Table II). A suitable separation column was 7 ft long, packed with 17.5% diethylene glycol succinate and 2.5% Carbowax 20M on acid-washed Chromosorb P. The 2,6-dimethylfluorenone, recrystallized from ethanol at −70°, formed yellow prisms: mp 82°; $\bar{\nu}_{max}^{KBr}$ (C=O) 1700 cm^{-1}; nmr ($CDCl_3$) τ 2.4–3.0 (m, 6 H), 7.65 (s, 3 H), 7.68 (s, 3 H).

Anal. Calcd for $C_{15}H_{12}O$: C, 86.5; H, 5.8. Found: C, 86.3; H, 5.8.

2,6-Dimethylfluorene.—A mixture of 34 mg of the foregoing ketone, 94 mg of 55% hydriodic acid (analytical grade), 48 mg of red phosphorus, and 2 ml of acetic acid was refluxed for 20 hr. The excess phosphorus was filtered off and washed with acetic acid, and the filtrate was treated with aqueous sodium bisulfite and neutralized with 5% potassium hydroxide. The fluorene derivative was extracted with benzene; thus 25 mg (79%) of 2,6-dimethylfluorene, mp 66–67° (from ethanol) (lit.[13] mp 67°), was obtained.

1,7-Dimethylfluorenone was obtained by chromatographic separation from its mixture with the 2,6-dimethyl isomer (see above): yellow crystals; mp 75–76° (from ligroin) (lit.[26] mp 76°); nmr ($CDCl_3$) τ 2.6–3.1 (m, 6 H), 7.44 (s, 3 H of C-1 CH_3), 7.69 (s, 3 H of C-7 CH_3).

1,7-Dimethylfluorene resulted in 78% yield when 55 mg of the foregoing ketone was reduced with red phosphorus and hydriodic acid in acetic acid, essentially in the manner described for the preparation of 2,6-dimethylfluorene: mp 107° (lit.[10] mp 107°); λ_{max}^{EtOH}, mμ (log ε), 269 (4.44), 275 (4.33), 293 (3.95), 297 (3.90), 304 (3.95) [lit.[26] 269 (4.31), 275 (4.22), 293 (3.82), 297 (3.72), 304 (3.92)].

The **1,3,5-trinitrobenzene derivative** melted at 96° (lit.[26] mp 98°).

2,3′-Bitolyl, 2,3′-Ditolyl Ketone, and 1,5-Dimethylfluorenone from *o*-Toluic Anhydride.—*o*-Toluic anhydride (5.1 g) was heated at 235° for 3 hr in the presence of 0.12 g of **1**. The neutral fraction was separated from 2.2 g (80%) of *o*-toluic acid and was shown by vapor phase chromatography (using either a 5-ft-long 10% SE-30 or a 5% Apiezon L column) to be composed of 1% **2,3′-bitolyl**, 34% **2,3′-ditolyl ketone**, 5% (10% of the theoretical value) **1,5-dimethylfluorenone**, and 7% colorless lactone $C_{16}H_{14}O_2$, mp 95°, with a retention time similar to that of 1,5-dimethylfluorenone [$\bar{\nu}_{max}^{KBr}$ 1780 cm^{-1}; nmr ($CDCl_3$) τ 2.48–3.06 (m, 7 H), 3.42 (s, 1 H), 7.25 (s, 3 H), 7.52 (s, 3 H), mol wt 238].

Both 2,3′-bitolyl and 2,3′-ditolyl ketone [$\bar{\nu}_{max}^{KBr}$ 1650 cm^{-1}; nmr ($CDCl_3$) τ 7.65 (s, 3 H), 7.70 (s, 3 H)] were identified by comparison with authentic samples.

The dimethylfluorenone was obtained as a yellow oil that crystallized from petroleum ether (bp 40–60°) and was separated from some pale yellow needles of mp 193–195° by recrystallization from the same solvent. It melted at 35–40°. The nmr spectrum (in $CDCl_3$) shows in addition to the expected signals at τ 7.38 (C-1 CH_3) and 7.61 (C-5 CH_3) the presence of some peaks possibly due to traces of another dimethylfluorenone (perhaps the 1,7-dimethyl isomer).

Anal. Calcd for $C_{15}H_{12}O$: C, 86.5; H, 5.8. Found: C, 86.7; H, 5.8.

1,5-Dicarboxyfluorenone.—The above dimethylfluorenone (50 mg), 0.25 g of potassium permanganate, and 30 ml of 10% aqueous sodium carbonate were refluxed for 6 hr with stirring. The mixture was acidified with dilute sulfuric acid and the manganese dioxide formed reduced by addition of sodium sulfite. The orange precipitate was filtered and recrystallized from glacial acetic acid, affording 5 mg of fluffy orange needles of the dicarboxylic acid, mp 290–295° (lit.[16] mp 295–299°).

2,6-Dichlorofluorenone was obtained (25 mol %/mol of anhydride, 50% yield) when 4.6 g of *p*-chlorobenzoic anhydride was heated with 0.2 g of **1** at 240° for 4 hr. The yield could not be improved by heating the reaction mixture for an additional 6-hr period, though during this time 60% of the chlorobenzoic acid, formed initially, was decarboxylated to chlorobenzene. The purification of the fluorenone derivative was achieved by gas chromatography using a 3-ft-long column packed with 10% SE-30 on Chromosorb W, at 210°; it was identified by comparison with an authentic sample:[14] mp and mmp 200°. Both samples also had identical ir, uv, and nmr spectra.

***p*-Deuteriobenzoic Acid.**—*p*-Bromodeuteriobenzene was best prepared by addition of 156 g of *p*-dibromobenzene in 400 ml of ether to a refluxing mixture of 80 g of the same dibromide, 28 g of magnesium, and 200 ml of ether in an atmosphere of nitrogen and at a rate so as to keep the mixture refluxing gently. After 2 hr at 34° and cooling to 0°, 30 ml of deuterium oxide was added and the mixture was worked up in the usual manner, giving after two successive fractional distillations 57 g (37%) of *p*-bromodeuteriobenzene:[27] bp 153°; nmr (AB spectrum) τ 2.48, 2.82 (J = 8 cps).

A Grignard solution prepared from 61 g of the foregoing compound and 8 g of magnesium in 240 ml of dry ether was added to a stirred slurry of 500 g of Dry Ice and 300 ml of ether. The mixture was allowed to warm to room temperature, hydrochloric acid was added, and the organic acid was extracted with 10% ammonia solution. The free deuterated acid was recrystallized once from water and once from heptane, affording 33 g (77%) of colorless crystals: mp 121°; nmr ($CDCl_3$) (AB spectrum) τ 1.78, 2.45 [J = 9 cps, 0.07 (COOH)].

Anal. Calcd for $C_7H_5DO_2$:[28] C, 68.3; H, 4.9. Found: C, 67.9; H, 4.8.

***p*-Deuteriobenzoic anhydride** was prepared in 56% yield by heating the foregoing acid with a twofold excess of acetic anhydride, followed by distillation of the acetic acid formed and the excess reagent. On trituration and two successive recrystallizations from petroleum ether (bp 40–60°), colorless crystals of mp 43° resulted: nmr ($CDCl_3$) (AB spectrum) τ 1.84, 2.50 (J = 8 cps).

Anal. Calcd for $C_{14}H_8D_2O_3$:[28] C, 73.7; H, 4.4. Found: C, 73.9; H, 4.5.

2,6-Dideuteriofluorenone was obtained in 91% yield (1 mol from 2 mol of anhydride) from 5.5 g of the foregoing anhydride and 0.2 g of **1** at 250° (3 hr). Purification was carried out by vapor phase chromatography on a 3-ft-long 10% SE-30 on Chromosorb W column, followed by recrystallization from benzene and hexane: yellow prisms, mp 83°.

Anal. Calcd for $C_{13}H_6D_2O$:[28] C, 85.7; H, 4.4. Found: C, 85.9; H, 4.7.

The mass spectrum indicates some contamination with mono- and undeuterated fluorenone.

α,β-Dinaphthyl Ketone (9) and Dibenzo[*a,i*]fluorenone (11) from α-Naphthoic Anhydride.—A mixture of 8.1 g of α-naphthoic anhydride and 0.27 g of **1** was heated at 240° for 4 hr. The resulting neutral fraction was separated by three successive chromatographies on alumina and fractional recrystallization from ethyl acetate, methanol, and nitromethane to yield 1.34 g (21%) of naphthalene, 1.0 g (14%) of **α,β-dinaphthyl ketone (9)**, and 1.13 g (32% of the theoretical yield) of **dibenzo[*a,i*]fluorenone (11)**. The naphthalene and the dinaphthyl ketone (mp 135°[29]) were compared with authentic samples. The red fluorenone derivative was found to be contaminated with traces of a colorless lactone from which it could be freed by heating with nitromethane (the lactone crystallizes from this solvent), and proved to have the properties reported in the literature: plates of mp 265°[29] (from ligroin); $\bar{\nu}_{max}^{KBr}$ (C=O) 1690 cm^{-1}; λ_{max}^{EtOH}, mμ (log ε), 236 (4.51), 262 (4.38), 299 (4.82), 376 (3.54), 396 (3.62), 460 (2.60);[30] mol wt (mass spectrograph) 280.

The colorless lactone was recrystallized from ligroin: mp 166–167°; its analysis corresponded to $C_{22}H_{14}O_2$; mol wt 310; $\bar{\nu}_{max}^{KBr}$ (C=O) 1763 cm^{-1}; λ_{max}^{EtOH}, mμ (log ε), 247 (4.34), 287 (4.11).

Styrene and Diphenethyl Ketone from Hydrocinnamic Anhydride.—The decomposition of 18 g of this anhydride by 1 was carried out at 300° (at a lower temperature the reaction proceeded extremely slowly). During a period of 3 hr 6.6 g of styrene (quantitative yield, assuming 1 mol of styrene/mol of anhydride) distilled off, characterized by comparison with an authentic sample. The residue was separated into 6.7 g (70%) of hydro-

(26) T.P. C. Mulholland and G. Ward, *J. Chem. Soc.*, 4676 (1954).

(27) L. H. P. Weldon and C. L. Wilson, *ibid.*, 235 (1946).

(28) The total hydrogen content is calculated as ^1H in accordance with the analytical methods.

(29) R. H. Martin, *ibid.*, 679 (1941).

(30) DMS UV Atlas, Vol. 2, Verlag Chemie, Weinheim and Butterworths, London, 1966, spectrum E7/T3.

cinnamic acid and 2.2 g (15%) of diphenethyl ketone. The latter compound was compared with a sample prepared by dry distillation of barium hydrocinnamate at 340–350°. Both absorbed at ν_{max}^{KBr} (C=O) 1700 cm^{-1}; nmr ($CDCl_3$) τ 2.83 (br s, 10 H), 7.19, 73.7, 7.58 [J = 5, 7, and 5 cps (sextet 4 H)].

The red **2,4-dinitrophenylhydrazone** melted at 115°[21] (from ethanol).

Reaction of Benzoic Anhydride with 1 in Aromatic Hydrocarbons as Solvents.—To a stirred solution of 0.41 g of 1 in 10 ml of *o*-xylene at 140°, there was added 0.1 g of benzoic anhydride. A yellow precipitate started to separate immediately. After heating for 30 min at 140°, the mixture was filtered, while still hot. On cooling of the filtrate to 0°, a second complex precipitated. It was found to be pure chlorocarbonylbis(triphenylphosphine)rhodium (6): mp 203–205°, ν_{max}^{Nujol} 1965 cm^{-1}.

Anal. Calcd for $C_{37}H_{30}ClOP_2Rh$: C, 64.3; H, 4.3; Cl, 5.1. Found: C, 64.0; H, 4.4; Cl, 5.4.[10b]

The first *insoluble* precipitate was heated either with benzene or better with methylene chloride to remove the still adhering compound 6 and dried at room temperature at 0.5 mm. Thus was obtained 0.104 g of yellow crystals, mp 232–233°, of chloro(phenyl)bis(triphenylphosphine)rhodium(II) (5, Ar = C_6H_5).

Anal. Calcd for $C_{42}H_{35}ClP_2Rh$: C, 68.2; H, 4.7; Cl, 4.8. Found: C, 68.0, 68.2; H, 4.9, 4.3; Cl, 4.8, 4.7.

The complex does not show any carbonyl absorption in the infrared spectrum and is too insoluble for nmr measurements. The esr spectrum, in which strong lines between g = 2.85 and 9.85 are observed, indicated the paramagnetic character of the compound.

(31) H. A. Weidlich and M. M. Delius, *Ber.*, **74**, 1195 (1941).

p-Toluic anhydride gave in the analogous experiment only chlorocarbonylbis(triphenylphosphine)rhodium (6); the same was the case for benzoic anhydride and 1 in boiling mesitylene, whilst in boiling benzene or toluene benzoic anhydride did not react with the rhodium complex 1 at all.

When a mixture of 0.59 g of *p*-chlorobenzoic anhydride, 0.185 g of 1, and 2 ml of toluene was refluxed for 1 hr, the orange-yellow crystals that separated proved to be a mixture of a rhodium–aroyl complex and 6, having strong absorption bands at 1685 and 1965 cm^{-1} (relative intensities of 1.4:1). When the experiment was repeated in 3 ml of o-xylene, the mixture showed the same absorption peaks, but the ratio of intensities was 1:2.5. Heating either of the two mixtures in boiling mesitylene for 30 min caused the aroyl carbonyl peak at 1685 cm^{-1} to disappear.

Registry No.—1, 14694-95-2; 5 (Ar = C_6H_5), 21537-43-9; 6, 13938-94-8; benzoic anhydride, 93-97-0; *o*-toluic anhydride, 607-86-3; *m*-toluic anhyride, 21436-44-2; *p*-toluic anhydride, 13222-85-0; *p*-chlorobenzoic anhydride, 790-41-0; *p*-deuteriobenzoic anhydride, 21494-28-0; 1,5-dimethylfluorenone, 21436-47-5; 2,6-dimethylfluorenone, 21436-48-6; 2,6-dideuteriofluorenone, 21436-49-7; *p*-deuteriobenzoic acid, 4551-62-6.

Acknowledgment.—The authors wish to thank Professor Ernst D. Bergmann for his advice.

The Synthesis, Spectral Properties, and Chemical Ring Opening of Tricyclo[3.3.0.0^{2,8}]octan-3-one, a Rigid Model for Unsymmetrical Cyclopropyl Ketone Participation

S. A. MONTI,[1,2] DAVID J. BUCHECK,[3] AND JOHN C. SHEPARD

The Departments of Chemistry, The University of Texas at Austin, Austin, Texas 78712, and Michigan State University, East Lansing, Michigan 48823

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Stereomodels reveal that the skeletal framework of tricyclo[3.3.0.0^{2,8}]octan-3-one (4) constitutes a rigid model for cyclopropyl ketone participation in an unsymmetrical conformation. Ketone 4 and three specifically deuterated derivatives (C_7-*d*, C_6-d_2, and C_8-*d*) were synthesized. These compounds were used, in conjunction with spin decoupling experiments, to interpret the nmr spectrum of ketone 4. Unambiguous chemical shift assignments for the C_1, C_2, C_4, C_5, and C_8 protons were made. The major fragmentation pathway of this tricyclic ketone in the mass spectrum involves the loss of ketene to give a base peak at *m/e* 80. Reductive cleavage of ketone 4 with lithium in liquid ammonia yielded as products 95% *cis*-bicyclo[3.3.0]octan-3-one (12) and 5% bicyclo[3.2.1]-octan-3-one (13). Treatment of ketone 4 with hydrogen bromide in methylene chloride gave, after reductive removal of the bromine atom, a mixture of 80% 12 and 20% 13. Interpretation of these results in terms of ground-state cyclopropyl ketone delocalization in an unsymmetrical conformation is discussed. The stereoselectivity of the dissolving metal cleavage is consistent with the known stereoelectronic requirements for reductive elimination of α-substituted ketones. The product mixture from the acid-catalyzed opening appears to reflect (in part) thermodynamic control. It is concluded that an evaluation of product composition data from either of these general chemical probes is not a valid method to assess ground-state cyclopropyl ketone delocalization.

It has been firmly established that freely rotating systems containing a cyclopropane ring adjacent to an electron-deficient center (carbonyl group[4] or carbonium ion[5]) adopt the symmetrical, bisected conformation A in preference to the unsymmetrical geometry B. Collectively, these data have been advanced in support of the theoretical prediction[6] that maximum delocalization should occur in the bisected conformation A. A more rigorous test of this hypothesis, however, requires a

A B

(1) To whom inquiries should be addressed at the University of Texas.

(2) Partial financial support from the University of Texas Research Institute is gratefully acknowledged.

(3) Predoctoral Fellow of the National Institutes of Health, 1966–1968.

(4) L. S. Bartell and J. P. Guillory, *J. Chem. Phys.*, **43**, 647, 654 (1965); L. S. Bartell, J. P. Guillory, and A. P. Parks, *J. Phys. Chem.*, **69**, 3043 (1965).

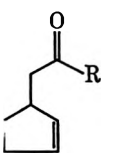
(5) N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, *J. Amer. Chem. Soc.*, **87**, 4533 (1965); C. U. Pittman, Jr., and G. A. Olah, *ibid.*, **87**, 5123 (1965); T. Sharpe and J. C. Martin, *ibid.*, **88**, 1815 (1966); H. C. Brown and J. D. Cleveland, *ibid.*, **88**, 2051 (1966); P. von R. Schleyer and G. W. VanDine, *ibid.*, **88**, 2321 (1966); H. G. Richey, Jr., and J. M. Richey, *ibid.*, **88**, 4971 (1966).

(6) R. Hoffman, *Tetrahedron Lett.*, 3819 (1965), and references cited therein; K. Shimizu, H. Kato, and T. Yonezawa, *Nippon Kagaku Zasshi*, **88**, 1050 (1967); *Chem. Abstr.*, **68**, 77601 (1968).

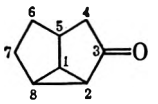
comparison of the delocalization possible in A with the delocalization possible in B. Clearly, conformationally mobile molecules are not suitable for such a study. In contrast, however, an examination of cyclopropyl participation in geometrically defined, rigid systems provides a way to individually evaluate both conformations (A and B).

The criteria for a model of cyclopropyl ketone delocalization held in the conformationally less favorable geometry B are fulfilled by the rigid, tricyclo[3.3.0.0^{2,8}]-octan-3-one (**4**) molecule. Stereomodels of **4** show that the π bond of the carbonyl group forms a dihedral angle of approximately 25° with the C_2–C_8 σ-cyclopropane bond. Thus, this bond is geometrically disposed for preferential overlap with the adjacent electron-deficient center. In addition to the synthesis and spectral properties of tricyclo[3.3.0.0^{2,8}]octan-3-one (**4**), the course of both the acid-catalyzed and the reductive ring-opening reactions of **4** are described. As discussed in detail below, it is concluded that an evaluation of product composition data from either of these general chemical probes[7] is not a valid method to assess ground-state cyclopropyl ketone delocalization. The use of proton and carbon-13 nuclear magnetic resonance to examine cyclopropyl ketone participation in rigid systems will be communicated separately.

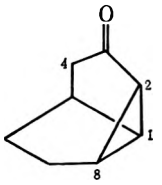
Synthesis and Spectral Properties.—The well-documented synthetic route to cyclopropyl ketones utilizing an intramolecular diazo ketone addition to a carbon–carbon double bond[8] seemed admirably suited for the preparation of tricyclo[3.3.0.0^{2,8}]octan-3-one (**4**). Conversion of 2-cyclopenten-1-acetic acid[9] (**1**) into its acid chloride (**2**), followed by treatment with ethereal diazomethane, furnished the diazo ketone **3a**. Decomposition of the latter with cupric sulfate in refluxing cyclohexane yielded the desired tricyclo[3.3.0.0^{2,8}]-octan-3-one (**4**).



1, R = OH
2, R = Cl
3a, R = CHN_2
3b, R = CDN_2



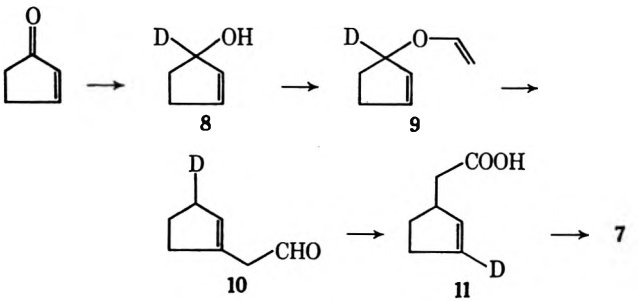
4



4
5, C_2-*d*
6, C_4-d_2
7, C_8-*d*

In order to interpret the nmr spectrum of **4** (*vide infra*), three specifically deuterated derivatives were prepared. Substitution of deuteriodiazomethane into the sequence described above gave, after decomposition of the deuteriodiazo ketone **3b**, the C_2-*d* ketone **5**. The C_4-d_2 ketone **6** was prepared smoothly by base-catalyzed deuterium exchange of the parent material **4**. Finally, specifically deuterated C_8-*d* ketone **7** was synthesized. As outlined[10] in Scheme I, the deuterium atom was introduced by lithium aluminum deuteride reduction of

SCHEME I



8 **9** **10** **11**

2-cyclopentenone to give the deuterated allylic alcohol **8**. Thermal rearrangement of the allyl vinyl ether **9**, prepared from **8** by mercuric acetate catalyzed exchange[11] with ethyl vinyl ether, yielded 2-cyclopenten-1-acetaldehyde-3-*d* (**10**). Silver oxide oxidation of aldehyde **10** then gave corresponding deuterated acid **11**. With the position of the deuterium atom in acid **11** firmly established by virtue of the synthetic sequence, this material was converted into the C_8-*d* ketone **7** using the procedure previously described.

The 100-MHz nmr spectrum of the parent ketone **4** is shown in Figure 1a. The low-field portion reveals three distinct one-proton signals, while the remaining seven protons of **4** appear in two broad multiplets of four and three protons each. Since all ten protons of **4** are nonequivalent, the detailed analysis of this spectrum was facilitated by examination of the spectra for the deuterated ketones **5**, **6**, and **7**.

The C_4-d_2 ketone **6** spectrum showed complete disappearance of the one-proton pair of doublets centered at 2.38 ppm (J = 9, 17 Hz). The high-field doublet marked in Figure 1a (1.56 ppm, J = 17 Hz) was also absent and integration revealed the loss of one proton from this high-field region. In addition, the broad one-proton signal at 2.9 ppm was sharpened considerably in the C_4-d_2 spectrum. Consequently, this resonance must be coupled strongly to the C_4 methylene group. The remainder of the spectrum was unchanged. Molecular models suggest that only one of the two C_4 methylene protons should be coupled with the C_5 proton, *i.e.*, $J_{5\text{-}endo\ 4} \approx 0$ (dihedral angle *ca.* 90°) and $J_{5\text{-}exo\ 4} > 0$ (dihedral angle *ca.* 30°).[12] Thus, the high-field doublet at 1.56 ppm is assigned to the C_4-*endo* proton, the low-field pair of doublets at 2.38 ppm to the C_4-*exo* proton, and the broad multiplet at 2.9 ppm to the tertiary C_5 proton.

The approximate position of the C_2 cyclopropyl proton was ascertained from the nmr spectrum of the C_2-*d* ketone **5**. The intensity of the "triplet" at 1.85 ppm in Figure 1 was reduced considerably in the spectrum of the partially deuterated **5** (71% d_1; see Experimental Section). As shown below, however, this *apparent* triplet results from overlap of two resonances and does not correspond to the exact chemical shift for the C_2 proton. In addition, the signal at 2.65 ppm appeared as a complex multiplet in the C_2-*d* ketone **5** spectrum. This observed coupling, the complex appearance of which undoubtedly reflects the partially deuterated nature of **5**, requires that the 2.65-ppm resonance be assigned to either the C_1 or the C_8 cyclopropyl proton.

(7) *Cf.* H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 47 (1968), and references cited therein; A. J. Bellamy and G. H. Whitham, *Tetrahedron*, **24**, 247 (1968); W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

(8) W. von E. Doering, E. T. Fossel, and R. L. Kaye, *Tetrahedron*, **21**, 25 (1965).

(9) J. T. Fitzpatrick and E. Marcus, U. S. Patent 3,014,960; *Chem. Abstr.*, **56**, P8590*d*. Commercially available from Aldrich Chemical Co.

(10) *Cf.* R. K. Hill and A. G. Edwards, *Tetrahedron Lett.*, 3239 (1964).

(11) W. H. Watanabe and L. E. Conlon, *J. Amer. Chem. Soc.*, **79**, 2828 (1957).

(12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

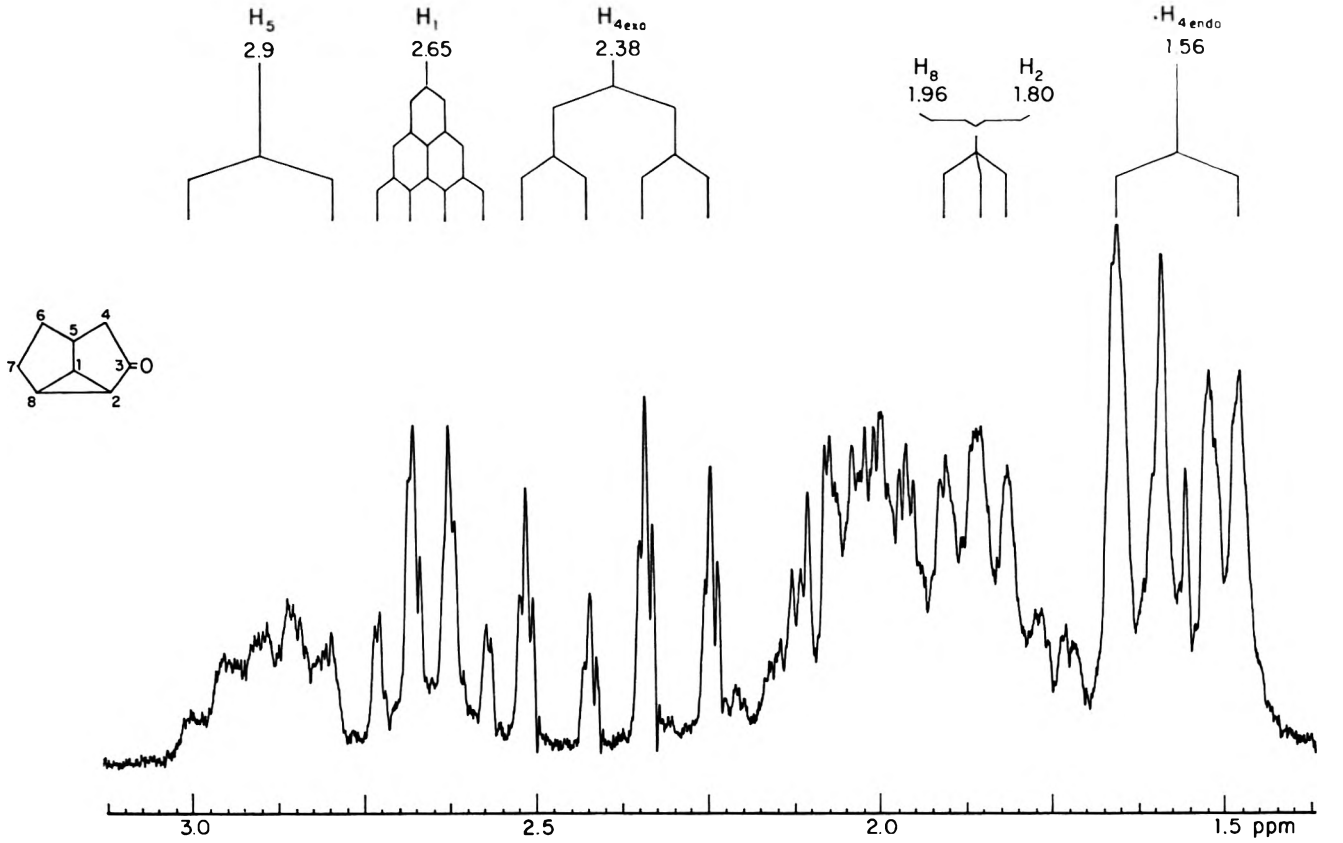


Figure 1a.—100-MHz nmr spectrum of tricyclo[3.3.0.0^{2,8}]octan-3-one (**4**).

The problems associated with making an unambiguous distinction between these two positions were resolved by the nmr spectrum of the C_8-*d* ketone **7**. This spectrum is presented in Figure 1b. A comparison of the two spectra in Figure 1 reveals that the one-proton signal at 2.65 ppm (a fortuitous quartet due to coupling with three different protons) has collapsed to a superimposed doublet of doublets which appears as a triplet; the *apparent* triplet at 1.85 ppm now appears as a doublet at 1.80 ppm; and integration shows that one proton has disappeared from the 2.0-ppm region. These data, coupled with the observations from the C_2-*d* ketone spectrum, allow the unique assignment of the 2.65-ppm resonance to the C_1 proton and the 1.80-ppm signal to the C_2 proton. The loss of a proton from the 2.0-ppm region and the appearance of a one-proton doublet at 1.80 ppm in the C_8-*d* spectrum indicates that the third (C_8) cyclopropyl proton resonance is close to that for the C_2 proton and results in the apparent triplet seen at 1.85 ppm in Figure 1a.

An approximate chemical shift for this C_8 cyclopropyl proton was obtained from spin decoupling experiments on the parent ketone **4**. Irradiation at 1.88 ppm resulted in collapse of the "quartet" at 2.65 ppm into a *doublet*, indicating decoupling of both remaining cyclopropyl protons. Assuming this frequency is *ca.* halfway between the C_2 and C_8 proton resonances, this gives an approximate chemical shift of 1.96 ppm for the C_8 proton. Finally, extensive spin decoupling experiments on both **4** and **7** were in complete accord with all the assignments made above. No attempt was made to assign the two sets of methylene resonances (two protons each, *ca.* 1.6 and 2.0 ppm) to the C_6 and C_7 protons or to evaluate the small, long-range couplings present.

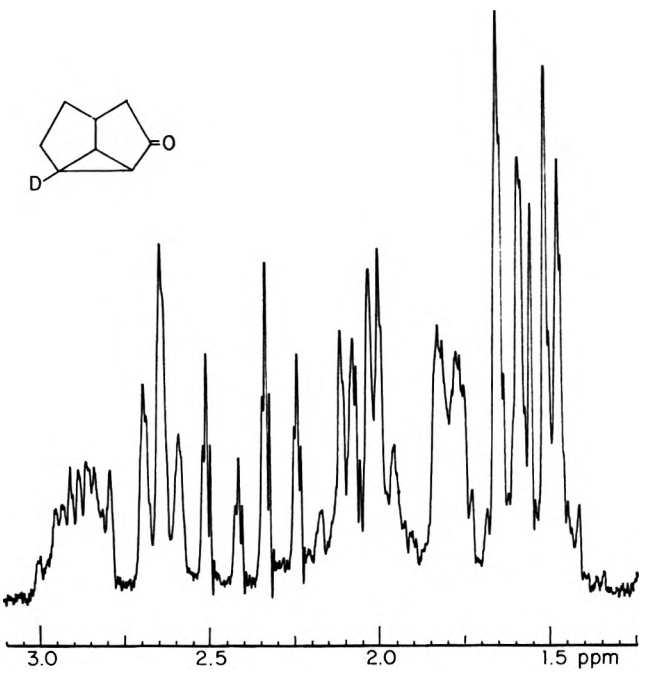


Figure 1b.—100-MHz nmr spectrum of tricyclo[3.3.0.0^{2,8}]octan-3-one-8-*d* (**7**).

The major fragments observed in the mass spectrum of tricyclo[3.3.0.0^{2,8}]octan-3-one (**4**) are given in Table I. The base peak, *m/e* 80, apparently results from loss of ketene from the parent ion. A metastable peak at *m/e* 52.5, corresponding to the fragmentation 122 → 80, is present. The mass spectra of the deuterated derivatives of **4** confirm the direct loss of the C_3 and C_4 carbon atoms. The C_4-d_2 ketone **6** showed a base peak at *m/e* 80, while both the C_2-*d* derivative **5** and the C_8-*d* ketone

TABLE I
MASS SPECTRUM OF TRICYCLO[3.3.0.0^{2,8}]OCTAN-3-ONE (4)

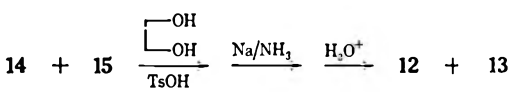
m/e (rel intensity)		
123 (1.5)	81 (11)	68 (5)
122 (15)	80 (100)	66 (6)
121 (2)	79 (40)	53 (10)
94 (5)	78 (5)	51 (4)
91 (4)	77 (10)	41 (6)

7 had base peaks at *m/e* 81. Loss of a hydrogen atom from the *m/e* 80 fragment to yield the only other significant fragment at *m/e* 79 for **4** (and **6** and at *m/e* 80 for **5** and **7**) is supported by a strong metastable peak at *m/e* 78.2.

Ring Cleavage.—In theory, ring cleavage of the tricyclic ketone **4** can yield two different bicyclic skeletons. For example, reductive opening (dissolving metal) of the C_2–C_8 bond yields *cis*-bicyclo[3.3.0]octan-3-one (**12**), while rupture of the C_1–C_2 bond gives bicyclo[3.2.1]octan-3-one (**13**). The initial bond cleavage in both cases furnishes a secondary center. In an analogous fashion, hydrobromic acid treatment of **4** gives the corresponding bromo ketones **14** and **15**. In practice the initial acid-cleavage products were converted into ketones **12** and **13**, as shown below. Thus, the actual course of both of these ring-opening reactions was monitored by vpc analysis of ketones **12** and **13**.

12, R = H
14, R = Br

13, R = H
15, R = Br



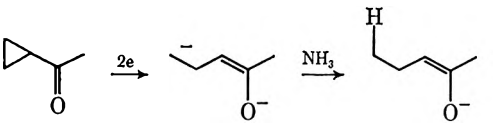
The reductive opening of ketone **4** was carried out using a limited amount of lithium in liquid ammonia. Under conditions resulting in approximately 50–65% reaction, the formation of alcoholic products was essentially avoided. Analysis of the resulting mixture of bicyclic ketones showed 95% *cis*-bicyclo[3.3.0]octan-3-one (**12**) and 5% bicyclo[3.2.1]octan-3-one (**13**).

Ketone **4** was treated with excess hydrogen bromide in methylene chloride solution (−10°, 2 hr). After removal of the bromine atom (as shown above), the product mixture contained 80% ketone **12** and 20% ketone **13**.

Both of these reactions yield predominantly the product expected from selective cleavage of the cyclopropane σ bond best oriented for overlap with the adjacent p orbital (*i.e.*, the bond darkened in B). In agreement with similar studies, the reductive opening[7] is more stereoselective than the acid-catalyzed opening.[13] Although this apparent stereoselectivity has been rationalized previously[7,13] on the basis of preferential overlap of one cyclopropane σ bond, as shown in B, a consideration of the individual mechanisms involved does not support this hypothesis.

(13) *Cf.* J. R. Williams and H. Ziffer, *Chem. Commun.*, 194 (1967); B. A. Shoulders, W. W. Kwie, W. Klyne, and P. D. Gardner, *Tetrahedron*, **21**, 2973 (1965).

The net stoichiometry of the dissolving metal opening of a cyclopropyl ketone requires a two-electron addition to yield an enolate ion and a carbanion (see eq 1). The

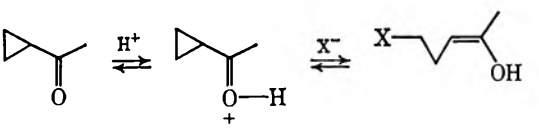


(1)

actual ring opening may occur at either the anion-radical or the dianion stage; but, in either case, the reaction is effectively *irreversible*, since the carbanion formed will be protonated by ammonia. A kinetically controlled bond rupture therefore determines the product composition.

It is well known that cyclohexanone derivatives containing α substituents such as halo, amino, acyloxy or hydroxy undergo reductive α elimination to yield the corresponding cyclohexanone enolate ion. These reactions show distinct stereoelectronic requirements. An axial substituent is eliminated in preference to an equatorial one. This conformational preference is due to the energetically favorable possibility of continuous overlap in the developing π framework of the enolate ion when the leaving group is axial.[14] The reductive opening of a cyclopropyl ketone can be viewed as simply an intramolecular example of such an α-elimination process. The same stereoelectronic requirements for continuous overlap in the developing enolate ion, therefore, should apply. Consideration of these leads to the stereoselective formation of the same product as predicted from B. For example, rupture of the C_2-C_8 σ bond in **4** results in maximum overlap during enolate formation. Thus, the stereoselective reductive opening of rigid cyclopropyl ketones is consistent with the general geometric requirements for elimination of an α substituent.[15] The presence of any preferential ground state participation analogous to that shown in B is not required.

A reasonable mechanism for the acid-catalyzed opening of a cyclopropyl ketone involves initial protonation of the carbonyl group followed by nucleophilic ring opening (stepwise *or* concerted) to yield a halo enol (see eq 2). In principle, the ring-opening step is



(2)

reversible. Consequently, the final product composition could reflect *both* kinetic and thermodynamic control. Although no specific equilibria data are available, the formation (in part) of the more stable product would account for the decreased stereoselectivity generally exhibited by these acid-catalyzed openings.[7,13,15] The formation of bromo ketones **14** (*ca.* 80%) and **15** (*ca.* 20%) from ketone **4** is in qualitative agreement with this hypothesis.

In conclusion, it has been shown that ground-state delocalization plays little or no role in determining the product compositions from either of these ring-opening reactions. Thus, the use of these chemical probes does

(14) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 56–57.

(15) Other nonconjugative factors may be important in determining the course of these ring openings; see, for example, A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89**, 3914, 3915, 3917 (1967).

not constitute a valid method to evaluate ground-state cyclopropyl ketone delocalization.

Experimental Section

Nmr spectra were obtained on a Varian Associates Model A-60 or HA-100 spectrometer; infrared spectra were measured on a Perkin-Elmer Model 237 or 257 grating infrared spectrometer; mass spectra were obtained on an AEI MS-9 double-focusing instrument. Vpc analysis was performed on a Model 600-C Aerograph HiFi instrument with a flame detector and nitrogen carrier gas, or on an Aerograph A-90-P3 instrument. Optimum separation of ring-cleavage products was obtained using a 15% QF-1 column (20 ft × 1/8 in., 100–120 mesh Chromosorb W). The order of elution was ketone **13**, followed closely by ketone **12**, and finally ketone **4**. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Tricyclo[3.3.0.0^{2,8}]octan-3-one (4) was prepared from 2-cyclopentene-1-acetic acid[9] (**1**) by the general method of Doering.[8] **1** gave 2-Cyclopentene-1-acetyl chloride (**2**), bp 82–83° (30 mm), ir (CCl_4) 1805 cm^{-1} (thionyl chloride method, 86%), and **3a**, not purified, ir (film) 2100 cm^{-1}. A solution of **3a** [from 6.0 g (0.042 mol) of acid chloride] in cyclohexane (40 ml) was added over a 4-hr period to a stirred, refluxing suspension of cupric sulfate (16 g) in cyclohexane (400 ml). After an additional 3 hr of heating, the mixture was cooled, filtered, and concentrated to furnish an orange oil. Distillation yielded impure **4**, bp 76–82° (6.8 mm). This yellow liquid was chromatographed on silica gel (64 g) in benzene to give a homogeneous material (tlc). Distillation furnished pure **4**; bp 76–77° (6.5 mm), yield 2.7 g (53% from acid chloride); mol wt (mass spectrum) 122; ir (CCl_4) 1723 cm^{-1}; nmr, Figure 1a. The semicarbazone derivative had mp 211–212°; the 2,4-dinitrophenylhydrazone had mp 163–165°.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.34; H, 8.23.

Tricyclo[3.3.0.0^{2,8}]octan-3-one-4-d_2 (6).—A solution of ketone **4** (600 mg, 4.9 mmol) and sodium methoxide (*ca.* 50 mg) in methanol-O-*d* (9 ml) was heated at reflux for 54 hr. The crude product obtained by ether extraction was resubmitted to the above procedure (19-hr reflux). Work-up and preparative vpc (4% QF-1, 130°) yielded the C_4-d_2 ketone **6**; yield 184 mg (31%); mass spectrum indicated 95% d_2, 5% d_1; ir (CCl_4) 2950, 2100, and 1723 cm^{-1}; nmr, see text.

Tricyclo[3.3.0.0^{2,8}]octan-3-one-8-*d* (7).—The sequence[10] is outlined in Scheme I.

2-Cyclopenten-1-ol-1-*d* (8).—A solution of freshly distilled 2-cyclopentenone[16] (5.00 g, 61 mmol) in ether (15 ml) was added over a 6-min period to a cold (ice bath), stirred suspension of lithium aluminum deuteride (0.80 g, 19 mmol) in ether (150 ml). After stirring for an additional 30 min at 0°, the excess hydride was carefully decomposed with water, the organic phase was decanted, and the residue was extracted with hot ether. The combined organic phases were dried ($MgSO_4$) and distilled to yield **8**; bp 65–69° (31 mm); yield 4.2 g (80%); ir (CCl_4) 3300, 2950, and 2150 cm^{-1}; nmr, no signal for allylic proton adjacent to OH.

2-Cyclopenten-1-yl-1-*d* vinyl ether (9) was prepared from alcohol **8** by mercuric acetate catalyzed[11] exchange with ethyl vinyl ether; bp 62–63° (31 mm); yield 2.7 g (59%, corrected for recovered alcohol); ir, no OH; nmr δ 6.2 (m, 1) and 4.0 (m, 2) (both O—CH=CH_2).

2-Cyclopentene-1-acetaldehyde-3-*d* (10) was prepared by pyrolysis of vinyl ether **9** (vertical tube, 320°, N_2 carrier gas); bp 72–79° (56 mm); yield 1.6 g (76%, corrected for recovered ether; ir (CCl_4) 1730 cm^{-1}.

2-Cyclopentene-1-acetic acid-3-*d* (11) was prepared by silver oxide oxidation[17] of aldehyde **10**; bp 79–80° (1.1 mm); yield 1.1 g (60%); ir (CCl_4) 1705 cm^{-1}; nmr δ 5.64 (m, 1, vinyl H).

C_8-*d* Ketone 7.—Acid **11** was converted to **7** as described above for **4**; bp 77–78° (6.8 mm); yield 400 mg (41% from acid); mass spectrum, 93% d_1; ir (CCl_4) 1723 cm^{-1}; nmr, Figure 1b.

Tricyclo[3.3.0.0^{2,8}]octan-3-one-2-*d* (5) was prepared from 2-cyclopenten-1-acetic acid (**1**) using the procedure previously described, except that diazomethane-d_2[18] was employed. Preparative vpc (10% FFAP, 180°) gave ketone **5**; mass spectrum indicated 71% d_1 and 29% d_0; ir (CCl_4) 1723 cm^{-1}; nmr, see text.

***cis*-Bicyclo[3.3.0]octan-3-one (12)** was prepared from ethyl 2-cyclopentanone-1-ylacetate (see below) by the method of Linstead and Meade[19] in an over-all yield of 10%. Pure **12** had bp 104–105° (4 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 2.60 (m, 2, C_1 H and C_5 H) and 1.3–2.4 (m, 10); the 2,4-dinitrophenylhydrazone derivative had mp 112–113° (lit.[20] mp 115°); the semicarbazone had mp 188–189° (lit.[19] mp 187–188°).

Ethyl 2-cyclopentanone-1-ylacetate was prepared from ethyl-(and methyl-) 2-cyclopentanone-1-ylcarboxylate by the method of Dev[9,20] in an overall yield of 51%. In one small-scale run, the desired keto ester was prepared from cyclopentanone and ethyl chloroacetate by the enamine procedure[21] in an over-all yield of 16%. Pure product had bp 89–92° (3 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 1.2, 4.1 (ethyl ester), and 1.6–3.0 (m, 9); the 2,4-dinitrophenylhydrazone derivative had mp 107–108°.

Bicyclo[3.2.1]octan-3-one (13) was prepared by the method of Moore[22] and purified by silica gel chromatography or *via* its semicarbazone.[23] Pure **13** (very volatile) had ir (CCl_4) 1715 cm^{-1}; nmr (CCl_4) δ 2.50 (m, 2, C_1 and C_5 H), 1.77 (m, 6, C_6, C_7, and C_8 H); the 2,4-dinitrophenylhydrazone derivative had mp 163–164° (lit.[22] mp 165–166°); the semicarbazone had mp 188–189°.

Lithium in Liquid Ammonia Reduction of Ketone 4.—A solution of ketone **4** (244 mg, 2.0 mmol) in ether (1 ml) was added over a 3-min period to a stirred solution of lithium (30 mg, 5.0 mmol) in liquid ammonia (50 ml). The reaction mixture turned white immediately. After stirring for 30 min, ammonium chloride (500 mg) was added and the ammonia was evaporated. The resulting residue was dissolved in a mixture of water (25 ml) and ether (25 ml). The aqueous phase was saturated with sodium chloride and extracted with ether. The combined ether phases were dried ($MgSO_4$) and carefully concentrated. Vpc analysis of this ether solution showed 65% reaction; the products were 95% ketone **12** and 5% ketone **13**.

Hydrogen Bromide Treatment of Ketone 4.—Excess, anhydrous hydrogen bromide gas was bubbled into a stirred solution of ketone **4** (488 mg, 4.0 mmol) in methylene chloride (30 ml) at −10°. This mixture was stirred at −10° for 2 hr, then poured onto ice (100 g) and extracted with ether. The ether extracts were washed with dilute sodium hydroxide solution, dried ($MgSO_4$), and evaporated. Distillation yielded a mixture of bromo ketones **14** and **15**, bp 115–118° (7 mm), yield 600 mg (61%). Treatment with ethylene glycol in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid yielded the corresponding bromo ketals, bp 70–72° (0.05 mm), yield 469 mg (64%). Removal of the bromine atom was effected by treatment with sodium (115 mg) in liquid ammonia (50 ml) and ether (10 ml). The crude ketal mixture was hydrolyzed with hydrochloric acid–water (40 ml, 1:1 mixture) and extracted into ether. After drying ($MgSO_4$), the ether was carefully concentrated. Vpc analysis of this solution showed 80% ketone **12** and 20% ketone **13**.

Registry No.—**4**, 20826-85-1; **4** (semicarbazone), 20826-86-2; **4** (2,4-dinitrophenylhydrazone), 20826-87-3; **5**, 20826-88-4; **6**, 20826-89-5; **7**, 20826-90-8; **8**, 20826-91-9; **9**, 20858-74-6; **10**, 20826-92-0; **11**, 20826-93-1; **12**, 19915-11-8; ethyl 2-cyclopentanon-1-ylacetate, 20826-94-2.

(16) K. Alder and F. H. Flock, *Chem. Ber.*, **89**, 1732 (1956).

(17) V. Migrdichian, "Organic Synthesis," Vol. I, Reinhold Publishing Co., Inc., New York, N. Y., 1957, p 258.

(18) D. W. Thomas and K. Biemann, *J. Amer. Chem. Soc.*, **87**, 5447 (1965).

(19) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1935).

(20) S. Dev, *J. Indian Chem. Soc.*, **30**, 815 (1953).

(21) *Cf.* G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 220 (1963).

(22) W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, **28**, 2200 (1963).

(23) *Cf.* W. Kraus, *Chem. Ber.*, **97**, 2719 (1964).

γ Elimination of a Sulfonyl Group to Form a Cyclopropane Ring

W. L. PARKER[1] AND R. B. WOODWARD

Chemistry Department, Harvard University, Cambridge, Massachusetts 02138

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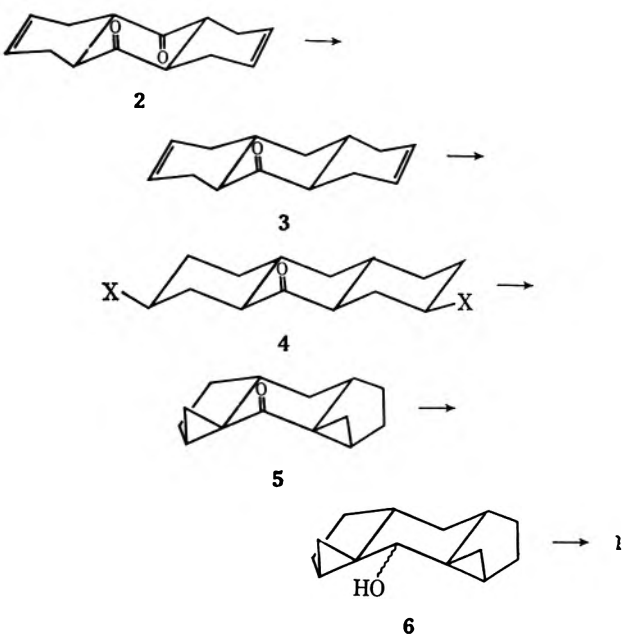
A model system, **1**, has been synthesized for a study of the isosterol rearrangement. A key step in this synthesis introduces a novel method for the formation of cyclopropane rings through base-catalyzed γ elimination of sulfinate ions from δ-keto sulfones; the method possesses special stereochemical advantages. The ketone, **5**, is of interest in possessing a dicyclopropyl ketone system of known fixed stereochemistry.

In the course of synthesizing **1** for a study of the isosterol rearrangement, an interesting and potentially versatile reaction for the formation of three-membered

1

rings was developed. The synthesis was carried out on the broad outline in Scheme I. Two major problems in

SCHEME I



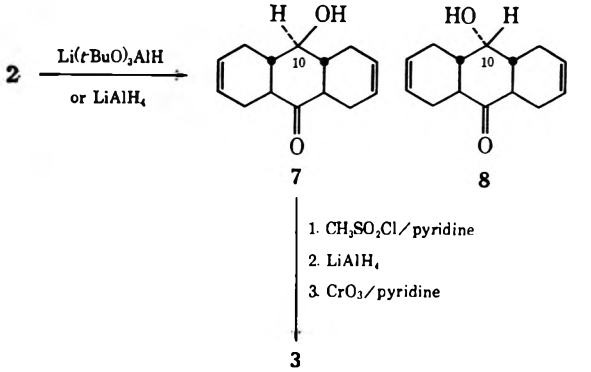
this route are regioselective addition to the double bonds of **3** to give leaving groups γ to the carbonyl group of **4**, and production of the stereochemistry shown for **4** in which the leaving groups are suitably disposed for γ elimination to form the cyclopropane rings.

The starting material for this sequence (**2**) was reported by Alder and Stein[2] to result from the base-catalyzed isomerization of the Diels–Alder adduct of butadiene and quinone. The stereochemistry of the octahydroanthraquinones, perhydroanthracenes, and other related systems has been studied by several groups.[3-7]

For the conversions of **2** to **3**, the selective reduction of one of the ketone groups of **2** was necessary. This was accomplished as described by Ireland and Marshall for the partial reduction of Δ^6-octaline-1,4-dione using lithium tri-*t*-butoxyaluminohydride.[8] Treatment of **2** with 1 equiv of this reagent in tetrahydrofuran gave the equatorial monoalcohol, **7**, in 61% yield and a mixture of monoalcohols containing much of the axial alcohol, **8**, in 30% yield. The configurations of the hydroxyl groups were assigned on the basis of nuclear magnetic resonance spectra in trifluoroacetic acid. The spectrum of **7** showed a triplet at 3.89 ppm with J = 8.5 Hz, while the spectrum of **8** had a singlet at 4.17 ppm with width at half-height of about 4.5 Hz (J < 2.3 Hz). These peaks were assigned to the protons at C-10. The magnitudes of the splittings are a function of the dihedral angles between these protons and the protons at the ring junctions.[9] In **7**, the dihedral angle is about 180° and a large coupling constant (*ca.* 9.2 Hz) is expected, while, in **8**, the angle is about 60°, which should give a small (*ca.* 1.7 Hz) coupling constant. Reduction of **2** with lithium aluminum hydride also gave **7** and **8**, but the yields are very poor by this method. The fact that a mixture of axial and equatorial alcohols was obtained provides excellent additional chemical evidence[3] for the *trans,syn,trans* configuration of **2**. The *trans,anti,trans* configuration, which has recently been proposed for this substance,[7] would have resulted in the formation of a racemic but otherwise homogeneous monoalcohol.

Treatment of **7** with methanesulfonyl chloride in pyridine followed by reduction of the mesylate with lithium aluminum hydride in refluxing tetrahydrofuran gave an alcohol that was oxidized to **3** with chromium trioxide–pyridine complex[10] (Scheme II).

SCHEME II



(1) To whom inquiries should be directed at the Squibb Institute for Medical Research, New Brunswick, N. J. 08903.

(2) K. Alder and G. Stein, *Ann.*, **501**, 283 (1933).

(3) R. K. Hill, J. G. Martin, and W. H. Stouch, *J. Amer. Chem. Soc.*, **83**, 4006 (1961).

(4) J. W. Cook, N. A. McGinnis, and S. Mitchell, *J. Chem. Soc.*, 286 (1944).

(5) W. S. Johnson, *Experientia*, **7**, 315 (1951).

(6) R. L. Clarke, *J. Amer. Chem. Soc.*, **83**, 965 (1961).

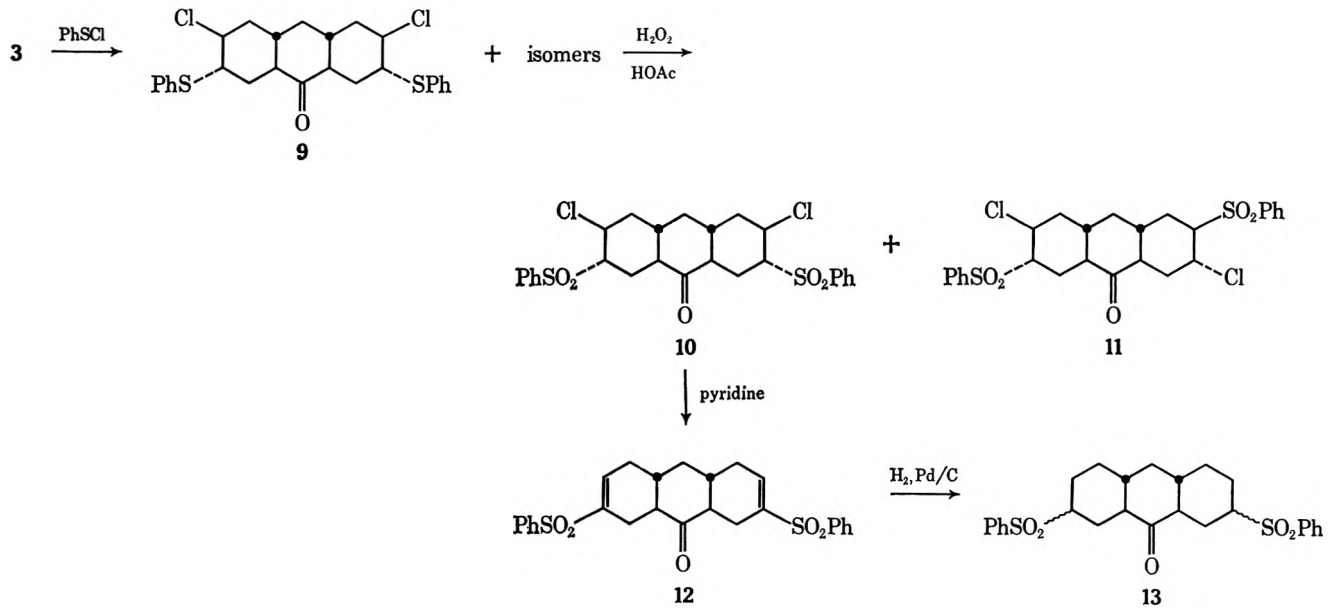
(7) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *ibid.*, **88**, 2999 (1966).

(8) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1620 (1962).

(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(10) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

SCHEME III



The selective placement of leaving groups at the carbon atoms γ to the carbonyl group depended on the long-range dipole interactions[11] of the carbonyl group, since the vinylic positions are nearly equivalent sterically. The choice of leaving groups was dictated by the means of introduction (electrophilic addition to the double bonds) and the capability of achieving the equatorial orientation necessary for γ elimination.[12] Sulfonyl groups[13] meet these requirements. They can be introduced by a reaction sequence involving the addition of sulfenyl halides[14,15] to the double bonds and would activate the adjacent protons, permitting equatorial orientation of the sulfonyl groups under conditions for a base-catalyzed elimination. The γ elimination of a sulfinate ion has been observed in an anomalous lithium aluminum hydride reaction[16] but formation of

$$R_2C(SO_2Et)_2 \xrightarrow{LiAlH_4} R_2C{=}CHCH_3$$

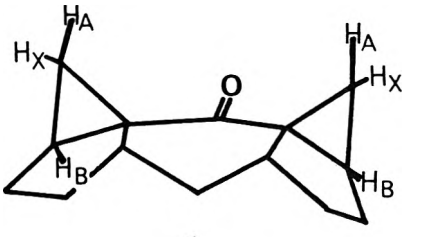
cyclopropanes by this route is unknown. Regarding the direction of addition of the sulfenyl halide, it was hoped that the carbonyl group would polarize the double bond such that the carbon atom γ to the carbonyl group would have a sufficiently increased electron density to cause attachment of the electrophile at that position.

Addition of 2 equiv of benzenesulfenyl chloride to **3** gave a mixture (assumed to be chiefly **9**) which was oxidized with hydrogen peroxide in acetic acid. Partial purification at this point gave impure **10** (70% from **3**) which melted at *ca.* 250–297°, and isomeric material, probably **11**, which melted at 133–136° but had a nearly identical infrared spectrum. Complete separation of the isomeric products for quantitative evaluation of the directive effect of the carbonyl group was impractical in this system, but the yields indicate that the effect was probably substantial. Dehydrohalogenation of **10** gave **12**, which was hydrogenated to give **13**. (See Scheme III.)

Several experiments were carried out to find the best conditions for elimination of benzenesulfinate from **13**. Prolonged refluxing of **13** in methanolic KOH gave no reaction, while brief treatment with NaH in dimethylformamide at 140° destroyed the starting material, giving little or no **5**. Encouraging results were obtained by heating **13** with potassium *t*-butoxide in dimethylformamide containing a little *t*-butyl alcohol at 80°. When the reaction was carried out on a preparative scale using these conditions and the products were separated by chromatography, a compound melting at 95–98.5° was obtained in 34% yield. The elemental analysis was in agreement with structure **5**.

The infrared spectrum (KBr) showed a carbonyl peak at 6.04 μ, and the near-infrared spectrum (in CCl_4) had a peak at 1.635 μ with an extinction coefficient of 0.603, confirming the presence of two cyclopropyl methylene groups.[17]

The nuclear magnetic resonance spectrum (in CCl_4) has a peak at 0.7 ppm, with two very small peaks (*not* spinning side bands) located at 9 Hz above and below it. Integration of this multiplet showed that it was caused by two protons. Examination of models of **5** shows



5

that two of the cyclopropyl methylene protons (H_A) are probably in the strongly deshielding region near the carbonyl group.[18] The nuclear magnetic resonance

(11) H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963).
(12) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).
(13) The chemistry of sulfones is reviewed by J. Strating in "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, Chapter 15.
(14) Sulfenyl compounds are reviewed in ref 13 by I. B. Douglass, F. A. Drahowzal, and N. Kharasch in Chapters 30, 31, and 32.
(15) S. J. Cristol, R. P. Arganbright, G. D. Brindell, and R. M. Heitz, *J. Amer. Chem. Soc.*, **79**, 6035 (1957).
(16) M. W. Cronyn, *ibid.*, **74**, 1225 (1952).
(17) P. G. Gassman and F. V. Zalar, *J. Org. Chem.*, **31**, 166 (1966).
(18) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p 124.

spectrum of 3α,5-cyclo-5α-cholestan-6-one in benzene was taken for comparison. It showed a high field multiplet with an area that indicated four protons. The C-18 angular methyl group, which is found in this region, combined with the 4β proton, gives the expected integration.

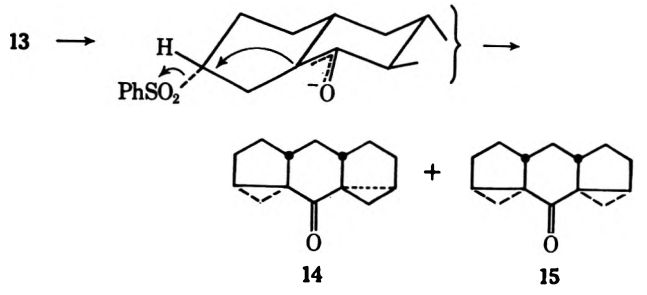
The high field absorption of **5** was considered to be the X part of an ABX system. The appearance of the spectrum in CCl_4 indicated that $J_{AX} = -J_{BX}$ and $\nu_A - \nu_B = 0$. Removal of the chemical shift degeneracy was accomplished by taking spectra in pyridine and in benzene. The H_X absorption in pyridine was a very poorly resolved triplet with two small peaks on either side, and in benzene a clean triplet was observed. Coupling constants (Table I) were estimated[19] from the spectra taken in CCl_4 and in pyridine. The values obtained are probably not very accurate because of uncertainty in measurements of the spectra, but they are in reasonable agreement with the range of values observed by other workers.

TABLE I

	Calcd, Hz	Usual range,[a] Hz
J_{AX}	−3.0	−4.2 to −6.0
J_{BX}	3.0	3.9 to 8.0
J_{AB}	8.5	7.3 to 11.2

[a] K. B. Wibert and B. J. Nist, *J. Amer. Chem. Soc.*, **85**, 2788 (1963); D. J. Patel, M. E. H. Howden, and J. D. Roberts, *ibid.*, **85**, 3218 (1963).

The formation of other isomers (**14** and **15**) of **5** from **13** would involve displacement of axially oriented sulfone groups (*via* the boat conformation). However,

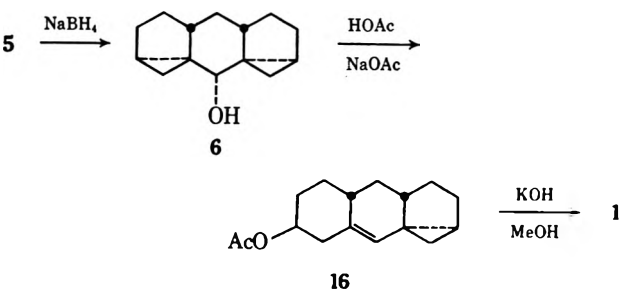


14 15

β elimination of sulfones is a well-known reaction[13] and would probably predominate over γ elimination involving the boat conformation, in analogy to the observation that 3α-tosyloxycholestan-6-one undergoes β elimination to give cholest-2-en-6-one rather than γ elimination to give 3β,5-cyclo-5β-cholestan-6-one.[12] Structure **14** is inconsistent with the nmr spectrum of **5** unless the cyclopropyl protons of the epimeric rings happen to have the same chemical shifts in several solvents and the same coupling constants.

The pentacyclic ketone, **5**, was reduced with sodium borohydride, giving **6** with the hydroxyl group probably in the equatorial position.

In acetic acid, 2% in sodium acetate, **6** rearranges rapidly to give the acetate of **1** (**16**) which is saponified by treatment with potassium hydroxide in methanol. The last three reactions (**5** → **6** → **16** → **1**) were very



clean, and, when run successively without purification of intermediates, gave **1** (after purification) in 96.6% yield from **5**. The formation of **16** from the acetolysis of **6** supports the configuration assigned to the cyclopropyl rings of **5**. If **15** were the product of the base-catalyzed elimination, the sequence of reactions used to produce **1** would probably have given a hydroxymethylcyclopentyl derivative, in analogy to the formation of α-hydroxymethyl-A-norcholest-5-ene from 3β,5-cyclo-5β-cholestan-6β-ol upon treatment with acid.[20]

Experimental Section

Melting points, unless noted otherwise, were taken on a Kofler hot stage microscope and are uncorrected. Nmr spectra were taken on a Varian A-60 spectrometer, ultraviolet and near-infrared spectra on a Cary 14 spectrophotometer, and infrared spectra on a Perkin-Elmer Infracord spectrophotometer. Elemental analyses were done by Scandinavian Microanalytical Laboratories. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter. 1,4,4aβ,5,8,8α,9aα,10aβ-Octahydroanthraquinone (**2**) was made as described by Alder and Stein.[2]

1,4,4aβ,5,8,8aα,9aα,10aβ-Octahydro-10-hydroxy-9-anthrones (7 and 8) by Lithium Aluminum Hydride Reduction.—To a solution of 0.177 g (0.818 mmol) of **2** in 20 ml of tetrahydrofuran, 0.60 ml (0.212 mmol) of a 0.353 *M* solution of lithium aluminum hydride in tetrahydrofuran was added under nitrogen with stirring over a period of 25 min. The solution was stirred for 15 min at room temperature and then was refluxed for 50 min. One ml of water was added and the resultant precipitate was filtered out. The solvent was removed and the residue was taken up in methylene chloride. The suspension was washed with water and dried ($MgSO_4$). Removal of solvent gave a solid from which a mixture of **7** and **8** was obtained by chromatography on alumina. (There was partial separation of **7** and **8** with the latter being eluted more quickly.) The mixture was recrystallized once from ethyl acetate to give somewhat impure **7** (13.8 mg), mp *ca.* 203°; ir (KBr) 5.89 μ.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.80; H, 8.43.

The residue from the filtrate was recrystallized several times from benzene, giving **8**, mp 151–165°; ir (KBr) 5.92 μ.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.96; H, 8.34.

Synthesis of 7 and 8 by Reduction of 2 with Lithium Tri-*t*-butoxyaluminohydride.—A solution of 29.4 g of $Li(t\text{-}BuO)_3AlH$ (0.116 mol) in 300 ml of tetrahydrofuran was added dropwise under nitrogen over a period of 1 hr with stirring to a solution of **2** (25.0 g, 0.116 mol) in 1.75 l. of tetrahydrofuran. After 3.5 hr at room temperature, the solvent was removed *in vacuo*, and the residue was dissolved in a mixture of *ca.* 1.1 l. of methylene chloride and 200 ml of 10% sulfuric acid. The methylene chloride solution was dried (K_2CO_3) and the solvent was removed *in vacuo*. The residue was recrystallized from ethyl acetate (*ca.* 300 ml), giving 15.3 g (60.7%) of **7**, mp 211.5–213.0°. A sample recrystallized several times from ethyl acetate melted at 214–214.5°; nmr (CF_3CO_2H) δ 3.89 (t, J = 8.5 Hz) and 5.78 (s).

A second crop from the recrystallization of the crude reaction product gave 7.54 g (29.8%) of product, mp 151–178°. A

(19) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 132 ff.

(20) G. H. Whitham, *Proc. Chem. Soc.*, 330 (1962); W. G. Dauben and J. A. Ross, *J. Amer. Chem. Soc.*, **81**, 6521 (1959); G. H. Whitham and J. A. F. Wickramasinghe, *J. Chem. Soc.*, 1655 (1964); G. Bauslaugh, G. Just, and E. Lee-Ruff, *Can. J. Chem.*, **44**, 2837 (1966).

sample was recrystallized several times from benzene to give material melting at 153–159°, which was largely **8**, nmr (CF_3CO_2H) δ 4.17 (s, $W_{1/2}$ = 4.5 Hz) and 5.78 (s). The nmr spectra identify **7** as the 10β-alcohol and **8** as the 10α-alcohol, as discussed before.

1,4,4aβ,5,8,8aα,9aα,10aβ-Octahydroanthrone (3).—A solution of **7** (38.4 g) in 410 ml of pyridine (freshly purified) was cooled to 0°. A cold solution (0°) of 46 ml of methanesulfonyl chloride in 200 ml of pyridine was added and the mixture was kept at 0° for 24 hr. The mixture was then poured into 3.5 l. of ice–water and extracted with *ca.* 3 l. of benzene. The benzene solution was washed successively with water, cold 5% sulfuric acid, water, 2% sodium bicarbonate solution, and water, and was dried ($MgSO_4$) and boiled down until the product crystallized. The first crop gave 40.2 g of tan solid (77.2%), mp *ca.* 180–193°, and the second crop gave 6.2 g (11.9%), mp 181.5–186.5° with some material remaining up to 192°. The over-all yield of the crude methanesulfonate of **7** was 89.1%. Recrystallization from benzene gave an analytical sample, mp 188–192°; ir (KBr) 5.83, 6.03, 7.43, 8.49, 8.58 μ; nmr δ ($CHCl_3$) (rel area) 5.80 (s, 3.98), 4.79 (t, J = *ca.* 8.5 Hz, 1.16), 3.11 (very sharp s, 2.93), and 2.29 (broad envelope, 11.91).

Anal. Calcd for $C_{15}H_{20}O_3S$: C, 60.78; H, 6.80; S, 10.82. Found: C, 60.83; H, 6.72; S, 10.92.

The methanesulfonate was dissolved in 1.5 l. of purified tetrahydrofuran. Lithium aluminum hydride (38 g) was added, and the mixture was refluxed ($CaCl_2$ tube) for 24 hr. Ethyl acetate (184 g) was added dropwise with stirring (by hand when necessary). After 1 hr, 10 ml of water was added, and 500-ml portions of the reaction mixture were poured into 2-l. portions of cold 5% sulfuric acid. These mixtures were extracted with methylene chloride and the combined extracts were taken to dryness *in vacuo*. The residue was dissolved in methylene chloride–tetrahydrofuran and and the solution was dried (K_2CO_3). Removal of the solvent gave 35.1 g of crude 1,4,4aβ,5,8,8aα,9,9aα,10,10aβ-decahydroanthran-9-ol. (The theoretical yield is 32.1 g.) A sample from a previous run was purified by chromatography on alumina to give analytical material, mp 143–145.5°; ir (KBr) 2.95 and 6.04 μ.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.27; H, 9.54.

Chromium trioxide (12.0 g) was added to 120 ml of pyridine (with caution),[10] and a solution of 12.2 g of the decahydroanthranol in 120 ml of pyridine was added to the mixture. The flask was kept at 39° for 9 hr, and the contents were then poured into 1 l. of water. Carbon tetrachloride (300 ml) was added, and the mixture was filtered. The organic layer was separated and the aqueous layer was washed with more carbon tetrachloride. The carbon tetrachloride solution was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was chromatographed on 100 g of alumina, and eluted with benzene to give 8.64 g of crude **3** and with acetone to give 2.67 g of unchanged starting material. The crude **3** was recrystallized from ethanol to give 8.31 g (87.9% based on unrecovered starting material) of purified **3**, mp 125–129.0°. A sample of **3** recrystallized several times from methanol melted at 125.5–126°; ir (KBr) 5.87 and 6.04 μ; nmr (CCl_4) δ (rel area) 5.74 (3.8) and 2.19 (broad envelope, 14.2).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.94; H, 8.97.

4aβ,8aα,9aα,10aβ-Perhydro-2α,7α-diphenylthio-3β,6β-dichloro-9-anthrone (9).—Benzenesulfenyl chloride was made by the procedure of Lecher and Holschneider.[21] A solution of 13.3 g (0.0658 mol) of **3** in 150 ml of carbon tetrachloride was kept at 13–25° while a solution of 19.0 g (0.132 mol) of benzenesulfenyl chloride in 150 ml of carbon tetrachloride was added dropwise with stirring over a period of 1.25 hr. The solution became turbid near the end of the addition. The mixture was stirred at room temperature for 12 hr, after which the solvent was removed *in vacuo*, giving a white solid residue which occluded a large amount of solvent. A sample recrystallized twice from carbon tetrachloride and three times from benzene melted gradually to 202°; ir (KBr) 3.26, 5.84, 6.36, 6.82 μ.

Anal. Calcd for $C_{26}H_{28}Cl_2OS_2$: C, 63.53; H, 5.74; Cl, 14.43; S, 13.05. Found: C, 63.92; H, 5.80; Cl, 14.61; S, 13.31.

4aβ,8aα,9aα,10aβ-Perhydro-2α,7α-diphenylsulfonyl-3β,6β-dichloro-9-anthrone (10).—A solution of 57.0 ml of 28.3% H_2O_2 (0.526 mol) in 385 ml of acetic acid was added to the residue from the previous reaction. The mixture was heated to 80° on a steam bath to dissolve the solid. The temperature rose to *ca.* 84° and a water bath was used to cool the solution back to 80°. The solution was then stirred and allowed to cool (in air) to 65°. This took about 1 hr, during which time a precipitate formed. The mixture was stirred at 62–67° for 18 hr and then at 18–20° for 1 hr. The precipitate was filtered, washed with acetic acid, and dried *in vacuo*, giving 25.5 g of **10** (70% from **3**), mp *ca.* 250–297°. A sample was recrystallized three times from acetic acid and chromatographed on silica gel, eluting with 10% ether in methylene chloride, to give analytical material, mp *ca.* 270–297.5°; ir (KBr) 3.25, 5.86, 6.32, 6.77, 7.66, 8.70 μ; nmr of crude product (CF_3CO_2H) δ (rel area) 7.2–8.1 (9.5), 4.82 (1.68), 3.72 (1.83), 1.4–3.5 (15.0).

Anal. Calcd for $C_{26}H_{28}Cl_2O_5S_2$: C, 56.21; H, 5.08; Cl, 12.77; S, 11.54. Found: C, 55.85; H, 5.12; Cl, 13.03; S, 12.03.

Addition of water to the acetic acid filtrate gave a precipitate (**11**), mp 133–136°. The infrared spectrum of this material is nearly identical with that of the high-melting product.

1,4,4aβ,5,8,8aα,9aα,10aβ-Octahydro-2,7-diphenylsulfonyl-9-anthrone (12).—A solution of **10** (25.5 g) in 250 ml of pyridine was refluxed for 24 hr. The pyridine was mostly removed *in vacuo* and the residue was taken up in *ca.* 600 ml of methylene chloride, and washed with water, dilute hydrochloric acid (1:4), 10% sodium bicarbonate solution, and water. The solution was dried ($MgSO_4$), decolorized with charcoal, and taken to dryness. The residue was recrystallized from dimethylformamide, giving 16.3 g (73.5%) of **12**, mp 255–266.5°. In another run, the product in methylene chloride was filtered through silica gel (washing with ether), recrystallized three times from dioxane, chromatographed on silica gel and eluted with 5% ether in methylene chloride, and recrystallized twice from dimethylformamide to give an analytical sample, mp 255–267.5°; ir (KBr) 3.24, 5.84, 6.04, 6.33, 6.77, 7.70, 8.75 μ.

Anal. Calcd for $C_{26}H_{26}O_5S_2$: C, 64.70; H, 5.43; S, 13.29. Found: C, 64.72; H, 5.51; S, 13.10.

4aβ,8aα,9aα,10aβ-Perhydro-2,7-diphenylsulfonyl-9-anthrone (13).—One liter of 97% formic acid was added to 5.40 g of 10% Pd–C under nitrogen (formic acid ignites when added to the catalyst in air). The product of the previous reaction (16.3 g) was added, and the mixture was hydrogenated at 1 atm. The catalyst is poisoned slowly by **12**, but hydrogenation is complete under these conditions before the catalyst dies. The mixture was heated to 100° and filtered through Supercel on sintered glass, washing with 200 ml of boiling formic acid. Removal of the solvent *in vacuo* gave 13.7 g (83.6%) of white solid. Quantitative yields were obtained in runs done on a smaller scale where the catalyst was washed more completely. Trifluoroacetic acid is a good solvent for **13** and can be used for washing the catalyst (but *not* as a solvent for the hydrogenation). A sample recrystallized several times from formic acid had mp *ca.* 317–342° on a Kofler block and 336–344° dec (corrected) in an evacuated capillary; ir (KBr) 3.24, 5.90, 6.32, 6.77, 7.68, 8.71 μ; nmr (CF_3CO_2H) δ (rel area) 7.4–8.2 (9.65), 3.29 (2.36), and 0.8–2.9 (17.98).

Anal. Calcd for $C_{26}H_{30}O_5S_2$: C, 64.17; H, 6.21; S, 13.18. Found: C, 63.90; H, 6.14; S, 13.07.

2α,9aα-Cyclo-7α,8aα-cyclo-4aβ,10aβ-perhydro-9-anthrone (5).—A solution of **13** (13.7 g) and potassium *t*-butoxide (17.0 g, MSA Research Corporation) in 1.11 l. of dimethylformamide (Eastman Spectro Grade, dried over molecular sieves) and 59 ml of dry *t*-butyl alcohol was stirred at 80° under nitrogen for 6 hr and then cooled to 0°. The reaction mixture was mixed with 5 l. of water and extracted several times with ether. The ether solution was washed well with water and then with saturated sodium chloride solution, and was dried ($MgSO_4$) and stripped *in vacuo*, giving 4.77 g of material that mostly solidified on standing. Chromatography on 300 g of Florisil, eluting with benzene, followed by recrystallization of fractions containing **5** from ethyl acetate gave 1.96 g of **5**, mp 95–98.5°. The yield from **13** was 34.3%. A sample recrystallized several times from ethyl acetate gave analytical material, mp 96.5–97.0°; ir (KBr) 3.22–3.31 (3 weak peaks), and 6.04 μ; near-ir (in CCl_4, c 0.970 M, l = 1 cm) 1.635 μ (ϵ 0.603); nmr (CCl_4) δ (rel area) 2.65–2.03 (envelope, 1.87), 2.03–0.91 (13.99), 0.91–0.33 (triplet with very intense center peak at 0.72, 2.11); uv λ_{max} (ethanol) 275 mμ (ϵ 69); end absorption, ϵ^{220} 6500 (cyclohexane).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.38; H, 8.99.

2α,9aα-Cyclo-7α,8aα-cyclo-4aβ,10aβ-perhydroanthran-9α-ol (6).—A solution of 1.70 g of **5** and 1.70 g of sodium borohydride

(21) H. Lecher and F. Holschneider, *Ber.*, **57**, 755 (1924).

in 62 ml of 80% aqueous ethanol, 0.2 *N* in sodium hydroxide, was refluxed with stirring for 1.5 hr. The volume was reduced *in vacuo* and the residue was dissolved in ether and water. The ether solution was washed with water until neutral, washed with saturated sodium chloride solution, dried (K_2CO_3), and stripped in nitrogen stream, and the residue was dried *in vacuo*, giving 1.71 g (99.5%) of **6**. Material that had been recrystallized several times from ethyl acetate, 0.1% in triethylamine, melted at 148–150°; ir (CCl_4) 2.70, 3.26 (shoulder), and 3.33 μ; nmr ($CDCl_3$) δ (rel area) 4.36 (d, J = *ca.* 8.5 Hz, 0.73), 0.20–2.6 (19.27); mass spectrum *m/e* (rel intensity) 204 (100), 202 (89), 186 (296).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.46; H, 9.83.

1,2,3,4 4aβ,5,6,8,10,10aβ-Decahydro-7α,8aα-cyclo-2β-acetoxyanthracene (16).—The alcohol **6** (1.71 g) was dissolved in 34 ml of acetic acid, 2% in sodium acetate, with brief heating on a steam bath. After 3 hr at room temperature, the solution was poured into 150 ml of water and extracted with ether. The ether solution was washed with water, 5% sodium bicarbonate solution, water, and saturated sodium chloride solution, dried ($MgSO_4$), stripped to a small volume in a nitrogen stream, seeded, and taken to dryness in nitrogen. The residue was dried briefly *in vacuo*, giving 2.05 g (99.5%) of **16**. Material that had been recrystallized several times from methanol melted at 65.0–66.5°; ir (KBr) 3.24, 5.77, 6.05 (very weak), 8.00 μ; nmr (CCl_4) δ (rel area) 5.08 (0.94), *ca.* 4.5 (0.89), 1.97 (sharp s), *ca.* 0.5 (complex m, 2.05).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.06; H, 8.97.

1,2,3,4,4aβ,5,6,8,10,10aβ-Decahydro-7α,8aα-cycloanthran-2β-ol (1).—A solution of 2.05 g of **16** in 50 ml of 10% methanolic potassium hydroxide was stirred for 1.5 hr at room temperature. The volume of the solution was reduced *in vacuo* and the viscous liquid was poured into water and extracted with ether. The ether solution was washed with water until neutral and then with saturated sodium chloride solution, dried ($MgSO_4$), and stripped in nitrogen stream, and the residue was dried briefly *in vacuo*, tiving 1.69 g. The product was recrystallized from ethyl acetate to give 1.66 g (97.3%) of **1**, mp 117–119°. Analytical material was obtained by several recrystallizations from ethyl acetate and melted at 117–119°; ir (KBr) 3.02 μ; nmr (CCl_4) δ (rel area) 4.98 (0.95), *ca.* 3.4 (1.23), and 0.25–0.80 (complex m, 2.36); uv (cyclohexane) λ_{max} 218 mμ (ϵ 12,300).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.18; H, 9.88.

Registry No.—**1**, 20843-76-9; **3**, 20843-77-0; **5**, 20843-78-1; **6**, 20843-79-2; **7**, 20843-80-5; **7** (methanesulfonate), 20843-81-6; **8**, 20843-82-7; **9**, 20843-83-8; **10**, 20843-84-9; **11**, 20843-85-0; **12**, 20843-86-1; **13**, 20843-87-2; **16**, 20843-88-3; 1,4,4aβ,5,8,8aα,9,9-aα,10,10aβ-decahydroanthran-9-ol, 20843-89-4.

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Arynes *via* Aprotic Diazotization of Anthranilic Acids[1]

LESTER FRIEDMAN AND FRANCIS M. LOGULLO[2]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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Aprotic diazotization of anthranilic acids generates the corresponding benzenediazonium-2-carboxylates which decompose *in situ* to give arynes, carbon dioxide, and nitrogen. Moderate to excellent yields of aryne-derived products are obtained when the reaction is conducted in the presence of suitable acceptors.

Arynes have been generated under a variety of conditions by fragmentation of suitable *ortho*-disubstituted benzenes.[3] Most of the methods suffer from either limited availability of benzyne precursor, involved experimental techniques, and/or low yields of benzyne-derived products. One of the more attractive benzyne precursors is benzenediazonium-2-carboxylate,[3f] in that benzyne formation can be effected in neutral aprotic media at moderate temperatures. However, this compound is extremely shock sensitive and hazardous to use. As a result, benzyne has not been utilized to the full extent that it could be.

In 1962, it was reported[4] that arylamines could be diazotized by amyl nitrite in excess benzene to give diazonium species which decompose *in situ* to give biaryls. If anthranilic acids[5] could be diazotized in a similar manner, the products would be benzenediazonium-2-carboxylates, which could, in principle, decompose as formed to arynes, nitrogen, and carbon dioxide.

Results and Discussion

It was found that anthranilic acids are readily diazotized by alkyl nitrites in aprotic media to give benzenediazonium-2-carboxylates, which undergo fragmentation to benzyne, nitrogen, and carbon dioxide. The intermediacy of benzyne[6] was demonstrated by trapping with anthracene (to give triptycene), furan (to give 1,4-dihydro-1,4-epoxynaphthalene), tetracyclone (to give 1,2,3,4-tetraphenylnaphthalene), iodine (to give diiodobenzene), and cyclopentadiene (to give benzonorbornadiene). This technique avoids the isolation and handling of the hazardous benzenediazonium-2-carboxylates and is a convenient preparative source of arynes.

(1) Part of this work was reported in a preliminary communication, L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963).

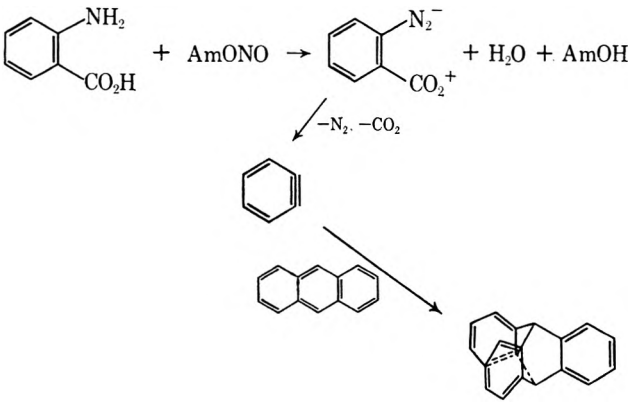
(2) (a) Abstracted in part from the Ph.D. Thesis of F. M. Logullo, Case Institute of Technology, June 1965.

(3) (a) E. LeGoff, *J. Amer. Chem. Soc.*, **84**, 3786 (1962); (b) L. Horner and H. Bruggerman, *Ann.*, **635**, 22 (1960); (c) J. A. Kampmeier and E. Hoffmeister, *J. Amer. Chem. Soc.*, **84**, 3787 (1962); (d) M. Stiles and R. G. Miller, *ibid.* **82**, 3802 (1960); (e) R. S. Berry, G. N. Spokes, and M. Stiles, *ibid.*, **82**, 5240 (1960); **84**, 3750 (1962); (f) M. Stiles, U. Burckhardt, and A. Haag, *J. Org. Chem.*, **27**, 4715 (1962); (g) G. Wittig and H. F. Ebel, *Angew. Chem.*, **72**, 564 (1960); *Ann.*, **650**, 20 (1961); (h) G. Wittig and R. W. Hoffmann, *Angew. Chem.*, **73**, 435 (1961); (i) E. McNelis, *J. Org. Chem.*, **28**, 3188 (1963), and references contained therein; (j) F. M. Beringer and S. J. Huang, *ibid.*, **29**, 445 (1964); (k) L. Verbit, J. S. Levy, H. Rabitz, and W. Kwalwasser, *Tetrahedron Lett.*, 1053 (1966); (l) C. D. Campbell and C. W. Rees, *Proc. Chem. Soc.*, 296 (1964); *Chem. Commun.*, 192 (1965); (m) E. K. Fields and S. Meyerson, *ibid.*, 474 (1965); 275 (1966); (n) M. P. Cava, M. J. Mitchell, D. C. DeJongh, and R. Y. Van Fossen, *Tetrahedron Lett.*, 2947 (1966); (o) R. F. C. Brown and R. K. Solly, *Chem. Ind.* (London), **181**, 1462 (1965); *Australian J. Chem.*, **19**, 1045 (1966).

(4) J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).

(5) A related example is diazotization of an alcoholic solution of sulfanilic acid with nitrous fumes to give the "internal" diazonium salt, benzenediazonium-4-sulfonate. R. Schmitt, *Ann.*, **112**, 118 (1859); **120**, 144 (1861).

(6) For an excellent recent review of benzyne chemistry, see G. Wittig, *Angew. Chem. Intern. Ed. Engl.*, **4**, 731 (1965); *Angew. Chem.*, **77**, 752 (1965).



Reaction can be effected by addition of a solution of the anthranilic acid to a stirred, *refluxing solution*[7] of alkyl nitrite and benzyne acceptor. Gas evolution occurs immediately and ceases within a few minutes after addition is complete. If all of the reactants are mixed at once, a vigorous reaction ensues and the yields of desired products are greatly diminished, *e.g.*, triptycene 9–16% (glpc). This is probably in part a result of reactions of benzyne and benzenediazonium-2-carboxylate with each other[8a] and with unreacted anthranilic acid to give acridone,[8b] N-phenylanthranilic acid, and other products.[8a] If reaction is attempted at room temperature or below, the diazotization step slowly occurs to give a precipitate of benzenediazonium-2-carboxylate[7,9] which decomposes only very slowly. To avoid buildup and inadvertent isolation of this hazardous intermediate, reactions should be conducted at temperatures $>$ *ca.* 40°. When higher boiling solvents are used (acetonitrile, 2-butanone, dioxane), it is *sometimes* advantageous to add the alkyl nitrite concurrently with the solution of anthranilic acid to minimize the thermally induced decomposition of alkyl nitrite.

In the synthesis of triptycene, it was found that unreacted anthracene is conveniently removed from the reaction mixture by formation of its Diels–Alder adduct with maleic anhydride[10] in diethyl carbitol (diethylene glycol diethyl ether) or diglyme (diethylene glycol dimethyl ether) followed by treatment with aqueous methanolic potassium hydroxide to precipitate, almost quantitatively, triptycene free of anthracene.

The results from the aprotic diazotization of anthranilic acid and substituted derivatives in the presence of anthracene to form triptycenes are listed in Table I. Since the yield of triptycene obtained is a measure of available benzyne, the reaction conditions were evaluated by relating the yields of triptycene. Best yields of triptycene were obtained by the rapid (*ca.* 0.5 hr) addition of a diglyme[11] or diethylcarbitol solution of anthranilic acid to a stirred refluxing mixture of anthracene and isoamyl or *n*-butyl nitrite in ethylene chloride.[12] The water-soluble high-boiling ethers were used because of their utility in the work-up procedure. Ethylene chloride was found to be the reaction medium of choice, since (a) its higher boiling point[12] decreases the reaction time necessary for diazotization to occur; (b) it facilitates the clean decomposition of benzenediazonium-2-carboxylate;[2] and (c) it is an exceedingly good solvent for anthracene and triptycene. The use of a molar excess of anthracene gave a 17% increase in yield (70 *vs.* 60%), and the use of a molar excess of anthranilic

TABLE I

APROTIC DIAZOTIZATION OF SUBSTITUTED ANTHRANILIC ACIDS IN THE PRESENCE OF ANTHRACENE[a]

Run	Anthranilic acid	Solvent system[b]	Yield of substituted triptycene, %
1	...	D2M[c]/ClC_2H_4Cl	60, 70,[d] 80[e]
2	...	D2M[c]/CH_2Cl_2	60
3	...	D2M/$CHCl_3$	55
4	...	CH_3CN[f]	52
5	...	Me_2CO	37,[g] 33[h]
6	...	MeCOEt[f]	53[i]
7	5-methyl-	D2M/$CHCl_3$	49[d,j]
8	5-methyl-	CH_3CN[f]	49[d]
9	3-methyl-	D2M/$CHCl_3$	58[d,j]
10	4:5-benzo-	D2M–THF[c]/CH_2Cl_2	10
11	4:5-benzo-	D2M/THF/$CHCl_3$	47[d]
12	5-chloro-	DEC/ClC_2H_4Cl	39[j]
13	5-chloro-	D2M/CH_3CN	42, 53[d]
14	5-chloro-	CH_3CN[f]	20[i]
15	5-chloro-	D2M/$CHCl_3$	39, 46[d]
16	3-chloro-	D2M/$CHCl_3$	11[d]
17	3-chloro-	Dioxane	18[d]
18	4-chloro-	D2M/CH_2Cl_2	19[j]
19	4-chloro-	D2M/$CHCl_3$	33
20	4-chloro-	D2M/ClC_2H_4Cl	55
21	5-bromo-	D2M/$CHCl_3$	54[d,j]
22	5-bromo-	CH_3CN[f]	75[d,j]
23	5-iodo-	D2M/$CHCl_3$	64[d]
24	5-iodo-	MeCOEt[f]	38[d]
25	3-nitro-[k]	D2M/CH_3CN	0
26	4-nitro-[k]	D2M/CH_3CN	46
27	5-nitro-[k]	D2M/CH_3CN	44
28	5-nitro-[k]	D2M/CH_2Cl_2	24
29	5-nitro-[k]	D2M/ClC_2H_4Cl	58
30	6-nitro-[k]	D2M/ClC_2H_4Cl	38

[a] In general, reaction was effected by the addition of a solution of the anthranilic acid to a stirred, refluxing mixture of anthracene (1 equiv), isoamyl or *n*-butyl nitrite (excess), and solvent; in lower boiling reaction solvents, *e.g.*, CH_2Cl_2, maximum yields were obtained only when anthranilic acid solution was added slowly (*ca.* 3–4 hr). [b] First solvent refers to that used to form the anthranilic acid solution; the second, the reaction medium. [c] D2M = diglyme; DEC = diethyl carbitol; THF = tetrahydrofuran. [d] 2 equiv of anthracene used. [e] 0.5 equiv of anthracene. [f] Solution of the alkyl nitrite added concurrently with the anthranilic acid. [g] *t*-AmONO used. [h] *t*-BuONO used. [i] *Ca.* 1.5 equiv of anthracene. [j] New compound; for melting point and analytical data, see Table II. [k] Data from D. F. Lindow.

(7) Diazotization of anthranilic acid in tetrahydrofuran (and other solvents) with isoamyl nitrite at ambient temperatures or lower slowly gives benzenediazonium-2-carboxylate *via* the brick-red precursor, 2,2′-dicarboxydiazoaminobenzene. In the presence of catalytic amounts of trichloro- or trifluoroacetic acid, almost quantitative yields of benzenediazonium-2-carboxylate are obtained in about 1 hr.[2]

(8) (a) T. Miwa, M. Kato, and T. Tamano, *Tetrahedron Lett.*, 2743 (1968); (b) S. F. Dyke, A. R. Marshall, and J. P. Watson, *Tetrahedron*, **22**, 2515 (1966).

(9) *Cf.* T. F. Mich, E. J. Nienhouse, T. E. Farina, and J. J. Tufariello, *J. Chem. Ed.*, **45**, 272 (1968).

(10) G. Wittig, *Org. Syn.*, **39**, 75 (1959).

(11) (a) Other solvents may be used for anthranilic acid in the aprotic diazotization reaction. The necessary criteria are stability toward amyl nitrite, a poor benzyne trap, and, obviously, a good solvent. The following solvents (with solubility of anthranilic acid in grams/100 ml at 25–28°)[11b] were found to be useful: acetonitrile (12), acetone (69), dioxane (62), ethyl acetate (28), glyme (42), methyl acetate (31), methyl ethyl ketone (60), tetrahydrofuran (60), diglyme (40), and diethyl carbitol (40). (b) Determined by L. R. Rice and D. M. Smith.

(12) When methylene chloride was used as the reaction solvent, addition of the anthranilic acid solution had to be extended to *ca.* 4 hr to obtain comparable yields of triptycene. The yield dropped to 44% when the time of addition was decreased to 1 hr. This is probably a result of the side reactions of unreacted anthranilic acid with benzyne or benzenediazonium-2-carboxylate.[8]

acid gave a 33% increase in yield (to 80%). Thus, for maximum yields, an excess (*ca.* 1 equiv) of either benzyne acceptor or precursor is suggested. The choice is dictated by the availability of the reactants and economics. Lower yields of triptycene (run 5) were obtained with *t*-alkyl nitrites, probably as a result of their decreased stability.

The yields of substituted triptycenes formed from substituted anthranilic acids and anthracene vary from 11 to 75%[13] (runs 7–30, Table I). It was found that the diglyme–methylene chloride solvent system did not work well with several substituted anthranilic acids, apparently due to the low boiling point of the mixture; *i.e.*, the diazotization of the anthranilic acid is slow and/or the rate of decomposition of the diazonium carboxylate formed *in situ* decreases, and apparently side reactions predominate. However, higher yields were obtained in the solvent system diglyme–chloroform (or in the system diglyme–ethylene chloride) than in the system diglyme–methylene chloride (*cf.* runs 11 and 19 *vs.* 10 and 18), which also obviated the necessity of concurrent addition of alkyl nitrite. Apparently, with these solvents, the rates of diazotization and decomposition of the diazoniumcarboxylate are favorably increased, while alkyl nitrite decomposition is still relatively slow.

Slow addition of a solution of 0.109 mol of anthranilic acid to a stirred, refluxing solution of tetracyclone (0.100 mol) and isoamyl nitrite in methylene chloride[15] discharged the purple color of the solution and gave, upon work-up, a 95% yield of 1,2,3,4-tetraphenylnaphthalene. Assuming that the starting materials were pure, the efficiency of the formation and capture of benzyne from anthranilic acid in this instance is at least 92%.

Aprotic diazotization of anthranilic acid in the presence of excess furan gave a 65% yield of the Diels–Alder adduct, 1,4-dihydro-1,4-epoxynaphthalene. In a similar manner, benzyne adducts of 2-methyl- and 2,5-dimethylfuran are also easily prepared.

The preparation of benzonorbornadiene by aprotic diazotization of anthranilic acid in the presence of cyclopentadiene was beset by concurrent tar formation, and initially low yields (12–13%) were obtained. In addition, there was discrepancy between glpc yields (29–68%) obtained from small-scale runs and those obtained by isolation upon preparative scale-up. In part, this may have been a result of concurrent dimerization of cyclopentadiene during the longer reaction times or destruction of product during work-up. However, reasonably good yields were obtained by slightly modifying the reaction conditions. Thus, instead of conducting the reaction in the usual way, an acetone or dioxane solution of anthranilic acid and cyclopentadiene was added to a refluxing solution of isoamyl nitrite and methylene chloride. The product was easily separated from the accompanying tar by extraction with petroleum ether or steam distillation. Pure benzonorbornadiene was obtained in 50–60% yield.[16] Larger scale runs (> 0.5 mol) gave lower yields. Attempts to overcome this shortcoming were unsuccessful.

The reaction of arynes (from benzenediazonium-2-carboxylate) with iodine to give *o*-diiodoarenes[17] can also be accomplished *via* aprotic diazotization. For example, addition of a dioxane solution of anthranilic acid to a refluxing mixture of iodine and isoamyl nitrite in chloroform conveniently gave *o*-diiodobenzene in *ca.* 50% yield.

The results described are indicative of the preparative usefulness of generating arynes from benzenediazonium-2-carboxylates prepared and decomposed *in situ*. Since the preliminary report,[1] the technique of aprotic diazotization of anthranilic acids has been widely utilized to safely extend the range of benzyne chemistry.[8b,9,18]

Experimental Section

Triptycene.—To a mechanically stirred, mildly refluxing solution of anthracene (75 g, 0.42 mol), *n*-butyl nitrite (48 g, 0.46 mol) or isoamyl nitrite (59 g, 0.46 mol), and ethylene chloride (1.2 l.) contained in a 3-l., three-necked flask, a filtered solution of anthranilic acid (60 g, 0.44 mol) in diethylcarbitol (300 ml) was added dropwise over a period of about 0.5 hr. When the addition was completed, the mixture was refluxed for 20 min and the flask was refitted for distillation. Distillation was continued until a head temperature of 150–160° was reached. The mixture was cooled somewhat, maleic anhydride (30 g) was added, and the mixture was then brought to reflux for 2–3 min. The heating mantle was then replaced by an ice bath, and a solution of methanol (1 l.), water (500 ml), and potassium hydroxide (120 g) was added to the almost black, stirred reaction mixture. The cold (0–10°) mixture was then suction filtered and the crude, tan product was washed with 80% methanol–water (4:1 v/v) until the washings were colorless (200–400 ml). The almost-white to light tan triptycene, after drying at 100°, weighed 60.9–64.2 g (57–60%), mp 251–254°.

The triptycene can be further purified by dissolving 25 g in 2-butanone (250 ml) (slight warming), treating with charcoal (2-3 g), filtering, concentrating to 175 ml, adding methanol (200 ml), and cooling in ice. The almost-white to white triptycene was suction filtered and washed with cold methanol (70 ml). The first crop weighed 19.4–19.7 g, mp 254–255.5°. Concentrating the combined filtrates to 120 ml gave a second crop of off-white triptycene, 3.2–3.7 g, mp 253.5–255.0°. Addition of two volumes of water to the filtrates gave a third crop of less pure material, 1.3–1.6 g, mp 248–253.5°. Total recovery was about 97%. The triptycene obtained was glpc pure (20% silicon grease on 60–80 mesh Chromosorb P, 180°); however, a somewhat whiter product could be obtained by recrystallizing from methylcyclohexane (19 ml/g).

Known triptycenes reported in Table I were identified by melting point and nmr comparison to literature data. Data for new compounds are listed in Table II.

1,2,3,4-Tetraphenylnaphthalene.—A solution of anthranilic acid (16.0 g, 0.117 mol) in tetrahydrofuran (85 ml) was added dropwise to a stirred, refluxing solution of tetraphenylcyclo-

(13) With the exception of anthranilic acid, no attempt was made to find the optimum conditions for aprotic diazotization. However, the data in Table I are typical and indicate that some anthranilic acids[14] are better aryne precursors than others and that, with a given anthranilic acid, better yields would be expected in ethylene chloride or acetonitrile.

(14) The low yields of triptycenes from 3-chloro- and 3-nitroanthranilic acids *via* aprotic diazotization and from the corresponding isolated diazoniumcarboxylates will be discussed elsewhere.

(15) The reaction (*i.e.*, addition time) can be shortened to *ca.* 0.5 hr when ethylene chloride is used.

(16) *Cf.* ref 9.

(17) L. Friedman and F. M. Logullo, *Angew. Chem.*, **77**, 217 (1965).

(18) For example: (a) R. K. Hill and R. M. Carlson, *Tetrahedron Lett.*, 1157 (1964); (b) W. Ried and M. Silion, *Angew. Chem. Intern. Ed. Engl.*, **3**, 67 (1964); (c) G. A. Reynolds, *J. Org. Chem.*, **29**, 3733 (1964); (d) F. Minisci and A. Quilico, *Chim. Ind.* (Milan), **46**, 428 (1964); (e) H. Gilman, S. G. Cottis, and W. H. Atwell, *J. Amer. Chem. Soc.*, **86**, 1596, 5584 (1964); (f) C. Paget and A. Burger, *J. Org. Chem.*, **30**, 1329 (1965); (g) E. C. Kornfeld, P. Barney, J. Blankley, and W. Faul, *J. Med. Chem.*, **8**, 342 (1965); (h) C. F. Wilcox, Jr., and F. D. Roberts, *J. Org. Chem.*, **30**, 1959 (1965); (i) L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, **43**, 1599 (1965); (j) E. Wolthuis and W. Cody, *Angew. Chem. Intern. Ed. Engl.*, **6**, 555 (1967); (k) T. D. Petrova, T. I. Savchenko, G. G. Yacobson, *Zh. Obshch. Khim.*, **37**, 1170 (1967) (Engl. Trans., p 1110); (l) B. H. Klanderman and J. W. H. Faber, *J. Polym. Sci., Part A-1*, **6**, 2955 (1968); (m) H. Heaney and B. A. Marples, *J. Chem. Educ.*, **45**, 801 (1968); (n) J. P. N. Brewer, H. Heaney, and T. J. Ward, *J. Chem. Soc.*, C, 355 (1969).

TABLE II

NEW TRIPTYCENES. MELTING POINT AND ELEMENTAL ANALYTICAL DATA

Substituent	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found,[a] % C	Found,[a] % H
1-Methyl-	190.5–192.5	$C_{21}H_{16}$	93.99	6.01	94.04	6.06
2-Methyl-	165–166	$C_{21}H_{16}$	93.99	6.01	94.01	6.02
2-Chloro-	168–169	$C_{20}H_{13}Cl$	83.18	4.54	83.32	4.59
2-Bromo-	167.5–169	$C_{20}H_{13}Br$	72.08	3.93	72.12	3.94
2-Iodo-	183–185	$C_{20}H_{13}I$	63.18	3.45	63.01	3.46

[a] Analyses by Galbraith Laboratories, Knoxville, Tenn.

pentadienone (38.4 g, 0.100 mol) and isoamyl nitrite (16.5 g, 0.13 mol) in methylene chloride (300 ml). After 3.5 hr, the purple reaction mixture turned a light orange and addition was stopped. Evaporation of the remaining tetrahydrofuran solution left 1.15 g (0.008 mol) of recovered anthranilic acid.

The reaction mixture was filtered from insolubles and evaporated under reduced pressure to *ca.* 100 ml. Addition of methanol (500 ml) and chilling in ice gave 39.26 g (95%) of 1,2,3,4-tetraphenylnaphthalene, mp 197–198°, remelt mp 205–205.5° (lit.[19] remelt mp 203–204°).

1,4-Dihydro-1,4-epoxynaphthalene.—A solution of anthranilic acid (41.10 g, 0.30 mol) and furan (50 ml, 0.78 mol) in dioxane (100 ml) was added over 4 hr to a stirred refluxing solution of furan (10 ml) and isoamyl nitrite (47 ml, 0.35 mol) in ethylene chloride (250 ml).

Solvents were removed under reduced pressure, and the dark residue was made basic with aqueous potassium hydroxide and extracted with petroleum ether (two 500-ml portions). The extracts were washed twice with water, treated with activated carbon, and dried, and the solvent was removed under reduced pressure to give an oil which partially crystallized on cooling. The oxide was triturated with a little cold petroleum ether and collected on a Büchner funnel. The yield of crude product, mp 48°, was 27.8 g. Recrystallization from petroleum ether gave material of mp 55.5–56° (lit.[20] mp 53–54.5° and 56°).

***o*-Diiodobenzene.**—A solution of anthranilic acid (60 g, 0.44 mol) in dioxane (300 ml) was added over 2 hr to a stirred, refluxing mixture of iodine (107 g, 0.42 mol) and isoamyl nitrite (83 ml, 0.60 mol) in chloroform (1 l.). The solution was then washed successively with 5% aqueous sodium bisulfite, water, 5% aqueous potassium hydroxide, and water, and dried over anhydrous calcium chloride. Solvents were removed by distillation and the residue was distilled under reduced pressure to give *o*-diiodobenzene, bp 132.7° (8–9 mm), 73.6 g (53%). A dark residue, 20 g, remained after distillation. Iodine was removed from the product by washing with aqueous sodium bisulfite. The *o*-diiodobenzene was crystallized from petroleum ether to give white crystals, mp 24° (lit.[21] mp 27°), glpc pure.

Benzonorbornadiene.[22]—A solution of anthranilic acid (68.5 g, 0.5 mol) and freshly distilled cyclopentadiene (33.0 g, 41.0 ml, 0.50 mol) in 300 ml of acetone was added over a period of 1.25–1.50 hr to a refluxing, mechanically stirred solution of isoamyl nitrite (65 g, 74 ml, 0.55 mol) in 700 ml of methylene chloride contained in a 2-l. three-necked flask. After the addition was completed, the dark reaction mixture was refluxed for 0.5 hr (glpc yield *ca.* 57–68%). It was then cooled and made basic with 100 ml of 10% aqueous KOH, and the low-boiling solvents were removed. The residual black oil was steam distilled, and about 300 ml of distillate was collected. The organic layer was separated and the aqueous layer was extracted with two 100-ml portions of ether. The combined material was dried over Na_2SO_4 and ether was removed. The residual yellow oil was fractionated (18-in. packed column) to give a forerun of isoamyl alcohol and dicyclopentadiene and then 35–42 g of benzonorbornadiene (50–60%), bp 78–79° (20 mm), $n^{25}D$ 1.5600. The pot residue (*ca.* 5 ml) is mainly isoamyl phenyl ether.

The yield could not be improved by changing the ratio of reactants or modifying the reaction conditions. On a 2-mol scale, the yield of isolated material drops to 28%.

Registry No.—Triptycene, 477-75-8.

(19) H. Herwig, W. Metlesics, and H. Zeiss, *J. Amer. Chem. Soc.*, **81**, 6203 (1959).

(20) (a) G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956); (b) E. Wolthuis, *J. Org. Chem.*, **26**, 2215 (1961).

(21) M. E. G. Korner and V. Wender, *Gazz. Chim. Ital.*, **17**, 491 (1887).

(22) Developed by Mr. D. M. Smith.

Isolable Stereoisomeric Methylenedihydroanthracenes. Conformationally Isomeric 9-(Dichloromethylene)-10-ethyl-10-methyl-1,8-dichloro-9,10-dihydroanthracenes[1]

DAVID Y. CURTIN AND Z. M. HOLUBEC[2]

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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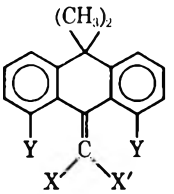
Two stereoisomeric 9-(dichloromethylene)-10-ethyl-10-methyl-1,8-dichloro-9,10-dihydroanthracenes (I) have been prepared and separated and found to be stable at room temperature owing to slow boat–boat inversion of the center ring. The isomers are interconverted at temperatures above 150°. The rates of interconversion (to an equilibrium mixture containing 12% *e*-ethyl I) of the two isomers in *sym*-tetrachloroethane have been found to be first order and with $k_1 + k_{-1} = 1.5 \times 10^{-5}$ sec^{-1} at 157°, $E_a = 42.8 \pm 0.6$ kcal/mol, and $\Delta S^{\ddagger} = 18 \pm 8$ eu. 9-(Bromomethylene)-10-ethyl-10-methyl-1,8-dichloro-9,10-dihydroanthracene (V) was prepared and preliminary work suggests that it can also be separated into *e*-ethyl and *a*-ethyl isomers. Syntheses and characterization are described for the three compounds 9-methylene-10,10-dimethyl-1,8-dichloro-9,10-dihydroanthracene (II), 9-(dichloromethylene)-10,10-dimethyl-9,10-dihydroanthracene (III), and 9-(bromomethylene)-10,10-dimethyl-1,8-dichloro-9,10-dihydroanthracene (IV), whose nmr temperature dependence has recently been reported.[3]

A number of disubstituted 9-methylene-10,10-dimethyl-9,10-dihydroanthracenes, A and B, have been

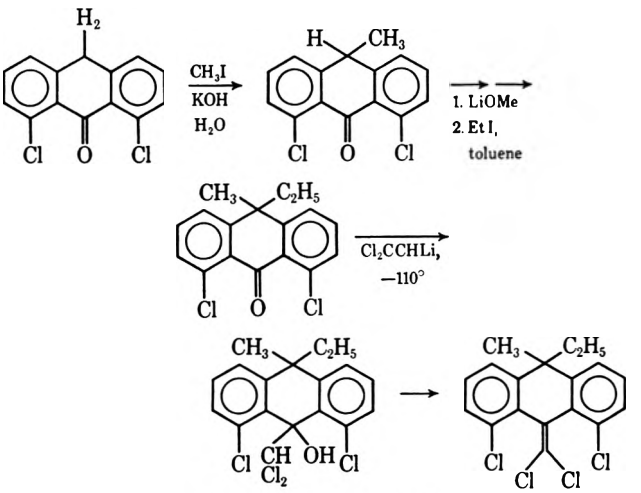


A, X,X′ = H
B, Y = H

shown to exist with the center ring in a boat conformation with a sufficient barrier for interconversion from one boat form to the other to permit observation of the inversion process by the use of nmr spectroscopy.[3,4] Inversion rate constants for all of these disubstituted compounds were greater than 1 sec^{-1}.

It was hoped that with an appropriate change of substituents it might be possible to synthesize molecules with barriers to ring inversion sufficiently large to permit isolation of stereoisomers. The tetrachloro compounds *a*-ethyl- and *e*-ethyl-I (Figure 1) have now been prepared and found to be separable and *conformationally* stable at room temperature.[5] Their synthesis, identification, and interconversion above 150° (Table I) are the subjects of this paper.

The synthesis of a mixture of *e*-ethyl-I and *a*-ethyl-I from 1,8-dichloroanthrone is outlined below. The *a*-ethyl isomer could be separated by crystallization. The *e*-ethyl isomer, however, was much more difficult



a-ethyl–I + *e*-ethyl–I
(87%) (13%)

to separate and was obtained (only after many unsuccessful attempts) by chromatography on alumina impregnated with silver nitrate. Configurational assignments to *a*-ethyl- and *e*-ethyl-I are based on the nmr spectra. The *equatorial methyl group* in the isomer assigned the *a*-ethyl-*e*-methyl configuration is 0.36 ppm downfield from the *axial methyl group* in the *e*-ethyl isomer; similarly, the *equatorial methylene group* in the *e*-ethyl isomer is 0.73 ppm downfield from the *axial methylene group* of the *a*-ethyl isomer. The axial and equatorial methyl proton positions in the 9,9-dimethyl-10-methylene-dihydroanthracenes A and B studied earlier were found to differ by 0.27–0.47 ppm, the lower field methyl group being assigned the protons in the equatorial position and the difference being ascribed primarily to the ring-current effect of the adjacent aromatic rings.[3,4,6]

The stereoisomers *a*-ethyl- and *e*-ethyl-I were found to be stable to prolonged treatment with refluxing

(1) Taken from the Ph.D. Thesis of Z. M. Holubec, University of Illinois, 1968, available from University Microfilms, Ann Arbor, Mich. We are very much indebted to the Army Research Office, Durham, for partial support of this work.

(2) National Institutes of Health Predoctoral Fellow, 1966–1968

(3) Z. M. Holubec and J. Jonas, *J. Amer. Chem. Soc.*, **90**, 5986 (1968).

(4) D. Y. Curtin, C. G. Carlson, and C. G. McCarty, *Can. J. Chem.*, **42**, 565 (1964).

(5) An alkyl group more nearly "axial" is here designated "*a*," one more nearly equatorial is designated "*e*." As nomenclature of such compounds becomes standardized, it may be preferable to take advantage of the sequence rules [see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962]. It will be seen that these compounds can be so named by extending the method applied to olefins [J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968)]. Thus, a reference plane through the 9 and 10 carbon atoms of the middle ring and parallel to the remaining four carbon atoms of that ring is employed. Then that isomer with the higher priority group (in this case, the ethyl group) on the same side of the plane as the methylene group at the opposite side of the ring is assigned a designation corresponding to the "Z" employed for olefins. The other isomer is of course analogous to that designated "E" in naming olefins. In the thesis of Z. M. H.[1] we have extended the Z-E nomenclature in this way. However, the editors of *Chemical Abstracts* have requested that these letters be reserved for the assignment of configurations to olefins only.

(6) A calculation of the expected effect of the ring current[7] by the method of Johnson and Bovey[7] gave a value of 0.6-ppm proton resonance for the difference in chemical shift between the axial and equatorial methyl proton resonance. It has been suggested,[8] however, that the method overestimates the magnitude of the ring-current effect.

(7) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(8) K. G. Kidd, G. Kotowycz, and T. Schaeffer, *Can. J. Chem.*, **45**, 2155 (1967).

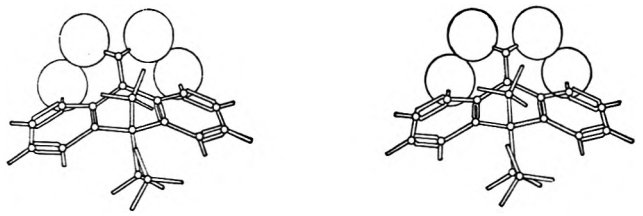


Figure 1.—Stereo view of 9-(dichloromethylene)-10-*e*-ethyl-10-*a*-methyl-1,8-dichloro-9,10-dihydroanthracene (*e*-ethyl-I). The *a*-ethyl isomer has the ethyl and methyl groups interchanged.

methanol. At temperatures above 150° it was found that either compound rearranges slowly to an equilibrium mixture which contained approximately 88% *a*-ethyl and 12% *e*-ethyl isomer. Rates of isomerization were conveniently followed in *sym*-tetrachloroethane by measuring the relative intensities of the 9-methyl absorptions of the two isomers. The data gave reasonable linear plots when a first-order approach to an equilibrium mixture was assumed. The value of the equilibrium constant, 7.5, did not vary significantly over the temperature range studied. Addition of hydrogen chloride or dimethylaniline (11%) gave an increase in

TABLE I

RATES OF INTERCONVERSION OF STEREOISOMERS *e*-ETHYL- AND *a*-ETHYL-I IN *sym*-TETRACHLOROETHANE AT 157–178°

Starting material	Concn, %	Temp, °C	Added acid or base	$k_{obsd} = k_1 + k_{-1}$ 10^5 sec^{-1} and standard deviation
e-Ethyl-I[a]	13.9	157.0	None	1.45 ± 0.01
	21	158		1.64 ± 0.01
e-Ethyl-I[a]	13.9	171.5	None	7.89 ± 0.09
e-Ethyl-I[a]	13.6	171.5	HCl[b]	8.98 ± 0.14
e-Ethyl-I[a]	15	171.5	Dimethyl-aniline[c]	8.96 ± 0.10
e-Ethyl-I[a]	13.9	178.5	None	16.54 ± 0.14
	16.1	178.5		15.90 ± 0.15
a-Ethyl-I	33	178.5	None	16.61 ± 0.86

[a] Although predominately *e*-ethyl-I the starting material contained 29–36% isomer *a*-ethyl-I. [b] Solution saturated with HCl gas. [c] 11% dimethylaniline.

the observed rate constant of only about 14%; the effect of added acid and base is clearly so small that it can be concluded that the isomerization under conditions when they have not been deliberately added is a reaction of neutral *e*- or *a*-ethyl-I, and is not being affected by traces of adventitious acid or base.

The detailed geometry of the transition state for inversion cannot be described at present, but it is of interest to compare the activation parameters with those for the unimolecular *cis–trans* isomerization of olefins. These data[9–12] are presented in Table II. A question which arises immediately is to what extent does a rotation around the axis of the carbon–carbon double bond occur when the $Cl_2C=$ group passes the two aromatic chlorine atoms in the course of the *e*-ethyl to *a*-ethyl inversion? Such a rotation should lead to a loss of some

(9) J. E. Douglas, B. S. Rabinovitch, and F. S. Looney, *J. Chem. Phys.*, **23**, 315 (1955).

(10) B. S. Ravinovitch and K. W. Michel, *J. Amer. Chem. Soc.*, **81**, 5065 (1959).

(11) (a) T. W. J. Taylor and A. R. Murray, *J. Chem. Soc.*, 2078 (1938); (b) G. B. Kistiakowsky and W. R. Smith, *J. Amer. Chem. Soc.*, **56**, 638 (1934).

(12) M. Calvin and H. W. Alter, *J. Chem. Phys.*, **19**, 768 (1951).

TABLE II

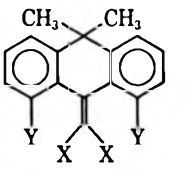
ACTIVATION PARAMETERS FOR THE THERMAL INTERCONVERSION OF *e*- ETHYL- AND *a*-ETHYL-I AND FOR *cis–trans* ISOMERIZATION OF OLEFINS

Compd	State	Temp, °C	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu
e- and *a*-ethyl-I[a]	Liquid	157–179	42.8 ±0.6	18 ±8
CHD=CHD[b]	Vapor	504–550	61	−3
$CH_3CH=CHCH_3$[c]	Vapor	461–502	62	0
$C_6H_5CH=CHC_6H_5$[d]	Liquid	214–223	37	−13
		280–341	43	−2
$C_6H_5CCl=CHC_6H_5$[e]	Liquid	226–246	37	−8
$C_6H_5CCl=CClC_6H_5$[e]	Liquid	175–200	34	−10
p-$CH_3OC_6H_4CH=CHC_6H_5$[f]	Liquid	272–299	36	−14
p-$NO_2C_6H_4CH=CHC_6H_5$[f]	Liquid	172–210	34	−14

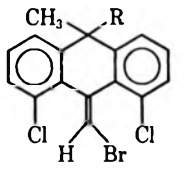
[a] Present work. The values and standard deviations reported were obtained from a least-squares plot of log k_{obsd} *vs.* $1/T$. [b] See ref 9. [c] See ref 10. [d] See ref 11. [e] See ref 11a. [f] See ref 12.

or all of the π-bond energy of the exocyclic double bond, and, if the $Cl_2C=$ grouping became nearly perpendicular to its original position, the activation energy for the *e*-ethyl to *a*-ethyl inversion might be comparable in magnitude to that for the uncatalyzed *cis–trans* isomerization of olefins. The data in Table II suggest that the orders of magnitude of the rate and activation parameters are not different from what might have been expected if the ring inversion involved a good deal of twist of the exocyclic $Cl_2C=$. A mechanism somewhat analogous to the *cis–trans* isomerization of olefins appears then to be favored by the evidence.

A further comparison which is of great interest is that of the ring inversion rate of *e*- and *a*-ethyl-I with the molecules II and III, whose rates of ring inversion at 41° are given below.[4] Extrapolation of the inversion



II, X = H, Y = Cl; $k^{41°} = 83$ sec^{-1}
III, X = Cl, Y = H; $k^{41°} = 6.9$ sec^{-1}



IV, R = CH_3
V, R = C_2H_5

rates of *e*-ethyl- and *a*-ethyl-I to 41° gives a value of approximately 10^{-13}. This means that replacement of a pair of chlorine atoms in I by hydrogens increases the inversion rate by a factor of 10^{13}–10^{14}.

In the course of this work, the two bromomethylene compounds IV and V were synthesized. That the inversion rates of these compounds are much slower than those of II and III was shown by the fact that their nmr spectra did not change appreciably at 180°. *A preliminary experiment suggested that the methyl ethyl compound V can be separated into e-ethyl and a-ethyl isomers, and further work along these lines is being continued.* Since a study of the temperature dependence of the nmr spectra has been reported[4] but not the syntheses and characterization of II and III, they are described in the Experimental Section.

Experimental Section

Melting points were obtained with a Thomas–Hoover capillary melting point apparatus. Infrared spectra (10% solutions in carbon tetrachloride unless otherwise noted) were obtained with

a Perkin-Elmer Model 137 Infracord or by Mr. D. Johnson, Mr. G. Swafford, and Mr. R. Thrift and their associates with a Perkin-Elmer Model 521 spectrophotometer. A number of nmr spectra (10–20% solutions in carbon tetrachloride unless otherwise indicated) were measured by Mr. O. Norton, Mr. D. Johnson, Mr. G. Swafford, and Mr. R. Thrift and their associates with Varian Associates Model A-60, A-60A, or 56/60 instruments. Ultraviolet spectra were obtained with a Bausch and Lomb Spectronic 505 spectrophotometer. Microanalyses were carried out by Mr. J. Nemeth and his associates. Molecular weights were determined from the parent ion peak of mass spectra obtained by Mr. J. Wrona with an Atlas CH4 instrument.

1,8-Dichloroanthrone [mp 167.5–168.5° (lit.[12] mp 167°); ir 1675 cm^{-1}; uv λ_{max} 273 mμ (ε 14,800); nmr τ 2.67 (broad), 5.85 (broadened)] was prepared by reduction of 1,8-dichloroanthraquinone with aluminum in sulfuric acid.[13]

10-Methyl-1,8-dichloroanthrone, mp 204–205.5° (lit.[14] mp 204°) was best prepared by a modification of the mono-C-alkylation of anthrone,[15] which gave the desired product in 72% yield (50% after recrystallization from glacial acetic acid). The ir spectrum showed carbonyl absorption at 1685 cm^{-1}. The nmr spectrum ($CDCl_3$) showed aromatic proton absorption at τ 2.70, the methine proton at τ 5.84, and the methyl doublet at τ 8.53. The uv spectrum (95% in ethanol) showed a maximum at 275 mμ (ε 14,250).

10,10-Dimethyl-1,8-dichloroanthrone.—1,8-Dichloroanthrone (20 g, 0.076 mol) was alkylated by a procedure employed previously for anthrone[16] by treatment of its lithium salt [from reaction of the ketone with lithium methoxide prepared from 1.16 g (0.167 g-atom) of lithium and 60 ml of reagent grade methanol in dried glassware under an argon atmosphere and distillation of the solvent at 40° and 13 mm] with 110 g (0.76 mol) of methyl iodide and 8 drops of *t*-butyl alcohol in a combustion tube at 150° for 24 hr. After cooling, the reaction mixture was extracted with ether and water and the ether layer was repeatedly extracted with Claisen's alkali, washed with water, and dried, and cyclohexane was added to make the solvent composition 3:2 cyclohexane–ether. The solution was passed through a column of 150 g of neutral Merck alumina, and the product was eluted with cyclohexane–ether (3:2) to give 11.0 g (50%) of yellow crystals, mp 161–163.5°. Recrystallization from cyclohexane gave 8.8 g, mp 163–164°. Sublimation and a further crystallization gave mp 164–164.5°. The nmr spectrum showed a complex multiplet at τ 2.65 and a singlet at τ 8.32. The uv spectrum (95% ethanol) showed λ_{max} 277 mμ (ε 14,000).

Anal. Calcd for $C_{16}H_{12}Cl_2O$: C, 66.0; H, 4.2; Cl, 24.4. Found: C, 66.2; H, 4.2; Cl, 24.6.

10-Ethyl-10-methyl-1,8-dichloroanthrone was prepared by ethylation of the lithium salt of 10-methyl-1,8-dichloroanthrone (from lithium methoxide and 15 g of the anthrone, as in the preceding reaction) with 126 g of ethyl iodide and 0.3 ml of *t*-butyl alcohol in a sealed tube at 150° for 30 hr. The work-up described for the dimethyl compound above was employed, except that carbon tetrachloride was employed initially for the chromatography on 220 g of silica gel. Elution with carbon tetrachloride gave 2.2 g (13% yield) of O-alkylated product, mp 112–114°. Further elution with benzene–carbon tetrachloride (3:1) gave 8.0 g (49%) of 10-ethyl-10-methyl-1,8-dichloroanthrone, mp 144–147°. Recrystallization from hexane gave 6.8 g, and further recrystallization from 95% ethanol and from ligroin gave mp 149–150°. The ir spectrum ($CHCl_3$) showed broad carbonyl absorption at 1680 cm^{-1}. The nmr showed a complex multiplet at τ 2.63, a quartet at τ 8.16 partially superimposed upon a singlet at τ 8.29, and a triplet at τ 9.48.

Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.9; H, 4.6; Cl, 23.3. Found: C, 66.9; H, 4.6; Cl, 23.0.

***cis*- and *trans*-9-Dichloromethyl-10-ethyl-9-hydroxy-10-methyl-1,8-dichloro-9,10-dihydroanthracene.**—Dichloromethyllithium, prepared by the method of Köbrich, Trapp, Flory, and Drischell,[17] by the addition of 24.5 mmol of *n*-butyllithium in 45 ml of hexane–petroleum ether to 1.6 ml of methylene chloride in 100 ml of tetrahydrofuran, 12 ml of ether, and 12 ml of petroleum ether (bp 50–60°) at −110°, was treated with a solution of 6.79 g (22.3 mmol) of the ethylmethyldichloroanthrone in 100 ml of 1:1 tetrahydrofuran–ether over a period of 75 min at −110°. After 2 hr of additional stirring, the reaction mixture was poured on crushed ice containing 2 g of ammonium chloride. After extraction with ether, drying of the ether layer over magnesium sulfate, and distillation of the ether, there was obtained a mixture of 8.38 g (97%) of the *cis* and *trans* alcohols which solidified on standing and had mp 97–102°. An analytical sample prepared by three recrystallizations from ligroin had mp 109.5–110.5°. The nmr showed a multiplet at τ 2.61, singlets at τ 3.34 and 3.44 in a ratio of 6.8:1, singlets at τ 4.64 and 4.87 in a ratio of 5.8:1, a quartet at τ 7.95 partially superimposed upon a singlet at τ 8.16, a singlet at τ 8.44, and triplets at τ 9.35 and 9.90 in a ratio of 1:6.6.

Anal. Calcd for $C_{18}H_{16}Cl_4O$: C, 55.4; H, 4.1; Cl, 36.4. Found: C, 55.5; H, 3.9; Cl, 36.0.

9-(Dichloromethylene)-10-ethyl-10-methyl-1,8-dichloro-9,10-dihydroanthracenes (*e*-Ethyl- and *a*-Ethyl-I).—Dehydration of 8.38 g of the mixture of carbinols just described was carried out by triturating it with 20 ml of sulfuric acid.[17] After pouring on ice, extraction with ether, washing with water, drying over magnesium sulfate, and distillation of the solvent, there was obtained 7.58 g (95%) of a mixture of *e*- and *a*-ethyl-I, mp 128–140°. After chromatography on alumina (elution with cyclohexane), the yield was 6.1 g (76%) of a mixture of *e*- and *a*-ethyl-I, mp 133–140°, whose nmr spectrum showed (relative areas of quartet at τ 7.59 and singlet at τ 8.62 compared with the quartet–singlet combination at τ 8.28) the composition to be 87% *a*-ethyl- and 13% *e*-ethyl-I.

The Isomer *a*-ethyl-I, mp 144.5–145.5°, was separated by recrystallization of the mixture from methanol. Additional recrystallization failed to change the melting point. The uv spectrum (cyclohexane) showed λ_{max} 259 mμ (ε 15,200). The nmr peaks (and areas) were a complex multiplet at τ 2.80 (6.0), a quartet at τ 8.29, a singlet at τ 8.27 (4.9), and a triplet at τ 9.25 (3.0). The mass spectrum showed molecular ion peaks at *m/e* (rel intensity) 370 (100), 372 (131), 374 (62.5), and 376 (15.5).

Anal. Calcd for $C_{18}H_{14}Cl_4$: C, 58.1; H, 3.8; Cl, 38.1. Found: 58.1; H, 3.8; Cl, 37.9.

***e*-Ethyl-I** was separated from the mother liquors remaining from crystallization of *a*-ethyl-I by repeated crystallization from methanol (which failed to give complete separation) followed by chromatography on a column of alumina impregnated with 23% silver nitrate following the directions of Schroepfer, *et al.*[18] Elution with hexane–ether (10:1) gave *e*-ethyl-I, mp 129–132°, which, after two recrystallizations from methanol, had mp 131.5–132° and was shown by the nmr spectrum to be free from appreciable amounts of *a*-ethyl-I. The nmr spectrum (8% in CCl_4) had peaks (and areas) as follows: a multiplet at τ 2.78 (5.7), a quartet at τ 7.56 (2.0), a singlet at τ 8.63 (3.2), and a triplet at τ9.22 (3.2). The mass spectrum was indistinguishable from that of *a*-ethyl-I.

Anal. Calcd for $C_{18}H_{14}Cl_4$: C, 58.1; H, 3.8; Cl, 38.1. Found: C, 57.9; H, 3.8; Cl, 37.4.

9,10,10-Trimethyl-9-hydroxy-1,8-dichloro-9,10-dihydroanthracene was prepared by the reaction of 63 mmol of methyllithium (from 8.9 g of methyl iodide and 0.79 g of finely cut lithium in 27 ml of ether) with 3.3 g (11 mmol) of 10,10-dimethyl-1,8-dichloro-9,10-dihydroanthracene at 0° in 1:1 ether–benzene. After a reaction time of 3 hr, the mixture was poured onto crushed ice containing 2 g of NH_4Cl, and, after extraction, washing, drying, and distillation of solvent, there remained 3.3 g (93%) of the alcohol, mp 118–122°. Recrystallization from cyclohexane and from *n*-pentane gave a sample with mp 127–128°. The ir spectrum showed absorption at 3595 cm^{-1} and the nmr showed a complex multiplet at τ 2.77 and singlets at τ 6.42, 7.86, 8.25, and 8.50.

Anal. Calcd for $C_{17}H_{16}Cl_2O$: C, 66.5; H, 5.2; Cl, 23.1. Found: C, 66.5; H, 5.1; Cl, 23.7.

9-Methylene-10,10-dimethyl-1,8-dichloro-9,10-dihydroanthracene (II).—The carbinol (1.23 g), mp 124.5–126°, was dehydrated with concentrated sulfuric acid[17] as in the preparation of the dichloro analog I. Distillation of the solvent after drying gave 1.04 g (88%) of crude olefin, mp 134–135.5°. Chromatography on alumina (elution with cyclohexane) gave 0.89 g (77%) of II,

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mp 135.5–136.5°, Additional recrystallizations from methanol left the melting point unchanged. The ir spectrum had weak C=C absorption at 1630 cm^{-1} and the nmr spectrum showed a complex multiplet centered at τ 2.75, a singlet at τ 3.71, and a pair of broad peaks at τ 8.25 and 8.58.

10,10-Dimethyl-9-dichloromethyl-9-hydroxy-9,10-dihydroanthracene was prepared by the addition of dichloromethyllithium[17] to 10,10-dimethylanthrone,[16] following a procedure employed for the corresponding synthesis of the tetrachloro compound described earlier. The crude product, mp 135–138° (92%), isolated by evaporation of the solvent after work-up, was purified by two recrystallizations from ligroin, after which it had mp 137.5–138°. The ir spectrum showed absorption at 3200 and 3550 cm^{-1}. The nmr had a complex multiplet at τ 2.10, a multiplet at τ 2.66, and singlets at τ 4.21, 6.79 (disappeared when washed with D_2O), 8.22, and 8.38.

Anal. Calcd for $C_{17}H_{16}Cl_2O$: C, 66.5; H, 5.3. Found: C, 66.5; H, 5.2.

9-(Dichloromethylene)-10,10-dimethyl-9,10-dihydroanthracene (III) was prepared by dehydration of the carbinol in the preceding section by treating it with 20 ml of 20% sulfuric acid in glacial acetic acid by the method of Garbisch.[19] After pouring on ice, extraction with ether, neutralization with sodium bicarbonate, washing with water, drying over magnesium sulfate, and distillation of the solvent, there was obtained crude olefin which was purified by chromatography on alumina (cyclohexane eluent) to give a 76% yield of white solid, mp 134–136°. Further purification by two recrystallizations from methanol followed by sublimation gave mp 138–139°. The nmr spectrum had a complex multiplet centered at τ 2.25, a multiplet at τ 2.75, and a pair of slightly broadened singlets at τ 8.15 and 8.60. The uv spectrum (cyclohexane) showed λ_{max} 268 mμ (ϵ 16,800).

Anal. Calcd for $C_{17}H_{14}Cl_2$: C, 70.6; H, 4.9; Cl, 24.5; mol wt, 289. Found: C, 70.3; H, 4.9; Cl, 24.9; mol wt, 289.

9-(Bromomethylene)-10,10-dimethyl-1,8-dichloro-9,10-dihydroanthracene (IV) was prepared by bromination of the olefin II, a method analogous to that of Carlson[16] for the unchlorinated analog. Addition over a 2-hr period of 1.14 g (7.1 mmol) of bromine in 2 ml of CCl_4 to 2.05 g (7.1 mmol) of the olefin II in 30 ml of CCl_4 followed by standing at ambient temperature for 10 hr, 4 hr of refluxing, and distillation of the solvent (reduced pressure) gave a tan residue which was purified by chromatography on alumina (cyclohexane–ether 2:1). There was obtained 2.4 g (92%) of IV, mp 177–180°. Further crystallization from hexane and from ethanol gave mp 180.5–181.5°. The nmr showed a multiplet at τ 2.75 and singlets at τ 2.91, 8.16, and 8.62.

Anal. Calcd for $C_{17}H_{13}BrCl_2$: C, 55.5; H, 3.6; Br, 21.7. Found: C, 55.8; H, 3.7; Br, 21.7.

9,10-Dimethyl-10-ethyl-9-hydroxy-1,8-dichloro-9,10-dihydroanthracene was prepared by the addition of methyllithium to the ethylmethyldichloroanthrone following the procedure used for the addition to the dimethyldichloroanthrone described previously. Removal of the solvent after the preliminary work-up gave 1.40 g (95%) of carbinol, mp 107–113°. Several recrystallizations from hexane gave mp 116–117°. The ir spectrum showed hydroxyl absorption at 3597 cm^{-1}, and the nmr spectrum showed multiplets at τ 2.72 and 7.85, singlets at τ 6.41, 8.32, and 8.45, and a broad triplet at τ 9.66.

Anal. Calcd for $C_{18}H_{18}Cl_2O$: C, 67.3; H, 5.7. Found: C, 67.4; H, 5.8.

9-Methylene-10-ethyl-10-methyl-1,8-dichloro-9,10-dihydroanthracene was prepared by dehydration of the carbinol of the preceding section by the method of Garbisch[1] as described for the syntheses of olefin III. Evaporation of solvent gave crude olefin, mp 110–116°, which was purified by chromatography on alumina (elution with cyclohexane) to give an 89% yield of product, mp 119–122°. Two recrystallizations from methanol gave mp 122–123°. The nmr spectrum showed a multiplet at τ 2.77, singlets at τ 3.76 and 8.37, and a triplet at τ 9.37.

Anal. Calcd for $C_{18}H_{16}Cl_2$: C, 71.3; H, 5.3; Cl, 23.4. Found: C, 71.6; H, 5.5; Cl, 23.5.

9-(Bromomethylene)-10-ethyl-10-methyl-1,8-dichloro-9,10-dihydroanthracene (V) was prepared by bromination of the olefin in the preceding section, following the procedure employed for the preparation of IV. Chromatography of the crude product on Two recrystallizations from methanol gave mp 138–141°. The nmr spectrum (15% in $CDCl_3$) showed a multiplet at τ 2.70, a singlet at τ 2.90, a quartet at τ 7.59, a singlet superimposed upon alumina (cyclohexane eluent) gave 68% of V, mp 135–141°. a quartet at τ 8.26–8.31, a singlet at τ 8.69, and two triplets overlapping at τ 9.26–9.35.

Anal. Calcd for $C_{18}H_{15}BrCl_2$: C, 56.6; H, 4.0; Br, 20.9. Found: C, 56.9; H, 4.3; Br, 20.7.

Measurement of the Kinetics of Interconversion of *e*-Ethyl- and *a*-Ethyl-I.—Rate measurements were carried out with sample tubes prepared as for the nmr studies reported elsewhere,[4] except that before the tubes wre sealed the air was replaced by nitrogen. Solutions were 13–33% w/v in 1,1,2,2-tetrachloroethane with tetramethylsilane as an internal standard. The tubes were heated in a constant temperature bath (±0.5°) at the temperature indicated, and cooled rapidly to room temperature after the specified time. The nmr spectrum was measured with a Varian A56/60 spectrometer with a 100-Hz sweep width and a sweep time of 250–500 sec. Isomerizations of mixtures with excess *e*-ethyl-I were followed by measuring the disappearance of the methyl peak at τ 8.63; the reaction of the *a*-ethyl isomer was followed by measuring the disappearance of the methyl and methylene absorption at τ 8.27. Since the methyl absorption of the *a*-ethyl isomer was overlapped by the methylene quartet, the total area due to the five protons was measured and multiplied by a constant factor of 3/5. Infinity points were determined at a minimum of eight half-lives. The average value for the composition at infinite time corresponding to 11.79% of the *e*-ethyl isomer was employed throughout. The rate constants and standard deviations were calculated assuming the relationship[20]

$$\ln (A_0 - A_e)/(A - A_e) = k_{obsd}t$$

(where the A's are concentrations at $t = 0$, time t, and after equilibrium has been reached, and $k_{obsd} = k_1 + k_{-1}$) using an IBM 7094 computer and employing a weighted least-squares program.[21] Results are summarized in Table I. Detailed data are available in the Ph.D. Thesis cited in ref 1. The values of E_a and $\Delta S^{\ddagger}$ (Table II) were obtained from a least-squares plot of log k_{obsd} *vs.* $1/T$. Error limits were estimated[22] assuming a 5% error in the rate constants.

Registry No.—I, 20888-10-2; II, 20888-11-3; III, 20888-12-4; IV, 20888-13-5; V, 20888-14-6; 10,10-dimethyl-1,8-dichloroanthrone, 20888-15-7; 10-ethyl-10-methyl-1,8-dichloroanthrone, 20888-16-8; *cis*-9-dichloromethyl-10-ethyl-9-hydroxy-10-methyl-1,8-dichloro-9,10-dihydroanthracene, 20888-17-9; *trans*-9-dichloromethyl-10-ethyl-9-hydroxy-10-methyl-1,8-dichloro-9,10-dihydroanthracene, 20888-18-0; 9,10,10-trimethyl-9-hydroxy-1,8-dichloro-9,10-dihydroanthracene, 20888-19-1; 10,10-dimethyl-9-dichloromethyl-9-hydroxy-9,10-dihydroanthracene, 20888-20-4; 9,10-dimethyl-10-ethyl-9-hydroxy-1,8-dichloro-9,10-dihydroanthracene, 20930-48-7; 9-methylene-10-ethyl-10-methyl-1,8-dichloro-9,10-dihydroanthracene, 20888-21-5.

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Reaction of "Sulfenes" with Aryl Nitrones and N-Phenylhydroxylamines to Form Benzoxathiazepines and o-Aminophenol Derivatives, Respectively

WILLIAM E. TRUCE, J. W. FIELDHOUSE,
D. J. VRENCUR, J. R. NORELL, R. W. CAMPBELL, AND D. G. BRADY

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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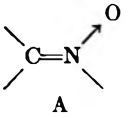
4,5-Dihydro-4-aryl-3H-1,2,5-benzoxathiazepine 2,2-dioxides are prepared by the reaction of diaryl nitrones with alkanesulfonyl chlorides and triethylamine. The seven-membered-ring azasultone structural assignment is supported by spectral data, chemical degradation, and alternate syntheses. A mechanism for the formation of the azasultone is proposed on the basis of ^{18}O-labeling studies. The analogous rearrangement of N-phenylhydroxylamines to *o*-aminophenol derivatives under like conditions was shown by ^{18}O-labeling studies to involve a different mechanism.

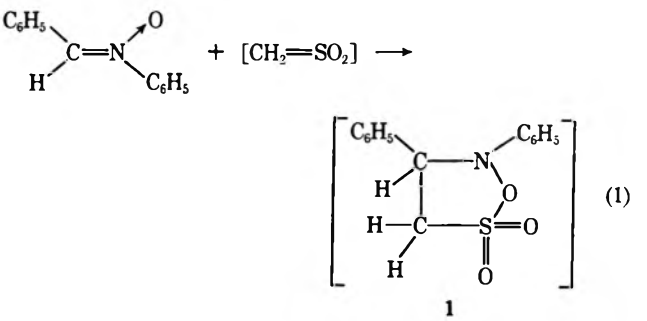
The intermediacy of sulfenes ($R_2C{=}SO_2$) in the alcoholysis of alkanesulfonyl chlorides in the presence of tertiary amines and deuterium-labeled alcohols (ROD) was demonstrated by the formation of monodeuterated sulfonate esters; no di- or trideuteration was observed.[1,2] Also, when an alkanesulfonyl chloride is treated with triethylamine in the presence of "nucleophilic" olefins such as enamines, ketene acetals, and ketene N,O-acetals, cycloaddition of the "sulfene" intermediate to the olefin results, and thietane 1,1-dioxides generally are formed.[3] Although sulfene readily undergoes 1,2 or 1,4 cycloaddition, there is only one known example of a 1,3 cycloaddition.[4] Attempts to effect cycloaddition of sulfene to 1,3-dipolar nitrile oxides resulted in the sulfonate esters of α-chloroaldoximes.[5]

Another 1,3-dipolar system with a considerable propensity for cycloaddition is a nitrone or anil N-oxide (A). 1,3 cycloaddition has been reported to occur between nitrones and methylene phosphoranes,[6] Michael olefins,[7] alkenes,[8] enamines,[9] enynes,[10], sulfinylamines,[11] acetylenic carboxylic esters,[12] ketene acetals,[13] isocyanates,[14] isothiocyanates,[14] and ynamines.[15] In view of this reactivity of nitrones toward 1,3-dipolar cycloaddition, we studied their behavior in sulfene systems.[16]



A

When equimolar quantities of N,α-diphenyl nitrone and triethylamine were stirred at room temperature in benzene, and a solution of methanesulfonyl chloride in benzene was added drpowise, there was immediate precipitation of triethylammonium chloride. A crystalline product, of elemental analysis and molecular weight consistent with the expected 1:1 adduct **1**, was obtained from the solution (eq 1). However, the spectral properties of the crystalline adduct agree not with **1**, but with the isomeric structure **2**. Although the infrared spectrum exhibits strong absorptions at 7.30 and 8.65 μ (SO_2O), a weak absorption at 3.00 μ can be attributed to NH or OH. Furthermore, the nmr spectrum is complex, consisting of a series of sharp singlets and a conical peak between δ 3.30 and 4.10 (3 H), two doublets centered at 4.68 (J = 2.2 cps) and 4.85 (J = 2.2 cps) (1 H), a multiplet at 6.68–7.30 (4 H), and a singlet at 7.4 (5 H). The nmr spectrum of **1** would be expected to display ten aromatic protons instead of the observed nine.



(1)

1

Treatment of N-(2-methylphenyl)-α- phenyl nitrone with ethanesulfonyl chloride and triethylamine gave a crystalline adduct **3** whose nmr spectrum shows a singlet at δ 7.4 (5 H), a multiplet at 6.70–7.25 (3 H), and other peaks due to aliphatic and amino protons. This suggests that the N-phenyl ring is trisubstituted, while the α-phenyl ring remains monosubstituted. These reactions are summarized below (eq 2 and 3), and the

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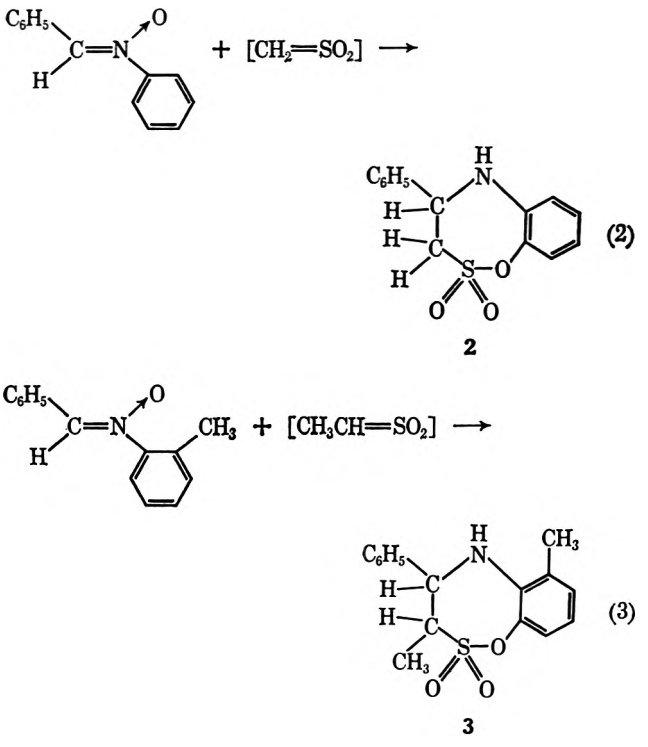
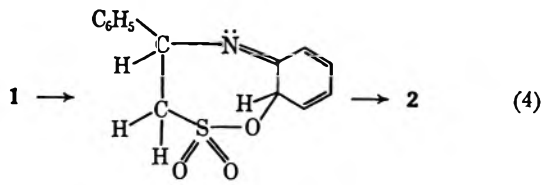
(16) (a) W. E. Truce, J. R. Norell, R. W. Campbell, D. G. Brady, and J. W. Fieldhouse, *Chem. Ind.* (London), 1870 (1965). (b) W. E. Truce and J. W. Fieldhouse, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, No. S 45; See also ref 5c.

physical properties and spectra of the products are consistent with structures **2** and **3**. Adducts **2** and **3**



could result from rearrangement of the initial cycloadduct, the oxathiazole, as illustrated for the formation of **2** (eq 4). This rearrangement is analogous to that



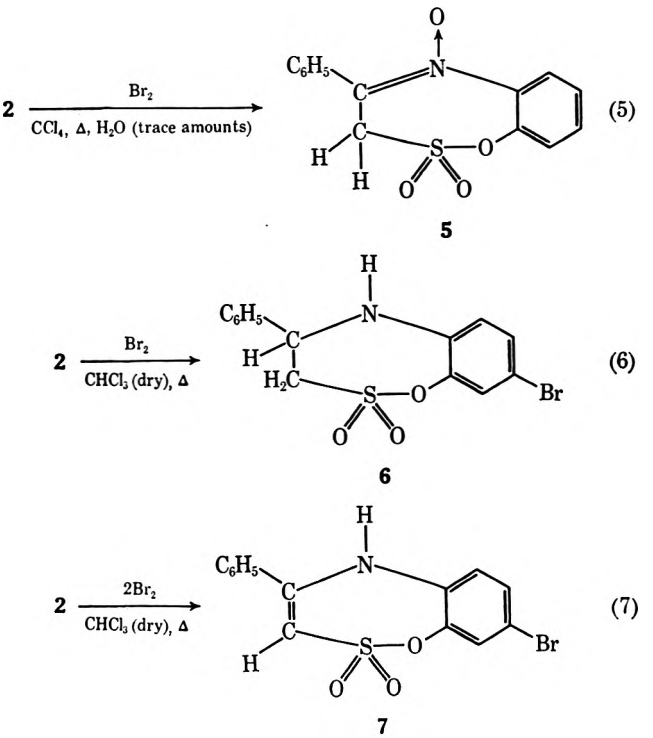
reported by Boyland[17] for N-phenylhydroxylamine-O-sulfonic acid.

That **2** contains an NH rather than an OH group is shown by acetylation to give an amide (**4**) having a carbonyl absorption at 6.0 μ, whereas aryl acetates give carbonyl absorptions at 5.7 μ.[18] The presence of three replaceable hydrogens, one on nitrogen and two α to the sulfonyl group, was demonstrated by the conversion of **2** into its corresponding trimethyl derivative by treatment with 3 equiv of sodium amide in liquid ammonia followed by reaction with 3 equiv of methyl iodide.

Azasultone **2** was reductively cleaved using lithium aluminum hydride in tetrahydrofuran or dioxane giving 2-phenylethanethiol, 2-aminophenol, and hydrogen. We know of no published examples of C–N bond cleavage in a phenyl benzyl amine by lithium aluminum hydride. Since the previously described alkylation on carbon using strong base indicates that the formation of a sulfonyl stabilized carbanion is possible, anion formation with attendant hydrogen evolution may be the initial step in the reduction. The next step in the reduction is postulated to be the reverse of the addition of an amine to an α,β-unsaturated sulfonyl system,[19] resulting in the formation of an α,β-unsaturated sulfonate ester (Scheme I).

Reduction of α,β-unsaturated sulfones to the corresponding saturated sulfides by lithium aluminum hydride has been reported by several workers.[20] The corresponding α,β-unsaturated sulfide was unaffected by the same conditions. These authors conclude that the sulfonyl group polarizes the double bond so that attack by hydride is possible, resulting in a sulfonyl stabilized carbanion. Precedence for the final reduction step in the proposed mechanism can be found in the work of Strating and Backer who found that phenyl methanesulfonate is reduced by lithium aluminum hydride to phenol and methanethiol.[21]

Compound **2** was independently synthesized and interrelated by a number of alternative procedures as shown in Scheme II. Bromination of **2** gives three different products depending upon conditions, *i.e.*, eq 5–7. The analytical and spectral data agree well with



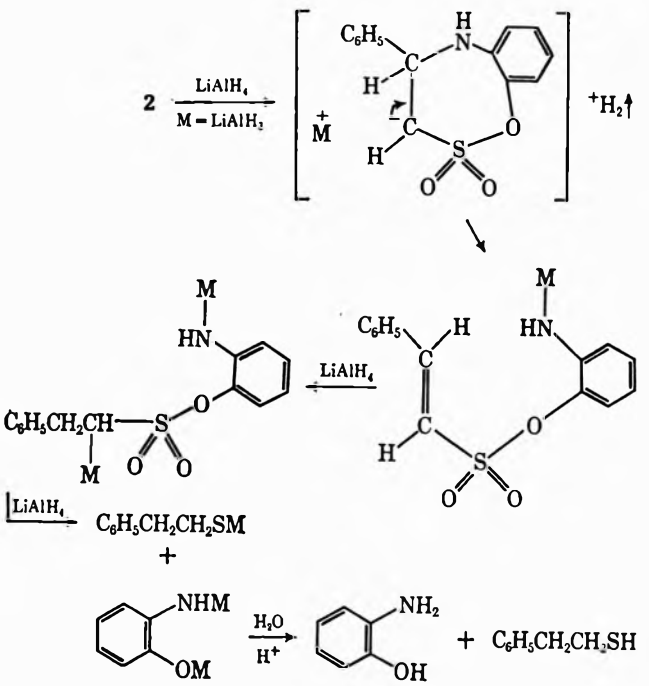
structures **5**, **6**, and **7**. Eloy and Van Overstraeten[5] reported the formation of **6** under similar conditions and have also prepared **6** from the reaction of N-(4-bromophenyl)-α-phenyl nitrone, methanesulfonyl chloride, and triethylamine.

To extend the scope of this cyclization to include the preparation of other seven-membered-ring azasultones, various nitrones and several sulfonyl chlorides were employed as summarized in Table I, p 3100.

Several attempts were made to establish the intermediacy of the oxathiazole **1**. For example, in attempts to preclude subsequent rearrangement of the oxathiazole, N-(2,6-dimethylphenyl)-α-phenyl nitrone, and N-methyl-α-phenyl nitrone were treated with methanesulfonyl chloride and triethylamine. In both

(17) E. Boyland and R. Nery, *J. Chem. Soc.*, 5217 (1962).
(18) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Son, Inc., New York, N. Y., 1958, pp 182, 213.
(19) S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc., B*, 343 (1967).
(20) (a) F. G. Bordwell and W. H. McKellin, *J. Amer. Chem. Soc.*, **73**, 2251 (1951); (b) G. Van Zyl and R. Koster, *J. Org. Chem.*, **29**, 3558 (1964).
(21) J. Strating and H. J. Backer, *Rec. Trav. Chim.*, **69**, 638 (1950).

SCHEME I



N-phenylhydroxylamine has been added to many activated double bonds.[23] We have found that N-phenylhydroxylamine readily adds to benzenesulfonylethylene, *p*-toluenesulfonylethylene, and *p*-tolyl *trans*-β-styrenesulfonate giving the corresponding 2-(N-phenylhydroxylamine)ethanesulfonyl derivative[24] (eq 8).

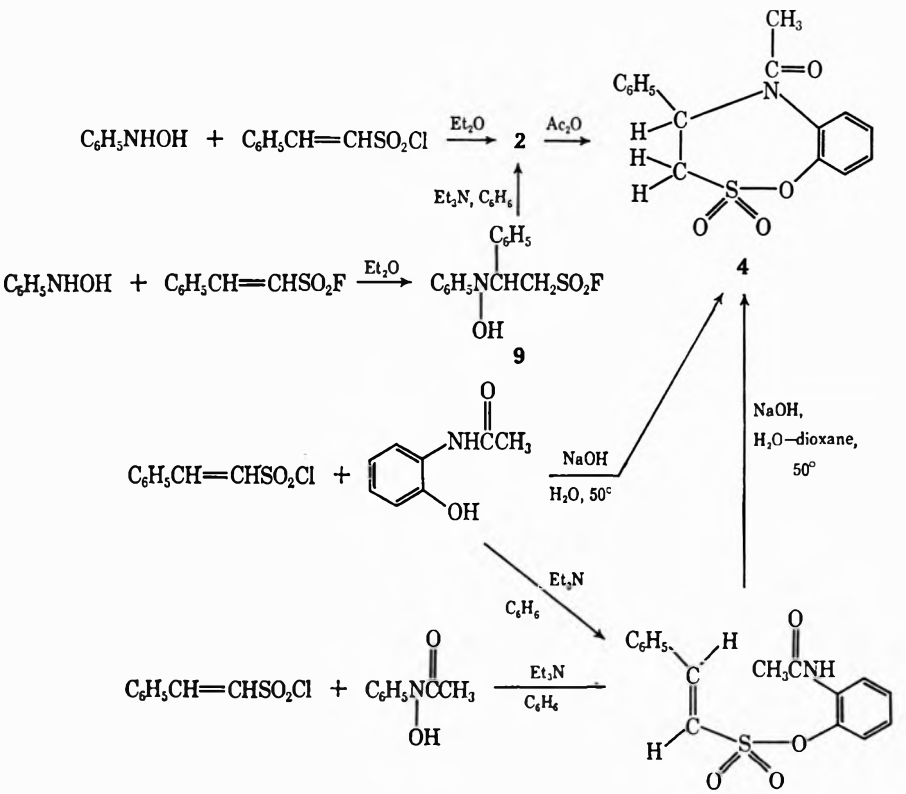
$$C_6H_5NHOH + RCH{=}CHSO_2R' \longrightarrow C_6H_5\underset{\displaystyle OH}{\underset{|}{N}}CHRCH_2SO_2R' \quad (8)$$

It was anticipated that the reaction of N-phenylhydroxylamine with β-styrenesulfonyl chloride would result in the formation of oxathiazole **1** as shown in eq 9.

$$C_6H_5NHOH + C_6H_5CH{=}CHSO_2Cl \xrightarrow{Et_2O} \left[C_6H_5\underset{\displaystyle C_6H_5}{\underset{|}{N}}(OH)CHCH_2SO_2Cl\right] \xrightarrow{-HCl} [1] \longrightarrow \mathbf{2} \quad (9)$$

8

SCHEME II



attempts only low yields of acyclic decomposition products were obtained; 2-amino-2-phenylethanesulfonic acid was obtained in both cases, together with traces of formaldehyde and N-methylbenzamide in the latter.

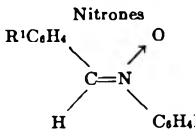
The second attempt at isolation of an oxathiazole 2,2-dioxide involved the addition of N-phenylhydroxylamine to an α,β-unsaturated sulfonyl chloride. The addition of hydroxylamine and methylhydroxylamine to vinyl sulfones has been reported by Sayigh,[22] while Oxathiazole **1** was not isolated, but only the rearranged adduct **2**. When the same reaction was carried out using β-styrenesulfonyl fluoride the sulfonyl fluoride (**9**) corresponding to **8** was isolated and character-

(22) A. A. R. Sayigh, H. Ulrich, and M. Green, *J. Org. Chem.*, **29**, 2042 (1964).

(23) J. Enrico, *Gazz. Chim. Ital.*, **68**, 488 (1938).

(24) J. W. Fieldhouse, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1968.

TABLE I
BENZOXATHIAZEPINES



Nitrones	Sulfonyl chlorides	Registry	Benzoxathiazepines Yield,	Mp,	Calcd, %				Found, %			
	$R^3CH_2SO_2Cl$	no.	%	°C	C	H	N	S	C	H	N	S
$R^1 = R^2 = H$	$R^3 = H$	5172-50-9	60	160	61.07	4.76	5.09	11.65	61.09	4.72	4.97	11.57
$R^1 = 4\text{-}NO_2$; $R^2 = 3\text{-}Cl$	$R^3 = H$	20646-62-2	87[a]	201–203	47.40	3.13	7.90	9.04	47.5	3.42	7.74	8.78
$R^1 = H$; $R^2 = 3\text{-}C\equiv N$	$R^3 = H$	20646-63-3	25	205	59.98	4.03	9.33	10.67	59.6	4.10	9.30	10.91
$R^1 = 4\text{-}NO_2$; $R^2 = H$	$R^3 = H$	16261-43-1	52	235–236	52.49	3.78	8.75	10.01	52.66	3.99	8.84	9.93
$R^1 = 3\text{-}NO_2$; $R^2 = H$	$R^3 = H$	20646-78-0	72	148–149	52.49	3.78	8.75	10.01	52.56	4.00	8.72	9.86
$R^1 = 4\text{-}NO_2$; $R^2 = 4\text{-}Cl$	$R^3 = H$	20646-65-5	52[b]	253–254	47.40	3.13	7.90	9.04	47.67	3.22	7.70	9.18
$R^1 = H$; $R^2 = 4\text{-}Cl$	$R^3 = H$	20646-66-6	59[c]	157–158	54.28	3.91	4.52	10.35	54.54	3.89	4.29	10.54
R^1 = benzo[*b*]; $R^2 = H$	$R^3 = H$	20646-67-7	35	151	66.44	4.65	4.31	9.85	66.51	4.74	4.40	9.81
$R^1 = 4\text{-}Cl$; $R^2 = H$	$R^3 = H$	16261-42-0	62[d]	168.5	54.28	3.91	4.52	10.35	54.02	4.05	4.38	10.51
$R^1 = 4\text{-}CH_3$; $R^2 = H$	$R^3 = H$	20646-69-9	58	167–168	62.26	5.23	4.84	11.08	61.99	5.30	4.63	11.21
$R^1 = 4\text{-}F$; $R^2 = H$	$R^3 = H$	20646-70-2	53[e]	173–174	57.32	4.13	4.78	10.93	57.43	4.16		11.03
$R^1 = 4\text{-}Br$; $R^2 = H$	$R^3 = H$	20646-71-3	61[f]	209	47.42	3.42	3.95	9.05	47.26	3.42	3.78	9.06
$R^1 = 2\text{-}Cl$; $R^2 = H$	$R^3 = H$	20646-72-4	62[g]	151–152	54.28	3.91	4.52	10.35	54.35	3.83	4.39	10.41
$R^1 = 4\text{-}C\equiv N$; $R^2 = H$	$R^3 = H$	20646-73-5	45	263–264	59.98	4.03	9.33	10.67	60.19	4.13	9.31	10.56
$R^1 = R^2 = H$	$R^3 = CH_3$	20646-74-6	37	159–166	62.26	5.20	4.84	11.08	62.27	5.53	4.81	11.36
$R^1 = H$; $R^2 = 2\text{-}CH_3$	$R^3 = CH_3$	20646-75-7	18	145–147	63.34	5.65	4.62	10.57	63.24	5.70	4.91	10.82
$R^1 = 4\text{-}CH_3$; $R^2 = H$	$R^3 = CH_3$	20646-76-8	24	185–190	63.34	5.65	4.62	10.57	63.24	5.94	4.43	10.53
$R^1 = 4\text{-}CH_3$; $R^2 = H$	$R^3 = C_6H_5$	20646-77-9	21	199–200	69.02	5.24	3.84	8.77	68.87	5.48	3.85	8.70
$R^1 = R^2 = H$	$R^3 = Br$	20647-16-9	26[h]	133–135	47.5	3.39	3.96	9.05	47.7	3.58	4.23	9.29

[a] Calcd: Cl, 10.0. Found: Cl, 10.3. [b] Calcd: Cl, 10.0. Found: Cl, 10.20. [c] Calcd: Cl, 11.44. Found: Cl, 11.15. [d] Calcd: Cl, 11.44. Found: Cl, 11.71. [e] Calcd: F, 6.48. Found: F, 6.67. [f] Calcd: Br, 22.56. Found: Br, 22.45. [g] Calcd: Cl, 11.44. Found: Cl, 11.21. [h] Calcd: Br, 22.56. Found: Br, 22.70.

ized. When it was treated with a benzene solution of triethylamine, only azasultone **2** could be isolated.[25]

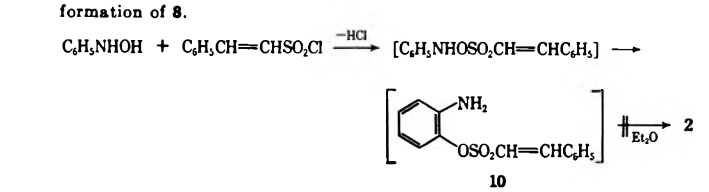
One question that remains unanswered is the nature of the rearrangement of oxathiazole **1** to azasultone **2**. There are at least three pathways by which rearrangement can occur (Scheme III). The asterisk in the diagram signifies ^{18}O label and the dotted lines represent the bonds being formed or broken in the transition state. In pathway a, the transition state is pictured as being a four-membered ring involving the nitrogen, the original nitrone oxygen, and two carbon atoms of the benzene ring. By using ^{18}O-labeled nitrone, the final azasultone should contain all the excess ^{18}O in the phenolic oxygen. Lithium aluminum hydride reduction should give 2-aminophenol which is enriched with ^{18}O to the same extent as the starting nitrone. In pathway b, the transition state is pictured as a six-membered ring. Complete rearrangement to azasultone would result in no excess ^{18}O being present in the phenolic oxygen, as determined by cleavage to 2-aminophenol. Pathway c represents complete cleavage of the N–O bond, and hence scrambling of all ^{18}O present. Cleavage of the azasultone would give 2-aminophenol containing one-third of the excess ^{18}O originally incorporated in the nitrone. The ^{18}O analyses were determined by comparison of the M and M + 2 peaks in the mass spectrum of both labeled and unlabeled materials.[26] As shown in Table II, trial 1 resulted in 78% retention of the excess ^{18}O,[27] while trial 2 resulted in 82.5% retention of the excess ^{18}O. This indicates that pathway a is predominantly (80% of the reaction) being followed, *i.e.*, a four-membered-ring transition state is occurring, with the other 20% of the reaction occurring through pathway b or c.[28]

TABLE II
^{18}O COMPOUNDS USED IN THE REARRANGEMENT OF DIARYL NITRONE[a]

Compound	P + 2/P, % Labeled	Unlabeled	Δ
Trial 1			
Nitrobenzene	1.74	0.72	1.02
N-Phenyl-α-(4-fluorophenyl) nitrone	2.39	1.35	1.04
2-Aminophenol	1.28	0.47	0.81
Trial 2			
Nitrobenzene	4.62	0.72	3.90
N-Phenyl-α-(4-fluorophenyl) nitrone	4.81	1.35	3.46[a]
2-Aminophenol	3.31	0.46	2.85

[a] The reduction of nitrobenzene-^{18}O to N-phenylhydroxylamine-^{18}O in $H_2{}^{16}O$ is known[27] to result in a 22% loss of ^{18}O; the formation of a nitrone from N-phenylhydroxylamine-^{18}O is known[26] to result in retention of 100% ^{18}O.

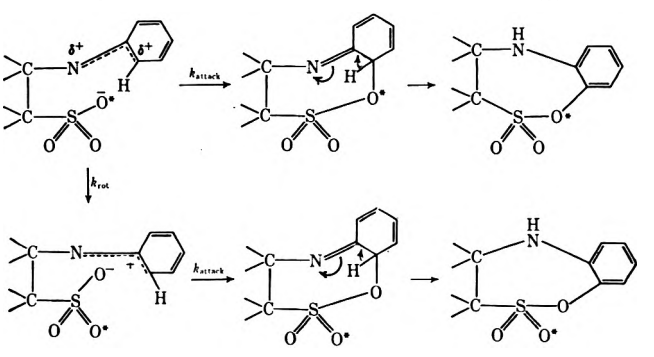
(25) An alternate mechanism shown below was precluded on the basis that **10** was synthesized and did not cyclize to **2** under the conditions of the formation of **8**.



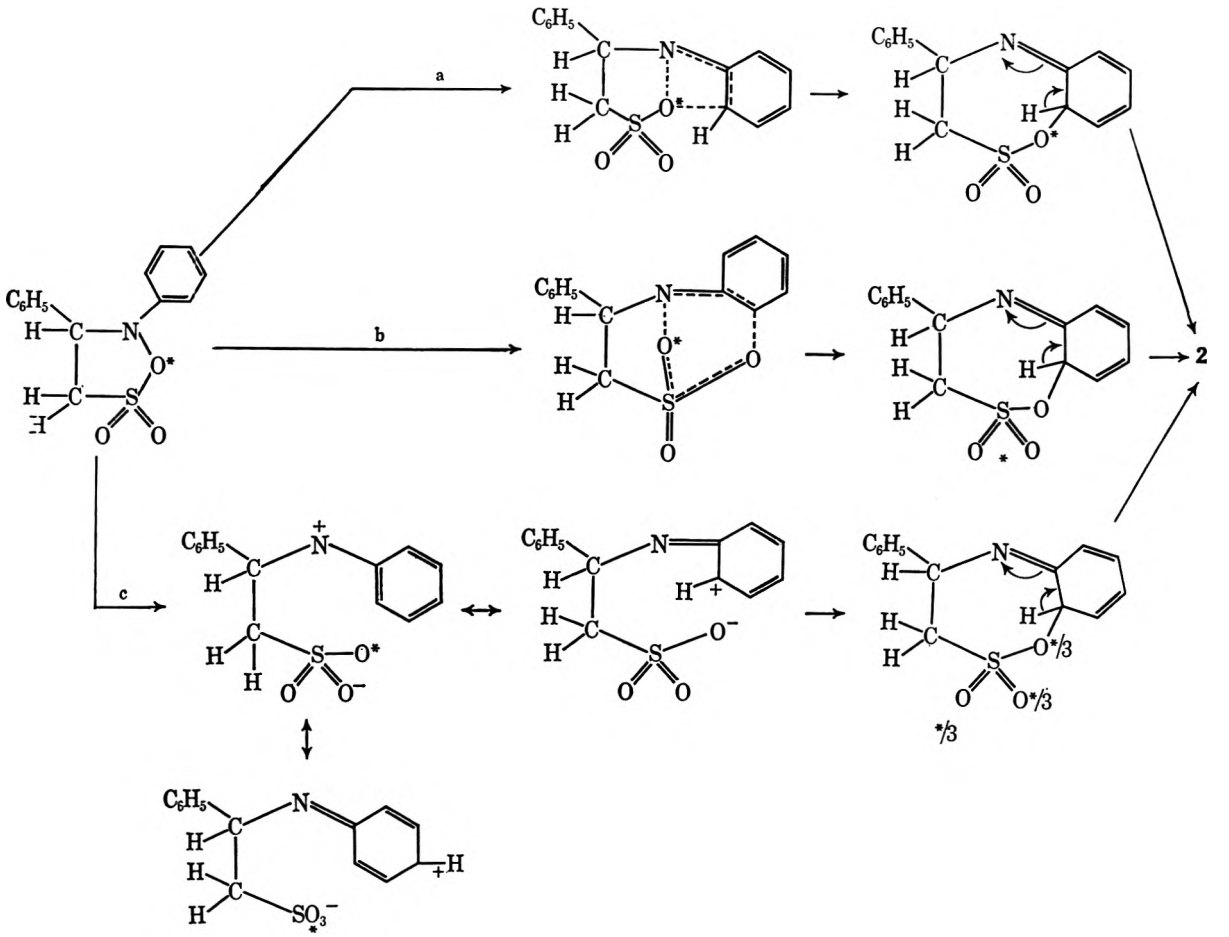
(26) L. A. Neiman, V. I. Maimind, and M. M. Shemyakin, *Tetrahedron Lett.*, 3157 (1965).

(27) S. Oae, T. Fukumoto, and M. Yamagami, *Bull. Chem. Soc. Jap.*, **36**, 728 (1963).

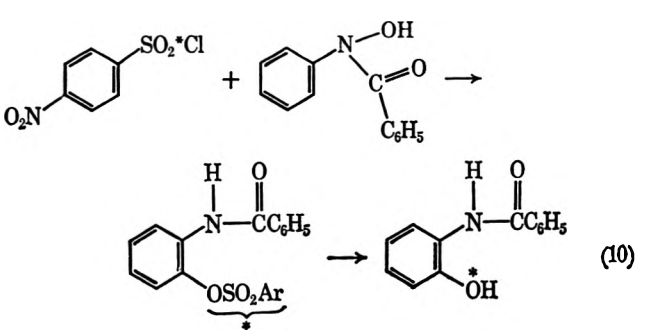
(28) An alternative explanation involves an ion pair which can either immediately attack the *ortho* position of the benzene ring or first rotate 120° and then attack the *ortho* position of the benzene ring. The 80% retention of ^{18}O and 20% loss of ^{18}O could then be rationalized if $k_{attack} > k_{rot}$.



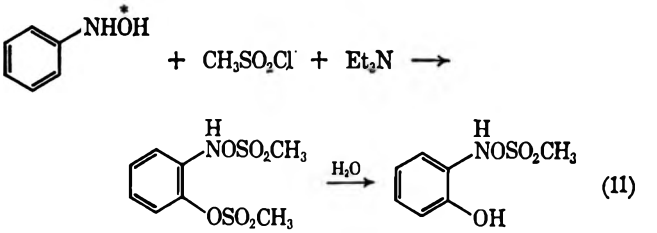
SCHEME III



A Framework Molecular Model indicates that the nitrone oxygen is about half as far from the *ortho* position of the benzene ring as the sulfonyl oxygens, which are effectively held back by the five-membered ring. This suggests that rearrangement of an acyclic N-sulfonyloxyaniline ($C_6H_5NOSO_2R$), where the constriction of the five-membered ring is absent, to the corresponding 2-aminophenol may involve attachment of a sulfonyl oxygen to the benzene ring. Work carried out by Lwowski, *et al.*,[29] and confirmed in this laboratory, has substantiated this point. Lwowski studied the reaction of *p*-nitrobenzenesulfonyl chloride-^{18}O with N-benzoyl-N-phenylhydroxylamine in the presence of triethylamine and found that all of the phenolic oxygen in the resulting *o*-hydroxybenzanilide (eq 10) was originally part of the sulfonyl oxygens. We have studied the reaction of N-phenylhydroxylamine-^{18}O with methanesulfonyl chloride in the presence of triethylamine (eq 11). Here, the N-methanesulfonyl-*o*-aminophenol



(10)



(11)

contained no excess ^{18}O as determined by mass spectral analysis. These results are in agreement with the six-membered-ring transition state proposed by Lwowski, *et al.*[29]

In summary, various diaryl nitrones react with sulfene in poor to excellent yields, depending on the substituent on the α-phenyl ring and the nature of the sulfonyl chloride. The probability of an intermediate 1,2,-5-oxathiazole 2,2-dioxide was demonstrated. Its rearrangement to an azasultone was shown to proceed predominantly *via* a four-membered-ring transition state probably owing to the inherent steric restrictions. In contrast to the rearrangement of the 1,2,5-oxathiazole, the rearrangement of N-sulfonyloxyanilines proceeds *via* a six-membered-ring transition state.

(29) G. T. Tisue, M. Grassmann, and W. Lwowski, *Tetrahedron*, **24**, 999 (1968).

Experimental Section[30]

Materials.—Triethylamine (Matheson Coleman and Bell, bp 88–90°) was used as obtained. α-Toluenesulfonyl chloride and methanesulfonyl chloride were Eastman Kodak White Label grade and were used without further purification. Anhydrous diethyl ether (Mallinckrodt) and benzene (Baker Analyzed reagent) were used as obtained. Tetrahydrofuran (Fisher Certified Reagent) was purified by distilling it from lithium aluminum hydride. Other starting materials were prepared according to the references cited. These included bromomethanesulfonyl chloride,[31] bp 87–89° (15 mm), $n^{18}D$ 1.5620; β-styrenesulfonyl chloride,[32] mp 89–90°; and N-aceto-N-phenylhydroxylamine,[33] mp 66–67°.

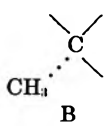
The nitrones used were prepared by warming ethanolic solutions of equimolar quantities of aldehyde and hydroxylamine for several minutes; cooling gave solids which were recrystallized from alcohols or benzene–hexane in yields of 50–90%.

General Procedure for the Reaction of Alkanesulfonyl Chlorides and Diaryl Nitrones.—All glassware was oven dried before use, and reactions were carried out under an atmosphere of dry nitrogen. A solution of 0.01–0.03 mol of nitrone in 200–300 ml of benzene was prepared in a 500-ml three-neck flask equipped with two dropping funnels and a mechanical stirrer. If solution was not complete at room temperature, external heat was applied as necessary. Equivalent amounts of alkanesulfonyl chloride and triethylamine, each in 50 ml of benzene, were added simultaneously over a period of 0.5 hr. During the course of the slightly exothermic reaction, triethylammonium chloride precipitated and an intense color often developed. The reaction mixture was stirred for 2–48 hr after the addition was complete. At this time, the reaction mixture was filtered, resulting in 70–99% yields of triethylammonium chloride. The filtrate was evaporated *in vacuo* yielding highly colored oils which were induced to crystallize by adding small amounts of ethanol or methanol. Cooling and filtration usually gave pure product (not analytically pure) on which the yield is based. A second crop of azasultone could often be obtained by concentration of the mother liquors. The residual oils, which were not characterized, showed only ionic sulfonate bands in the ir spectrum.

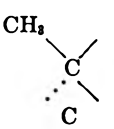
Reaction of Acetic Anhydride with 4,5-Dihydro-4-phenyl-3H-1,2,5-Benzoxathiazepine 2,2-Dioxide (2).—A solution of 2.00 g (0.00727 mol) of **2** in 25 ml of acetic anhydride was refluxed for 7 hr. Evaporation *in vacuo* gave a solid which was recrystallized from methanol giving 1.50 g (65%) of 5-acetyl-4,5-dihydro-4-phenyl-3H-1,2,5-benzoxathiazepine 2,2-dioxide (**4**): mp 164.5–165.5°; ir (Nujol) 6.00 (C=O), 7.25, 7.30, 8.50, 8.60 (SO_2O), and 7.60 μ (CN); nmr ($CDCl_3$) δ 1.87 (s, 3, CH_3), 3.36 (t, 2, J = 7 cps, CH_2SO_2O), 6.19 (t, 1, J = 7 cps, H—C—N), 7.27 (s, 5, aromatic), and 7.43 (s, 4, aromatic).

Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.50; H, 4.73; N, 4.41; mol wt, 317. Found: C, 60.44; H, 4.83; N, 4.38; mol wt, 317.

Reaction of 2 with Sodium Amide and Methyl Iodide.—To 0.0066 mol of sodium amide in 200 ml of liquid ammonia was added 0.60 g (0.0022 mol) of **2**. After 10 min of stirring, 0.060 mol of methyl iodide dissolved in 50 ml of ether was added dropwise over a 10-min period. The reaction mixture was stirred for 10 hr, during which time the ammonia was allowed to evaporate slowly. The solid remaining was washed with 50 ml of water, decolorized, and recrystallized from methanol giving 0.234 g (34%) of 4,5-dihydro-4-phenyl-3,3,5-trimethyl-3H-1,2,5-benzoxathiazepine 2,2-dioxide: mp 138.5–140.0°; ir (Nujol) 6.20 (C=C) and 7.40, 8.50 μ (SO_2O); nmr ($CDCl_3$) δ 1.40 (s, 3, B), 1.80 (s, 3, C), 2.81 (s, 3, NCH_3), 4.32 (s, 1, H—C—N), and 6.67–7.50 (m, 9, aromatic protons).



B



C

Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.38; H, 6.00; N, 4.40, S, 10.10; mol wt, 317. Found: C, 64.05; H, 5.93; N, 4.45; S, 10.04; mol wt, 323.

Reduction of 2 with Lithium Aluminum Hydride.—To a stirred solution of 3.00 g (0.0109 mol) of **2** in 40 ml of dry tetrahydrofuran, 0.42 g (0.011 mol) of lithium aluminum hydride suspended in 40 ml of tetrahydrofuran was added dropwise. A vigorous evolution of hydrogen gas resulted. After stirring 24 hr at room temperature, 10% sulfuric acid was cautiously added until a neutral solution resulted; 100 ml of water was then added; and the solution was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*, and the resulting oil was triturated with a few drops of chloroform and later hexane, giving a pale yellow solid. Sublimation at 125° (0.2 mm) gave 0.48 g (44%) of 2-aminophenol, mp 169–170°. The neutral aqueous solution was acidified to pH 1 and extracted with chloroform, and the extracts were added to the mother liquors of 2-aminophenol. Evaporation *in vacuo* and distillation gave 0.45 g 2-phenylethanethiol, bp 85° (10 mm) [lit. bp 133–140° (55 mm),[34] bp 95–98° (12 mm)[35]], which gave an infrared spectrum identical with that of an authentic sample.

Reaction of N-Phenylhydroxylamine and β-Styrenesulfonyl Chloride.—To a solution of 1.28 g (0.0118 mol) of N-phenylhydroxylamine in 100 ml of dry ether, a solution of 2.38 g (0.0118 mol) of β-styrenesulfonyl chloride in 30 ml of ether was added dropwise. After 24 hr of stirring at room temperature, a brown gum separated from the colorless solution; it was not characterized. The ethereal solution was filtered and allowed to evaporate at room temperature. Crystals separated slowly from the resulting purple oil. Addition of a small amount of 2-propanol facilitated crystallization. Filtration gave 1.90 g (58.5%) of 4,5-dihydro-4-phenyl-3H-1,2,5-benzoxathiazepine 2,2-dioxide (**2**), identical in all respects with that prepared by the reaction of N,α-diphenyl nitrone, methanesulfonyl chloride, and triethylamine.

Reaction of N-Phenylhydroxylamine and β-Styrenesulfonyl Fluoride.—To a solution of 1.50 g (0.00806 mol) of β-styrenesulfonyl fluoride in 50 ml of ether was added dropwise a solution of 0.88 g (0.00806 mol) of N-phenylhydroxylamine in 50 ml of ether. After 24 hr of stirring at room temperature, a small amount of dark solid was filtered and discarded, 50 ml of heptane was added to the filtrate, and the diethyl ether was removed by gentle heating. In two crops, 2.2 g (92%) of pale yellow 2-(N-phenylhydroxylamino)-2-phenylethanesulfonyl fluoride (**9**) was obtained: mp 84–86° dec; ir (Nujol) 2.80 (OH), 6.22 (C=C), and 7.10, 8.30 μ (SO_2F); nmr (CCl_4) δ 3.50–6.00 (m, 3, $CHCH_2SO_2F$), and 6.70–7.50 (m, 11, aromatic and OH).

Anal. Calcd for $C_{14}H_{14}FNO_3S$: C, 56.89; H, 4.78; F, 6.44; N, 4.75; S, 10.83. Found: C, 57.03; H, 4.93; F, 6.40; N, 4.71; S, 10.64.

Reaction of 2-(N-Phenylhydroxylamino)-2-phenylethanesulfonyl Fluoride with Triethylamine.—To a solution of 0.270 g (0.000915 mol) of the sulfonyl fluoride in 50 ml of benzene was added dropwise a solution of 0.10 g (0.0010 mol) of triethylamine in 25 ml of benzene. During the course of 4 hr of stirring at room temperature, a dark oil separated from the solution. At this time, the reaction mixture was washed with 100 ml of 1% HCl and then 100 ml of H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting oil crystallized upon the addition of 2 ml of ethanol yielding 0.170 g (67%) of **2**, mp 160–160.5°, identical in all respects with an authentic sample.

Reaction of 2-Hydroxyacetanilide and β-Styrenesulfonyl Chloride in the Presence of Dilute Sodium Hydroxide.—A solution of 3.33 g (0.0165 mol) of β-styrenesulfonyl chloride and 2.48 g (0.0165 mol) of 2-hydroxyacetanilide in 36 ml of dioxane was heated to 50° as 14 ml of 10% sodium hydroxide was added dropwise. The solution was immediately poured into 200 ml of ice water giving a yellow oily solid, which was recrystallized from methanol (three times) giving 1.35 g (26%) of the N-acetylbenzoxathiazepine **4**, identical with that prepared from **2** and acetic anhydride.

Reaction of 2-Hydroxyacetanilide with β-Styrenesulfonyl Chloride in the Presence of Triethylamine.—To a solution of 1.51

(30) All melting points and boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 with tetramethylsilane as internal standard. Mass spectra were recorded with a Hitachi RMU-6A spectrometer at 7 to 15 eV. Microanalyses were performed by Dr. C. S. Yeh and associates.

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g (0.010 mol) of 2-hydroxyacetanilide and 1.01 g (0.010 mol) of triethylamine in 100 ml of benzene at 65° was added dropwise a solution of 2.03 g (0.010 mol) of β-styrenesulfonyl chloride in 40 ml of benzene. After 11 hr of stirring at 65°, 1.20 g (88%) of triethylammonium chloride was collected by filtration. The filtrate was evaporated *in vacuo* yielding an oil that was crystallized and then recrystallized from 2-propanol. 2-Acetamidophenyl β-styrenesulfonate [2.45 g (77%)] was obtained: mp 108.5–109.0°; ir (Nujol) 3.05 (NH), 5.95, 6.00 (C=O), 7.30, 8.35, 8.45, 8.50, 8.60 (SO_3), 10.20 μ (*trans* C=C); nmr ($CDCl_3$) δ 1.94 (s, 3, CH_3), 6.78–8.20 (m, 12, aromatic, olefinic and amide protons). The olefinic protons are distinguishable as doublets (J = 15 cps) at δ 6.88 and 7.52.

Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.50; H, 4.73; N, 4.41; S, 10.10; mol wt, 317. Found: C, 60.44; H, 4.79; N, 4.44; S, 10.04; mol wt, 321.

Reaction of N-Aceto-N-phenylhydroxylamine with β-Styrenesulfonyl Chloride in the Presence of Triethylamine.—To a solution of 0.60 g (0.0040 mol) of N-aceto-N-phenylhydroxylamine and 0.40 g (0.0040 mol) of triethylamine in benzene at 72° was added dropwise a solution of 0.81 g (0.0040 mol) of β-styrenesulfonyl chloride in benzene. After 18 hr of stirring at 72°, 0.48 g (88%) of triethylammonium chloride was isolated by filtration. From the filtrate was obtained 0.47 g (37%) of 2-acetamidophenyl β-styrenesulfonate, identical with that prepared directly above.

Cyclization of 2-Acetamidophenyl β-Styrenesulfonate with 10% Sodium Hydroxide.—A solution of 1.75 g (0.55 mol) of 2-acetamidophenyl β-styrenesulfonate in 15 ml of dioxane was heated to 50° as 7 ml of 10% sodium hydroxide solution was added. After 2 hr of stirring at 50°, the reaction mixture was poured into 150 ml of ice water. Filtration and drying gave 0.60 g (34%) of the N-acetylbenzoxathiazepine **4**, identical with that prepared from **2** and acetic anhydride.

Reaction of 2 with Bromine in Refluxing Carbon Tetrachloride.—A solution of 0.500 g (0.00182 mol) of **2** in 50 ml of carbon tetrachloride was heated to reflux and a solution of 0.280 g (0.00175 mol) of bromine in 50 ml of carbon tetrachloride was then added slowly. After 1 hr at reflux the reaction mixture was stirred at room temperature for 12 hr giving 0.30 g of a pale yellow solid, mp 195–196°. Recrystallization from methanol gave 4-phenyl-3H-1,2,5-benzoxathiazepine-N-oxide 2,2-dioxide (**5**): mp 170°; ir (Nujol) 6.20, 6.30 (C=C), 6.35 (C=N), 7.25, 7.30, 7.40, 7.50, 8.45, 8.55 (SO_2O), and 8.20 μ (NO); nmr ($CDCl_3$) δ 4.54 (s, 2, CH_2SO_2O), 7.35–8.30 (m, 9, aromatic).

An analytical sample was prepared by column chromatography on alumina with 3:1 hexane–benzene as eluent.

Anal. Calcd for $C_{14}H_{11}NO_4S$: C, 58.10; H, 3.81; N, 4.85; S, 11.07; mol wt, 289. Found: C, 57.89; H, 3.93; N, 4.68; S, 11.16; mol wt, 287.

Reaction of 2 with Bromine in Refluxing Chloroform.—A solution of 1.00 g (0.00364 mol) of **2** in 100 ml of chloroform was heated to reflux and a solution of 0.655 g (0.00409 mol) bromine in 50 ml of chloroform was then added dropwise. Hydrogen bromide was evolved during the addition. After being stirred at reflux for 1 hr, the bright yellow solution was washed with 100 ml of concentrated sodium bisulfite solution, dried ($MgSO_4$), decolorized, and evaporated *in vacuo*. A yellow solid resulted, which was recrystallized from methanol giving 0.77 g (59%) of 8-bromo-4,5-dihydro-4-phenyl-3H-1,2,5-benzoxathiazepine 2,2-dioxide (**6**): mp 165° (lit.[5c] mp 161–162°); ir (Nujol) 3.00, 3.05 (NH), 6.25, 6.35 (C=C), and 7.30, 7.48, 8.60 μ (SO_2O); nmr ($CDCl_3$) δ 3.30–4.20 (m, 3-CH_2SO_2O and NH), 4.62–4.77 (m, 0.5, C_6H_5CH), 4.81–4.92 (m, 0.5, C_6H_5CH), 6.60–7.27 (m, 3) and 7.40 (s, 5 aromatic).

Anal. Calcd for $C_{14}H_{12}BrNO_3S$: C, 47.50; H, 3.39; Br, 22.60; N, 4.00; S, 9.05; mol wt, 354. Found: C, 47.26; H, 3.40; Br, 22.40; N, 3.98; S, 9.13; mol wt, 354.

Reaction of 2 with 2 Mol of Bromine in Refluxing Carbon Tetrachloride.—A solution of 1.00 g (0.00364 mol) of **2** in 100 ml of carbon tetrachloride was heated to reflux and a solution of 1.310 g (0.00728 mol) of bromine in 100 ml of carbon tetrachloride was then added dropwise. An orange precipitate formed which dissolved after 12 hr at reflux giving a clear yellow solution. Evaporation *in vacuo* gave a yellow oil which crystallized upon trituration with methanol and cooling. Two recrystallizations from methanol gave 0.50 g (39%) of 8-bromo-4-phenyl-5H-1,2,5-benzoxathiazepine 2,2-dioxide (**7**): mp 165° dec; ir (Nujol) 3.00 (NH), 6.25 (C=C aromatic), 6.38 (C=C, olefin), and 7.40, 8.45, 8.52, 8.67 μ (SO_2O); nmr ($CDCl_3$) δ 6.16 (s, 1, C=C—H), 7.30–7.69 (m, 8, aromatic protons), and 7.78–8.21 (m, 1, NH).

Anal. Calcd for $C_{14}H_{10}BrNO_3S$: C, 48.00; H, 2.87; N, 3.98; Br, 22.70; S, 9.10; mol wt, 353. Found: C, 48.28; H, 2.98; Br, 22.70; S, 8.83; mol wt, 343.

Preparation of Labeled Materials.—In a typical experiment, 2.0 g of potassium nitrate, 4.0 g of ^{18}O-labeled H_2O (Bio Rad Laboratories), and 0.1 ml of concentrated nitric acid were sealed in an ampoule and heated to 70° for 40 hr.[36] The tube was then cooled and opened, and the depleted H_2O-^{18}O was distilled. This recovered H_2O-^{18}O was then allowed to exchange with a second 2.0-g portion of potassium nitrate under the same conditions.

The labeled potassium nitrate thus obtained, 3.80 g (0.038 mol), was ground to a fine powder and suspended in 30 ml of benzene (Baker Spectroscopic grade) and the benzene suspension was cooled to 5°; 2.0 g (0.015 mol) of anhydrous aluminum chloride was added portionwise during a 20-min period,[37] while an internal temperature of 5–10° was maintained. At the end of 3 hr of stirring at 5°, 10 ml of H_2O was added. The benzene layer was separated and the aqueous layer was extracted three times with 10 ml of benzene. The combined benzene extracts were evaporated *in vacuo* and the residue was steam distilled yielding 1.5 g of nitrobenzene-^{18}O (32% based on potassium nitrate).

Following this method, from H_2O-1.6%^{18}O, nitrobenzene-1.2%^{18}O was prepared; from H_2O-10%^{18}O, nitrobenzene-5.7%^{18}O was prepared. The nitrobenzene was reduced to N-phenylhydroxylamine by known methods.[38] The nitrone was prepared as described above.

Registry No.—**4**, 16261-61-3; **5**, 20647-18-1; **6**, 16261-57-7; **7**, 20647-20-5; **9**, 20647-23-8; 4,5-dihydro-4-phenyl-3,3,5-trimethyl-3H-1,2,5-benzoxathiazepine 2,2-dioxide, 20647-22-7; 2-acetamidophenyl β-styrenesulfonate, 20647-21-6.

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Base-Induced α Nitration of Sulfones

W. E. TRUCE, T. C. KLINGLER, J. E. PAAR, H. FEUER, AND D. K. WU

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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Sulfones are converted into their α-nitro derivatives *via* displacement by sulfone-stabilized carbanions on alkyl nitrates. The α-nitro sulfones are readily converted into the corresponding α-nitro-α-halo sulfones by sequential treatment with base and halogen or by treatment with N-halosuccinimides. Conversion of α-nitro-α-bromobutyl butyl sulfone with potassium amide in liquid ammonia into an octenesulfonamide constitutes a novel extension of the Ramberg–Bäcklund reaction.

In an extension of our studies of the chemistry and synthetic utility of sulfur-stabilized carbanions[1] and of the alkyl nitrate nitration of active methylene compounds,[2] we have found base-induced nitrations with alkyl nitrates to be a useful method for the preparation of α-nitro sulfones.

Base-catalyzed nitration of active methylene groups with alkyl nitrates has previously afforded a synthetic route to simple α-nitronitriles, ketones, and amides.[2,3] Recently, this method has been utilized for the preparation of α-nitrosulfonamides.[1d,4]

The first direct synthesis of an α-nitro sulfone involved the displacement by sodium benzenesulfinate on chloronitromethane to yield nitromethyl phenyl sulfone.[5] Nitration of trissulfonylmethanes was effected by Backer[6] with the use of concentrated nitric and sulfuric acids. A third synthetic approach to α-nitro sulfones involving decarboxylative nitration of β-keto sulfides with alkyl nitrates, followed by oxidation of the crude α-nitro sulfide with acidic hydrogen peroxide, has been reported.[7]

The nitration of sulfone-stabilized carbanions (eq 1)

$$RCH_2SO_2R' \xrightarrow[2.\ R''ONO_2]{1.\ \text{base}} [RC(NO_2)SO_2R']^- \qquad (1)$$

was found to be influenced by (a) the strength of the base used for carbanion formation, (b) the relative molar ratios of reactants, and (c) the nitration time. Benzylic sulfones were found to undergo nitration in good to excellent yield using the potassium *t*-butoxide–tetrahydrofuran (THF) base–solvent system (see Table I). Reaction periods as noted in the Experimental Section have been optimized. Shorter reaction times resulted in reduced yields. In all cases, material balances were excellent (90–99%). Use of stronger base–solvent systems, *i.e.*, *n*-butyllithium–THF, for the anion formation with benzylic sulfones greatly diminished the yield of product (Table I).[8] Tetramethylethylenediamine (TMEDA) in conjunction with *n*-butyllithium reduced yields even more drastically.

The nitration of alkyl sulfones by treatment with potassium *t*-butoxide in THF produced only low yields of nitration products. However, yields were substantially increased when nitration was performed with the potassium amide–liquid ammonia system[2e] (Table II). The maximum yields were obtained when 3 equiv of potassium amide to 4.5 equiv of alkyl nitrate were employed. Acidification with ammonium chlo-

TABLE I

NITRATIONS OF SULFONES WITH ALKYL NITRATES

Starting material	Product	Yield, %
$C_6H_5CH_2SO_2C_6H_5$[a]	$C_6H_5CH(NO_2)SO_2C_6H_5$ (1)	81
$C_6H_5CH_2SO_2C_6H_5$[b]	$C_6H_5CH(NO_2)SO_2C_6H_5$	36
p-$CH_3C_6H_4SO_2CH_2C_6H_5$[a]	p-$CH_3C_6H_4SO_2CH(NO_2)C_6H_5$ (2)	79
$(C_6H_5CH_2)_2SO_2$[a]	$C_6H_5CH_2SO_2CH(NO_2)C_6H_5$ (3)	82
$(C_6H_5CH_2)_2SO_2$[b]	$C_6H_5CH_2SO_2CH(NO_2)C_6H_5$	40
$(C_6H_5CH_2)_2SO_2$[c]	$C_6H_5CH_2SO_2CH(NO_2)C_6H_5$	9
$C_6H_5CH_2SO_2C_2H_5$[a]	$C_6H_5CH(NO_2)SO_2C_2H_5$ (4)	42
$(n$-$C_3H_7)_2SO_2$[d]	n-$C_3H_7SO_2CH(NO_2)CH_2CH_3$[e] (5)	39
$(n$-$C_4H_9)_2SO_2$[d]	n-$C_4H_9SO_2CH(NO_2)CH_2CH_2CH_3$ (6)	79
$(n$-$C_4H_9)_2SO_2$[a]	n-$C_4H_9SO_2CH(NO_2)CH_2CH_2CH_3$	33
$(CH_3)_2SO_2$[d]	$CH_3SO_2CH_2NO_2$ (7)	37
n-$C_3H_7SO_2C_6H_5$[a]	$CH_3CH_2CH(NO_2)SO_2C_6H_5$ (8)	8
$CH_3SO_2C_6H_5$[b]	$NO_2CH_2SO_2C_6H_5$ (9)	22
p-$CH_3C_6H_4SO_2CH(CH_3)_2$[b]	p-$CH_3C_6H_4SO_2C(CH_3)_2NO_2$ (10)	19
$CH_2(CH_2)_3SO_2CH_2$[d]	$CH_2(CH_2)_3SO_2CHNO_2$ (11)	17

[a] KO-*t*-Bu–THF. [b] *n*-BuLi–THF. [c] *n*-BuLi–TMEDA. [d] K-NH_2–NH_3. [e] Nmr ($CDCl_3$) δ 1.13 (t, 6, CH_3), 1.5–2.6 (m, 4, CH_2CH_3), 2.8–3.4 (m, 2, CH_2SO_2), and 5.5 (q, 1, $HCNO_2SO_2$); ir (Nujol) 1577 (NO_2), 1351–1333 and 1153 cm^{-1} (SO_2); calcd mol wt, 195.2; found mol wt, 195.7; however, elemental analysis indicated that impurities were present.

TABLE II

NITRATION OF *n*-BUTYL SULFONE WITH AMYL NITRATE (POTASSIUM AMIDE–LIQUID AMMONIA)

KNH_2, mol	Time of anion formation, hr	$AmONO_2$ mol	Acidifying agent	Yield, %	Recovered sulfone
0.11	0.5	0.15	CH_3CO_2H	41.8	35.0[a]
0.11	12.0	0.15	CH_3CO_2H	39.4	35.1[a]
0.2	2.0	0.3	CH_3CO_2H	58.7[b]	20.7[a]
0.2	2.0	0.3	NH_4Cl(s)	65.0[b]	23.2[b,c]
0.3	2.0	0.45	NH_4Cl(s)	78.8[b]	12.2[b,c]
0.4	2.0	0.6	NH_4Cl	77.3[b]	2.1

[a] The recovered sulfone was obtained by recrystallization from an ether–petroleum ether mixture. [b] Average value of two experiments. [c] The sulfone was recovered by distillation *in vacuo*.

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ride, rather than glacial acetic acid, was found also to give higher yields. Excess alkyl nitrate was necessary to prevent loss of product by destruction of the alkyl nitrate by the base[2e] (eq 2). When dimethyl sulfone

$$RONO_2 + KNH_2 \longrightarrow K^+OR^- + O_2NNH_2 \qquad (2)$$

was subjected to the same nitration conditions potassium amide–liquid ammonia, followed by acidification with ammonium chloride or glacial acetic acid, only the potassium salt, **12**, of nitromethyl methyl sulfone (**7**) was obtained. Careful acidification of **12** with dry hydrogen chloride in ether at −5° produced a 37% yield of **7** (eq 3).

$$CH_3SO_2CH_3 \xrightarrow[\text{3. } NH_4Cl \text{ or } HOAc]{\text{1. } KNH_2 \text{ 2. } AmONO_2} \underset{\mathbf{12}}{[CH_3SO_2CHNO_2]^-K^+} \xrightarrow[\text{ether, } -5^\circ]{HCl} \underset{\mathbf{7}}{CH_3SO_2CH_2NO_2} \qquad (3)$$

Halogenation of α-nitro sulfones proceeded in excellent yields (Table III). Treatment of a nitro sulfone with sodium alkoxide followed by addition of bromine in carbon tetrachloride at 0° afforded maximum yields of products (eq 4). Bromination of **12** yielded the dibromo rather than the monobromo product (eq 5).

TABLE III
HALOGENATION OF α-NITRO SULFONES

Product	Halogenating agent	Yield, %
$C_6H_5C(NO_2)(Br)SO_2C_6H_5$	Br_2–CCl_4	97
$C_6H_5C(NO_2)(Br)SO_2CH_2C_6H_5$	Br_2–THF	82
$C_6H_5C(NO_2)(Br)SO_2CH_2C_6H_5$	NBS	80
$C_6H_5C(NO_2)(Cl)SO_2CH_2C_6H_5$	NCS	73
n-$C_4H_9SO_2C(NO_2)(Br)(CH_2)_2CH_3$	Br_2–CCl_4	86
$CH_3SO_2CBr_2NO_2$	Br_2–CCl_4	32

$$RCH(NO_2)SO_2R' \xrightarrow[\text{2. } Br_2\text{–}CCl_4]{\text{1. } R''O^-} RC(NO_2)(Br)SO_2R' \qquad (4)$$

$$CH_3SO_2CH_3 \xrightarrow[\text{2. } AmONO_2]{\text{1. } KNH_2\text{–}NH_3} \xrightarrow[CCl_4]{Br_2} CH_3SO_2CBr_2NO_2 \qquad (5)$$

Halogenation of α-nitrobenzylic sulfones was readily carried out with N-halosuccinimides in refluxing carbon tetrachloride.

Recently the Ramberg–Bäcklund rearrangement of α-halo sulfones has received considerable attention.[9] Treatment of α-nitro-α-bromo-n-butyl butyl sulfone with potassium amide in liquid ammonia to yield 4-octene-4-sulfonamide probably proceeded through an analogous pathway (eq 6).

$$C_3H_7C(NO_2)(Br)SO_2CH_2C_3H_7 \xrightarrow[NH_3\,(l)]{KNH_2} C_3H_7CH{=}C(SO_2NH_2)C_3H_7 \qquad (6)$$

Experimental Section[10]

Reagents.—n-Butyllithium was obtained as a 1.6 M solution in hexane from Foote Mineral Corp. Potassium t-butoxide was purchased from MSA Corp and purified by sublimation. Reagent grade THF was distilled from lithium aluminum hydride prior to use. Ethyl nitrate was purchased from Eastman Organic Chemicals and amyl nitrate (a mixture of n-amyl and isoamyl nitrates) was graciously donated by Ethyl Corp. The sulfones were either obtained commercially or prepared by oxidation of the commercially available sulfides with hydrogen peroxide and glacial acetic acid.

General Procedure for the Base-Induced Nitration of Sulfones. A.—The sulfone (0.1 mol) was dissolved in 400 ml of freshly dried THF and the system was flushed with dry nitrogen. Sublimed potassium t-butoxide (0.125 mol) was added and stirring continued at room temperature for 4 hr. After cooling to −35°, 0.15 mol of alkyl nitrate was added dropwise and stirring was continued 4 hr. Glacial acetic acid (0.2 mol) was added dropwise and the reaction mixture was allowed to warm to 25°. After the potassium acetate was filtered off, the solvent was removed *in vacuo*, the crude α-nitro sulfone was treated with 10% aqueous sodium hydroxide, and starting material was removed by filtration. Then the aqueous solution was cooled to 0° and carefully acidified with glacial acetic acid, and the α-nitro sulfone was filtered.

B.—The sulfone (0.1 mol) in 400 ml of freshly dried THF under nitrogen was cooled to −35° and 0.1 mol of n-butyllithium in hexane was added. After the mixture had stirred for 15 min, 0.125 mol of alkyl nitrate was added dropwise and stirring was continued for 4 hr. The subsequent work-up was carried out as in procedure A.

C.—In a dry 500-ml flask, flushed with nitrogen, were placed 0.3 g-atom of potassium in 250 ml of anhydrous ammonia and a small crystal of $Fe(NO_3)_3 \cdot 9H_2O$. Stirring was continued until the blue slurry had turned gray, at which time 0.1 mol of sulfone in 50 ml of dry THF was added with stirring at −33° over a 5-min period. After the mixture had stirred for 2 hr, 0.45 mol of amyl nitrate was added[11] over a period of 5 min and the reaction mixture was stirred an additional 10 min. The reaction mixture was cooled to −50° and 0.4 mol of solid ammonium chloride was slowly added. The ammonia was replaced with anhydrous ether over a 6-hr period and the solution was acidified with 0.16 mol of glacial acetic acid. The residue, after filtration and removal of solvent, was treated in the same manner as described in procedure A to obtain pure product.

α-Nitrobenzyl Phenyl Sulfone (1). **A.**—Benzyl phenyl sulfone (24 g, 0.103 mol) was treated according to procedure A with potassium t-butoxide (15 g, 0.135 mol) and ethyl nitrate (22 g,

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(10) All melting points are uncorrected. The nmr spectra were obtained using a Varian A-60 spectrophotometer. Microanalyses were performed by Dr. C. S. Yeh and staff. Molecular weights were determined with a vapor phase osmometer, Model 301A.

(11) Care must be exercised in the addition of the first few drops of alkyl nitrate to prevent violent reaction.

0.252 mol). Recrystallization from ethanol gave 22.3 g (81%) of 1: mp 137–139°; nmr ($CDCl_3$) δ 6.50 (s, 1, $HCNO_2SO_2$) and 7.1–7.8 (m, 10, aromatic H).

Anal. Calcd for $C_{13}H_{11}NSO_4$: C, 56.32; H, 4.00; N, 5.05; S, 11.54; mol wt, 277. Found: C, 56.25; H, 4.17; N, 5.04; S, 11.40; mol wt, 280.

B.—When benzyl phenyl sulfone (10 g, 0.043 mol) was treated according to procedure B with *n*-butyllithium in hexane (0.052 mol) and ethyl nitrate (6.4 g, 0.07 mol), 4.3 g (36%) of 1 was isolated.

α-Nitrobenzyl *p*-Tolyl Sulfone (2).—*p*-Tolyl benzyl sulfone (24.6 g, 0.1 mol) was treated according to procedure A with potassium *t*-butoxide (16.8 g, 0.15 mol) and ethyl nitrate (14.6 g, 0.16 mol). Recrystallization from ethanol gave 23 g (79%) of 2: mp 162–163°; nmr ($CDCl_3$) δ 2.45 (s, 3, $C_6H_4CH_3$), 6.41 (s, 1, $HCNO_2SO_2$), and 7.39 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{13}NSO_4$: C, 57.80; H, 4.47; N, 4.82; S, 11.0; mol wt, 291. Found: C, 57.66; H, 4.48; S, 11.03; mol wt, 296.

α-Nitrobenzyl Benzyl Sulfone (3). A.—Benzyl sulfone (64.64 g, 0.262 mol) was treated according to procedure A with potassium *t*-butoxide (32.6 g, 0.290 mol) and ethyl nitrate (24.7 g, 0.272 mol). Recrystallization from absolute ethanol gave 62.5 g (82%) of 3: mp 153–154°; nmr ($CDCl_3$) δ 4.6 (q, 2, SO_2CH_2), 6.2 (s, 1, $HCNO_2SO_2$), and 7.35 (m, 10, aromatic H).

B.—To a solution of *n*-butyllithium (0.048 mol) in 300 ml of dry THF under nitrogen was added TMEDA (5.57 g, 0.048 mol) dropwise at 5°. After stirring for 30 min, the solution was cooled to −20° and benzyl sulfone (10 g, 0.0423 mol) dissolved in 100 ml of THF was added dropwise. The solution was stirred for 30 min at −35° and ethyl nitrate (6.83 g, 0.075 mol) was added. After 4 hr the reaction mixture was acidified with glacial acetic acid and 3 was isolated (9%).

Anal. Calcd for $C_{14}H_{13}NSO_4$: C, 57.72; H, 4.50; N, 4.81; S, 10.98; mol wt, 291.3. Found: C, 57.55; H, 4.66; N, 4.72; S, 11.14; mol wt, 293.

α-Nitrobenzyl Ethyl Sulfone (4).—Benzyl ethyl sulfone (9.2 g, 0.05 mol) was treated according to procedure A with potassium *t*-butoxide (11.2 g, 0.1 mol) and ethyl nitrate (10.0 g, 0.11 mol). The product was purified by chromatography on a silica gel column eluting with CH_2Cl_2. Recrystallization from ether gave 4.8 g (42%) of 4: mp 50–51°; nmr ($CDCl_3$) δ 1.15 (t, 3, CH_2CH_3), 3.25 (q, 2, CH_2CH_3), 6.45 (s, 1, $HCNO_2SO_2$), and 7.45 (m, 5, aromatic H).

Anal. Calcd for $C_9H_{11}NSO_4$: C, 47.15; H, 4.84; N, 6.11; S, 13.99. Found: C, 47.35; H, 5.11; N, 6.20; S, 14.05.

1-Nitrobutyl Butyl Sulfone (6). A.—According to procedure C, *n*-butyl sulfone (17.8 g, 0.1 mol) was treated with potassium amide (0.3 mol) and amyl nitrate (59.9 g, 0.45 mol). Distillation of the product gave 17.6 g (78.8%) of 6: bp 110–112° (0.5 mm); $n^{20}D$ 1.4690–1.4700; ir (film) 2981 and 2880 (CH), 1569 (NO_2), and 1141 cm^{-1} (SO_2); nmr (CCl_4) δ 5.33 (q, 1, $HCNO_2SO_2$), 3.17 (t, 2, H_2CSO_2), 2.1–2.6 (m, 2, H_2CCHNO_2), 1.2–2.1 (m, 6, CH_2), and 0.78–1.2 (t, 6, CH_3).

Anal. Calcd for $C_8H_{17}NO_4S$: C, 43.0; H, 7.69; N, 6.28; S, 14.34. Found: C, 43.19; H, 7.67; N, 6.06; S, 14.44.

B.—By treating *n*-butyl sulfone (8.9 g, 0.05 mol) according to procedure A with potassium *t*-butoxide (8.4 g, 0.075 mol) and amyl nitrate (6.8 g, 0.05 mol), there was obtained 3.70 g (33.2%) of 6.

Nitromethyl Methyl Sulfone (7).—To a suspension of potassium amide (0.3 mol) in 250 ml of liquid ammonia, 9.4 g (0.1 mol) of methyl sulfone was slowly added at −33°, and the reaction mixture was stirred for 2 hr. Then, 59.9 g (0.45 mol) of amyl nitrate was rapidly added (5 min). Stirring was continued for 10 min more; then the ammonia was replaced by anhydrous ether at room temperature. During this time the yellow, crude potassium salt 12 precipitated. The reaction mixture was cooled to −5° and anhydrous hydrogen chloride was introduced for 2 hr. The solid material was removed by filtration, and ether and HCl were removed *in vacuo*. The remaining liquid was dissolved in 50 ml of ether and the solution was extracted with water. After the ether was removed *in vacuo*, the remaining liquid was dissolved in 25 ml of absolute ethanol. On the addition of 350 ml of petroleum ether (bp 60–70°), 5.2 g (37%) of 7 precipitated. Recrystallization from methanol followed by sublimation at −30° (0.2 mm) gave pure 7: mp 51.5–52.5°; ir (KBr) 3028–2950 (CH), 1569–1558 (NO_2), 1332 and 1178–1137 cm^{-1} (SO_2); nmr (d_6-DMSO) δ 3.39 (s, 3, O_2SCH_3) and 6.49 (s, 2, $O_2SCH_2NO_2$).

Anal. Calcd for $C_2H_5NO_4S$: C, 17.26; H, 3.62; N, 10.01; S, 23.00. Found: C, 17.48; H, 3.60; N, 9.95; S, 22.89.

1-Nitropropyl Phenyl Sulfone (8).—Phenyl *n*-propyl sulfone (27.65 g, 0.15 mol) was treated according to procedure A with potassium *t*-butoxide (22.4 g, 0.2 mol) and ethyl nitrate (20 g, 0.22 mol). Recrystallization from methanol gave an 8% yield of 8: mp 58–60°; nmr ($CDCl_3$) δ 1.05 (t, 3, CH_2CH_3), 2.3 (m, 2, CH_2), 5.4 (q, 1, SO_2CHNO_2), and 7.5–7.9 (m, 5, aromatic H).

Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.17; H, 4.84; N, 6.11; S, 13.96; mol wt, 229. Found: C, 47.16; H, 4.71; N, 5.82; S, 13.85; mol wt, 230.

1-Nitromethyl Phenyl Sulfone (9).—Phenyl methyl sulfone (5.0 g, 0.032 mol) was treated according to procedure B with *n*-butyllithium (0.035 mol) and ethyl nitrate (3.46 g, 0.038 mol). Recrystallization from 95% ethanol afforded 1.48 g (22%) of 9: mp 150–150.5° (lit.[7] mp 151°); nmr ($CDCl_3$) δ 5.82 (s, 2, CH_2) and 7.70 (m, 5, aromatic H).

(α-Nitroisopropyl) *p*-Tolyl Sulfone (10).—*p*-Tolyl isopropyl sulfone (7.93 g, 0.04 mol) was treated according to procedure B with *n*-butyllithium (0.042 mol) and ethyl nitrate (4.0 g, 0.044 mol). The nitration mixture was acidified after 5 min. Purification on a silica gel column (eluent, CH_2Cl_2) gave 1.82 g (19%) of 10: mp 110.5–111°;[12] nmr ($CDCl_3$) δ 1.98 (s, 6, *i*-$PrCH_3$), 2.50 (s, 3, $C_6H_4CH_3$), and 7.68 (m, 4, aromatic H).

Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.50; H, 5.38; N, 5.76; S, 13.20. Found: C, 49.68; H, 5.62; N, 5.80; S, 13.06.

2-Nitrotetrahydrothiopyran 1,1-Dioxide (11).—Tetrahydrothiopyran 1,1-dioxide (6.7 g, 0.05 mol) was treated according to procedure C with potassium amide (0.15 mol) and amyl nitrate (30 g, 0.225 mol) to obtain 1.6 g (17%) of 11: mp 136–137°; nmr ($CDCl_3$) δ 1.8 (m, 4, CH_2), 2.45 (m, 2, CH_2CHNO_2), 3.50 (m, 2, CH_2SO_2), and 6.20 (q, 1, $CHNO_2$).

Anal. Calcd for $C_5H_9NO_4S$: C, 33.5; H, 5.08; N, 7.81; S, 17.85. Found: C, 33.54; H, 5.03; N, 7.51; S, 17.55.

α-Bromo-α-Nitrobenzyl Phenyl Sulfone.—Sodium (0.23 g, 0.01 g-atom) was dissolved in 150 ml of absolute ethanol and 2.8 g (0.01 mol) of 1 was added. After the mixture had stirred for 7 hr at room temperature, bromine dissolved in ethanol was added dropwise until a yellow color persisted and the reaction mixture was stirred overnight. Removal of solvent, extraction with water, and recrystallization from ethanol gave 3.4 g (97%) of the brominated nitro compound, mp 90–91°.

Anal. Calcd for $C_{13}H_{10}BrNO_4S$: C, 43.87; H, 2.81; N, 3.93; S, 8.95; Br, 22.45. Found: C, 43.93; H, 3.04; N, 3.74; S, 9.07; Br, 22.78.

1-Bromo-1-nitrobutyl Butyl Sulfone.—To a suspension of sodium methoxide (1.4 g, 0.026 mol) in 100 ml of anhydrous ether, 5.8 g (0.026 mol) of 6 was slowly added at 0°. After the mixture had stirred for 3 hr, a 5% solution of bromine in carbon tetrachloride was slowly added over a 6-hr period until the bromine color persisted. The solution was concentrated and extracted with aqueous base and dilute acetic acid. Distillation yielded 6.75 g (86%) of product: bp 110–112° (0.5 mm); $n^{20}D$ 1.5002; ir (film) 2949 and 2862 (CH), 1581 (NO_2), and 1379–1290 and 1156 cm^{-1} (NO_2 and SO_2); nmr (CCl_4) δ 3.08–3.91 (m, 2, CH_2SO_2), 2.30–3.08 (m, 2, CH_2CBrNO_2), 1.28–2.30 (m, 6, CH_2), and 0.78–1.28 (t, 6, CH_3).

Anal. Calcd for $C_8H_{16}BrNO_4S$: C, 31.79; H, 5.34; Br, 26.40; N, 4.63; S, 10.60. Found: C, 31.96; H, 5.40; Br, 26.60; N, 4.44; S, 10.37.

Dibromonitromethyl Methyl Sulfone.—To the crude potassium salt 12 was added a 5% solution of bromine in carbon tetrachloride at 0° until the color of bromine persisted (6 hr). The solution was filtered and solvent was removed *in vacuo*. The residue was taken up in ether and extracted with water, the ether was removed, and the residue was recrystallized from a 1:3 ether–carbon tetrachloride mixture to yield 4.0 g (32%) of dibromonitromethyl methyl sulfone, mp 165–168°. Subliming at 80° (0.2 mm) gave the analytical sample: mp 167–168°; ir (KBr) 3030 and 2941 (CH), 1588 (NO_2), and 1343–1207 and 1156 cm^{-1} (NO_2 and SO_2); nmr ($CDCl_3$) δ 3.67 (s, 3, O_2SCH_3).

Anal. Calcd for $C_2H_3Br_2NO_4S$: C, 8.10; H, 1.02; Br, 53.85; N, 4.72; S, 10.80. Found: C, 7.89; H, 1.00; Br, 53.66; N, 4.78; S, 10.97.

α-Bromo-α-nitrobenzyl Benzyl Sulfone. A.—Under a nitrogen atmosphere at −40°, 3 (5.83 g, 0.02 mol) was added to a solution of 2.24 g (0.02 mol) of potassium *t*-butoxide in 75 ml of

(12) This experiment was performed by L. W. Christensen, Ph.D. Thesis, Purdue University, 1969.

THF. After stirring for 3.5 hr, this solution was added slowly to 2.19 ml (0.04 mol) of bromine dissolved in 100 ml of dry THF at −40°. Stirring at this temperature was continued for 4 hr and then the solution was allowed to warm to 25°. The solvent was removed *in vacuo;* the residue was taken up in 200 ml of chloroform and extracted with water. After the extract was dried ($MgSO_4$) and decolorized with charcoal, the solvent was removed. The remaining oil crystallized on standing at 0° and was recrystallized from ethanol to yield 6.01 g (81.3%) of α-bromo-α-nitrobenzyl benzyl sulfone, mp 108–109°.

B.—In 500 ml of Spectrograde carbon tetrachloride was suspended 10 g (0.0342 mol) of **3** and 13 g (0.07 mol) of N-bromosuccinimide. The suspension was refluxed under nitrogen and irradiated with a sun lamp for 14 hr. After chilling, the solution was filtered, the solvent was removed *in vacuo*, and the residue was recrystallized from ethanol to give 9.6 g (80%) of α-bromo-α-nitrobenzyl benzyl sulfone.

Anal. Calcd for $C_{14}H_{12}BrNO_4S$: C, 45.42; H, 3.27; N, 3.78; Br, 21.58; S, 8.66; mol wt, 370.2. Found: C, 45.52; H, 3.50; N, 3.68; Br, 21.70; S, 8.65; mol wt, 372.

α-Chloro-α-nitrobenzyl Benzyl Sulfone.—Compound **3** (5 g, 0.0171 mol) and N-chlorosuccinimide (4.55 g, 0.0342 mol) dissolved in 250 ml of carbon tetrachloride were refluxed and irradiated under nitrogen for 19 hr. Cooling, filtration, and removal of solvent yielded an oil. Eluting through a silica gel column with chloroform and recrystallizing from ethanol gave 4.1 g (73%) of α-chloro-α-nitrobenzyl benzyl sulfone, mp 81–82°.

Anal. Calcd for $C_{14}H_{12}ClNO_4S$: C, 51.6; H, 3.72; N, 4.30; Cl, 10.9; S, 9.85. Found: C, 51.8; H, 3.81; N, 4.38; Cl, 10.95; S, 10.09.

4-Octene-4-sulfonamide.—Stirring 9.0 g (0.03 mol) of 1-bromo-1-nitrobutyl butyl sulfone with potassium amide (0.09 mol) in 150 ml of liquid ammonia for 1 hr at −33° gave a brown solution. Solid ammonium chloride (0.1 mol) was slowly added at −50°, the ammonia was replaced by ether, and glacial acetic acid was added until the ether solution was neutral. After filtration, the ether layer was concentrated to 40 ml and extracted with two 30-ml portions of 10% aqueous potassium hydroxide. The aqueous layer was acidified with acetic acid and extracted with ether. The extract was concentrated to 30 ml and 30 ml of petroleum ether (bp 60–70°) was added. Further concentration to 40 ml and cooling gave 2.2 g (40%) of colorless crystals, mp 94.5–97°. Recrystallization from a 1:1 benzene–petroleum ether (60–70°) mixture and subsequent sublimation at 80° (0.2 mm) gave pure product: mp 97–98°; ir (KBr) 3330 and 3213 (NH_2), 2940 (CH), and 1317 and 1167 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 6.64 (t, 1, HC=C), 5.07 (s, 2, NH_2), 1.90–2.60 (m, 4, CH_2C=C), 1.17–1.90 (m, 4, CH_2), and 0.76–1.17 (t, 6, CH_3).

Anal. Calcd for $C_8H_{17}NO_2S$: C, 50.19; H, 8.96; N, 7.36; S, 16.86. Found: C, 49.98; H, 9.06; N, 7.11; S, 16.91.

Registry No.—**1**, 21272-78-6; **2**, 21272-79-7; **3**, 21272-80-0; **4**, 21272-81-1; **6**, 21272-82-2; **7**, 21272-83-3; **8**, 21272-84-4; **9**, 21272-85-5; **10**, 21272-86-6; **11**, 21272-87-7; α-bromo-α-nitrobenzyl phenyl sulfone, 21272-88-8; 1-bromo-1-nitrobutyl butyl sulfone, 21272-89-9; dibromonitromethyl methyl sulfone, 21272-90-2; α-bromo-α-nitrobenzyl benzyl sulfone, 21272-91-3; α-chloro-α-nitrobenzyl benzyl sulfone, 21272-92-4; 4-octene-4-sulfonamide, 21272-93-5.

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The Isomerization of the Xylenes Using Zeolite Catalysts

M. A. LANEWALA AND A. P. BOLTON

Union Carbide Corporation, Linde Division, Molecular Sieve Department, Tonawanda, New York 14150

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The isomerization of the xylenes, catalyzed by partially multivalent metal cation exchanged, partially decationized Type Y zeolites, is invariably accompanied by transalkylation, and the degree of isomerization is proportional to the extent of transalkylation. An equilibrium distribution of the xylenes is obtained when over 50% transalkylation has occurred in agreement with calculated values. Data from the transalkylation of the trimethylbenzenes with benzene indicated that this reaction proceeds *via* a bimolecular mechanism. Such a mechanism, involving a diphenylalkane-type transition state, is proposed for xylene isomerization and satisfactorily accounts for the observed results.

The isomerization of the xylenes has received considerable attention in the literature, and the xylenes are used as model compounds in the elucidation of reaction mechanisms for the positional isomerization of alkylaromatics. The usually accepted mechanism[1] involves the addition of a proton, furnished by an acid catalyst, to the alkylbenzene at the ring carbon holding the alkyl group, followed by a 1,2 shift of the methyl group. However, such a mechanism neglects to account for the presence of transalkylation products which are considered to be derived from side reactions. Unseren and Wolf[2] have shown that 1,2 shifts can only compete with the transalkylation reactions, and Allen, Yats, and coworkers[3,4] have shown that the product isomers derived from the isomerization of alkylaromatics can be due to both intra- and intermolecular reactions, the individual contributions being a function of the structure of the alkylaromatic. Recent work on the isomerization of the diethylbenzenes[5] and *t*-butylphenols[6] has shown that a mechanism for positional isomerization *via* transalkylation satisfactorily accounts for the occurrence of transalkylated products. The objective of this study was to follow closely the composition of the transalkylation products formed during the isomerization of xylenes with a crystalline catalyst derived from a Type Y zeolite and determine the role of transalkylation in this reaction.

Results

Initial experiments showed that the isomerization of the xylenes over a zeolite catalyst is accompanied by a transalkylation reaction. To determine the extent of

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(2) E. Unseren and A. P. Wolf, *J. Org. Chem.*, **27**, 1509 (1962).
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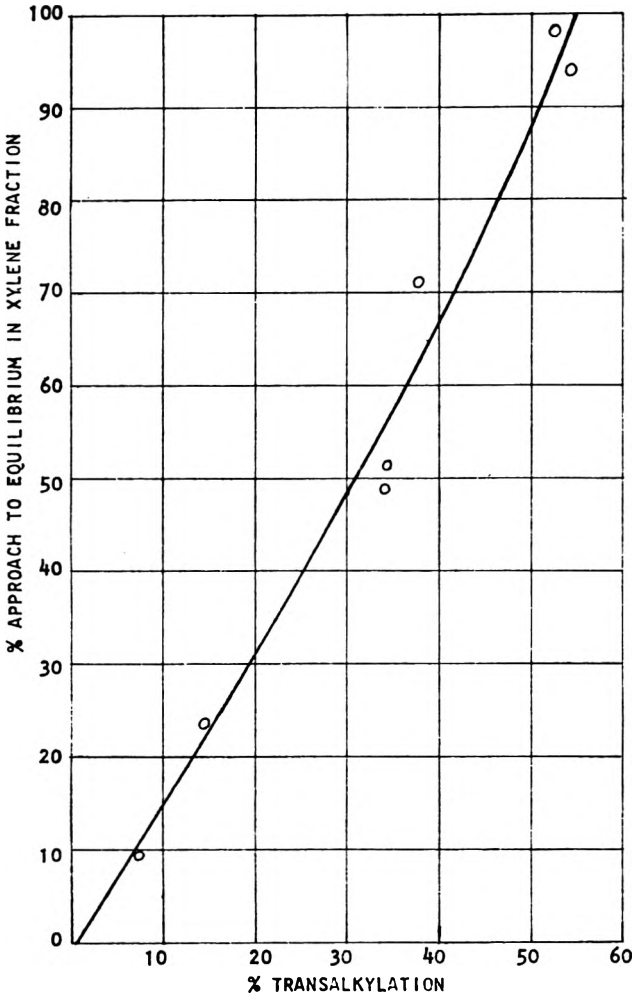


Figure 1.—Dependence of *o*- and m-xylene isomerization on extent of transalkylation (batch reactor).

transalkylation at equilibrium distribution of the xylene isomers, the batchwise isomerization of *o*-xylene was carried out at 250° for varying periods of time. The results, plotted in Figure 1, show that a good correlation is obtained between the per cent approach of *o*-xylene to its equilibrium value and the extent of transalkylation. Figure 1 also shows that over 50% transalkylation is required before *o*-xylene reaches its equilibrium value. Table I shows that the principal transalkylation products obtained from the isomerization of *o*- and *m*-xylenes at 300° are toluene and the trimethylbenzenes.

TABLE I

THE ISOMERIZATION OF *o*- AND *m*-XYLENE

Feed	Product composition, mol %, after 20 hr at 300° and 190 psig: *o*-Xylene	*m*-Xylene
Benzene	1.7	2.6
Toluene	16.3	18.9
o Xylene	9.6	9.8
m Xylene	27.8	25.6
p Xylene	9.3	9.8
123 Trimethylbenzene	2.7	2.7
124 Trimethylbenzene	22.6	20.4
135 Trimethylbenzene	9.9	9.8
	—Transalkylation, %—	
	53.2	54.8
	—Normalized distribution, %—	
o Xylene	23.5	21.6
m Xylene	53.8	56.8
p Xylene	22.7	21.6
123 Trimethylbenzene	7.5	8.1
124 Trimethylbenzene	64.3	61.3
135 Trimethylbenzene	28.2	30.6

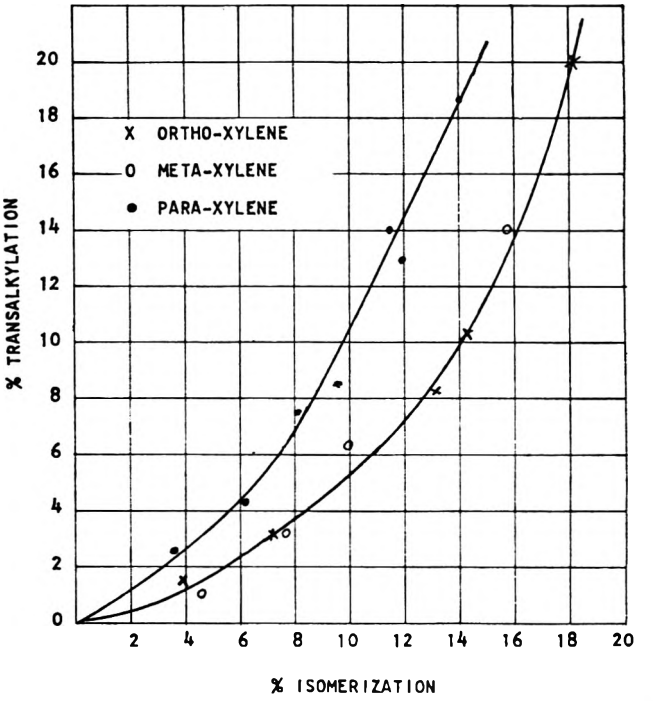


Figure 2.—Dependence of extent of isomerization upon transalkylation for the xylene isomers.

The isomerization of the three xylene isomers was also studied in a continuous flow reactor, principally to follow the composition of the xylene and the trimethylbenzene fractions at low conversions. The space velocity of the feed was varied to obtain different conversion levels. The results obtained using *o*-xylene (Table II) show that both the extent of transalkylation and the per cent approach to equilibrium in the xylene fraction increase with conversion. At low conversion, the concentration of the *p*-xylene in the xylene fraction approaches zero while the concentration of the 1,2,4 isomer in the trimethylbenzene fraction approaches 100%; the 1,3,5 isomer concentration decreases with decreasing conversion while that of the 1,2,3 isomer remains constant. The *meta* isomer (Table III) yields both *o*- and *p*-xylene at low conversions; the trisubstituted fraction is predominantly the 1,2,4 isomer, but contains a significant amount of the 1,3,5 isomer. At low conversions, the *para* isomer (Table IV) yields both the *o*- and the *m*-xylene, unlike the products from $AlCl_3$ and related catalyst systems. Both the 1,3,5 and the 1,2,3 isomers in the trisubstituted fraction approach zero concentration at low conversions, leaving the 1,2,4 isomer as the principal product.

The data from the isomerization of the xylenes under nonequilibrium conditions show a higher amount of transalkylate accompanying *p*-xylene isomerization than is found with the *ortho* and the *meta* isomers. These data are shown in Figure 2, and similar results have previously been observed with different catalyst systems.[7]

(7) R. H. Allen and L. D. Yats, *J. Amer. Chem. Soc.*, **81**, 5289 (1959).

TABLE II

THE ISOMERIZATION OF *o*-XYLENE AT 300°

% conversion	Product distribution, mol %				Isomer distribution (normalized)					
					Xylenes			Trimethylbenzenes		
	Benzene	Toluene	Xylenes	Trimethylbenzenes	*o*	*m*	*p*	1,3,5	1,2,4	1,2,3
20.0	0.8	8.8	80.0	11.2	81.8	15.8	2.3	16.3	79.7	4.0
10.2	0.4	4.6	89.8	5.4	85.6	12.5	1.9	14.6	81.7	3.7
8.2	0.3	3.7	91.8	4.3	86.8	11.9	1.3	12.0	84.0	4.0
3.2	0.1	1.5	96.8	1.6	92.8	6.7	0.5	8.0	87.7	4.3
1.5	0.1	0.5	98.5	0.8	96.1	3.7	0.2	3.5	91.5	5.0

TABLE III

THE ISOMERIZATION OF *m*-XYLENE AT 300°

% conversion	Product distribution, mol %				Isomer distribution (normalized)					
					Xylenes			Trimethylbenzenes		
	Benzene	Toluene	Xylenes	Trimethylbenzenes	*o*	*m*	*p*	1,3,5	1,2,4	1,2,3
14.0	0.7	7.3	86.0	6.1	8.9	84.1	7 0	31.1	63.1	5.8
6.7	0.1	4.2	92.3	4.1	5.5	89.9	4 6	30.1	63.0	6.9
6.3	0.1	3.4	93.7	2.9	5.3	90.3	4 4	28.2	68.6	3.2
3.2	0.0	1.8	96.8	1.3	4.0	92.3	3 4	15.8	81.2	3.0
0.9	0.0	0.5	99.1	0.4	3.4	95.4	1 2	11.0	87.5	1.5

TABLE IV

THE ISOMERIZATION OF *p*-XYLENE AT 300°

% conversion	Product distribution, mol %				Isomer distribution (normalized)					
					Xylenes			Trimethylbenzenes		
	Benzene	Toluene	Xylenes	Trimethylbenzenes	*o*	*m*	*p*	1,3,5	1,2,4	1,2,3
18.8	2.7	7.8	81.2	8.3	3.1	11.0	85.9	15.7	78.2	6.1
14.0	2.6	5.6	86.0	5.8	2.5	9.1	88.4	14.0	80.1	5.9
7.5	0.4	3.6	92.5	3.5	1.8	6.3	91.9	13.5	81.6	4.9
4.3	0.5	1.9	95.7	2.0	1.5	4.7	93.8	10.5	85.5	4.5
2.6	0.5	0.9	97.4	1.2	0.9	2.7	96.4	5.3	91.2	3.5

TABLE V

THE TRANSALKYLATION OF 1,2,3-TRIMETHYLBENZENE WITH BENZENE AT 300°

% conversion	Product distribution, mol %					Isomer distribution (normalized)					
						Xylenes			Trimethylbenzenes		
	Benzene	Toluene	Xylenes	Trimethylbenzenes	Tetramethylbenzenes	*o*	*m*	*p*	1,3,5	1,2,4	1,2,3
7.6	45.7	4.5	5.7	42.4	1.8	33.5	51.0	15.5	6.8	39.0	54.2
5.6	46.8	3.1	4.3	44.4	1.4	42.3	45.3	12.4	4.3	30.9	64.8
3.9	47.7	2.1	2.9	46.1	1.1	46.8	43.1	10.1	3.1	25.3	71.6
2.9	48.1	1.5	2.3	47.1	1.0	48.7	40.7	10.6	2.8	24.3	72.9
2.6	48.3	1.2	2.1	47.4	1.0	49.7	40.3	10.0	2.5	22.2	75.3
1.8	48.8	0.8	1.4	48.2	0.7	53.1	38.5	8.4	1.8	20.0	78.2

TABLE VI

THE TRANSALKYLATION OF 1,3,5-TRIMETHYLBENZENE WITH BENZENE AT 300°

% conversion	Product distribution, mol %				Isomer distribution (normalized)					
					Xylenes			Trimethylbenzenes		
	Benzene	Toluene	Xylenes	Trimethylbenzenes	*o*	*m*	*p*	1,3,5	1,2,4	1,2,3
27.1	29.7	21.6	25.7	22.9	22.7	55.5	21.8	42.3	52.0	5.7
15.6	39.6	12.5	13.5	34.4	22.0	56.6	21.4	63.8	33.4	2.8
6.1	46.2	4.5	5.4	43.9	23.5	59.2	17.3	75.6	22.7	1.7
2.1	47.4	2.1	2.6	47.9	22.9	60.4	16.7	84.7	14.0	1.3
1.7	48.4	1.3	2.0	48.3	25.6	61.7	12.7	87.7	11.5	0.8
1.4	49.2	1.0	1.4	48.6	26.4	62.3	11.3	90.0	9.3	0.7

Since it was the objective of this study to determine the role of transalkylation in the isomerization of the xylenes, the reactions between the three trimethylbenzene isomers and benzene were studied. Benzene was chosen in preference to toluene in order to differentiate between the xylene isomer formed by the removal of a methyl group from the trimethylbenzene and that formed by the transfer of a methyl group to toluene. These experiments were also carried out in a flow reactor using equivalent amounts of benzene and the trimethylbenzene isomer. The 1,2,3-trimethylbenzene–benzene feed yielded a xylene fraction containing a higher than equilibrium amount of the *ortho* isomer, the concentration increasing to over 50% with decreasing conversion (Table V). With the 1,3,5-trimethylbenzene–benzene feed, a xylene fraction consisting of equilibrium distribution was obtained, but the relative concentrations of the *ortho* and the *meta* isomers increased as the conversion approached zero (Table VI). The 1,2,4-trimethylbenzene–benzene feed produced an equilibrium distribution of the xylene isomers, but at low conversion levels a significant increase in the relative concentration of the *o*-xylene occurred (Table VII). This experiment was repeated substituting toluene in

TABLE VII
THE TRANSALKYLATION OF 1,2,4-TRIMETHYLBENZENE WITH BENZENE AT 300°

% conversion	Product distribution, mol %					Isomer distribution (normalized)					
						Xylenes			Trimethylbenzenes		
	Benzene	Toluene	Xylenes	Trimethylbenzenes	Tetramethylbenzenes	o	m	p	1,3,5	1,2,4	1,2,3
15.4	35.0	14.8	14.1	34.6	1.5	22.6	56.8	20.6	30.0	65.1	1.9
7.4	43.3	5.9	6.6	42.6	1.5	29.8	50.5	19.8	13.1	84.2	2.7
5.9	45.0	3.8	5.5	44.1	1.5	34.0	48.1	17.9	6.4	91.1	2.5
5.5	45.3	3.6	5.2	44.5	1.4	32.6	48.9	18.7	7.1	87.8	3.1
3.5	46.7	2.5	3.5	46.5	0.8	36.1	47.3	16.6	4.6	93.0	2.4
2.1	47.5	1.8	2.2	47.9	0.6	37.7	46.4	15.9	3.4	94.2	2.4

TABLE VIII
THE TRANSALKYLATION OF 1,2,4-TRIMETHYLBENZENE WITH TOLUENE AT 300°

% conversion	Product composition, mol %					Isomer distribution (normalized)					
						Xylenes			Trimethylbenzenes		
	Benzene	Toluene	Xylenes	Trimethylbenzenes	Tetramethylbenzenes	o	m	p	1,3,5	1,2,4	1,2,3
19.6	1.39	33.1	31.6	30.4	4.4	25.4	48.4	26.2	23.2	69.8	7.0
16.9	1.03	35.6	27.1	33.1	3.2	26.5	46.9	26.6	20.1	71.8	8.1
13.6	0.76	37.4	22.2	36.4	3.2	27.8	45.6	26.6	17.1	75.0	7.9
10.9	0.55	41.5	12.7	39.1	3.2	28.0	45.0	26.5	13.0	80.0	7.0
8.5	0.46	43.1	12.0	41.5	2.8	31.5	42.1	26.4	8.8	84.9	6.3
7.3	0.38	43.2	10.8	42.7	2.4	32.3	42.1	25.6	8.2	86.3	6.0

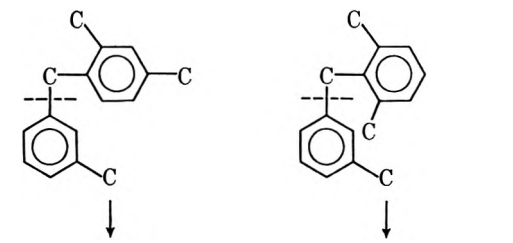
the feed for benzene (Table VIII). The results show that both the *ortho* and the *para* isomers are formed in excess of the equilibrium distribution.

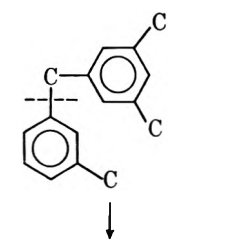
Discussion

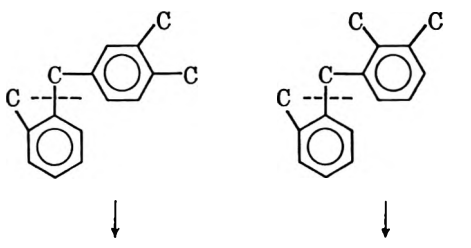
The initial results with zeolite catalysts show that xylene isomerization does not occur in the absence of transalkylation and that the more extensive the transalkylation, the greater the degree of isomerization. Since the trimethylbenzenes are present during xylene isomerization and since it has been demonstrated that under the same reaction conditions they reconvert to the xylene isomers, at least part of the isomerization must be intermolecular over a zeolite catalyst.

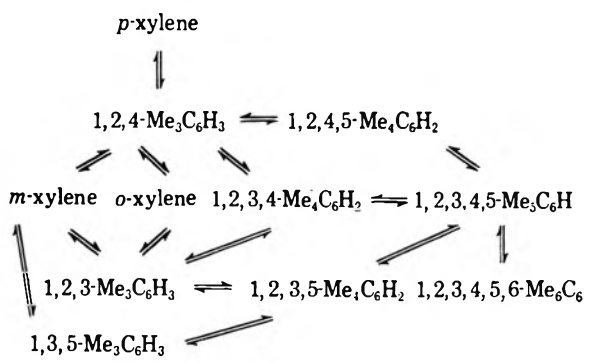
The isomerization of the xylenes may be explained by transalkylation mechanisms similar to those previously proposed;[5,8,9] these mechanisms, involving diphenylalkane-type intermediates, impose limitations on the possible isomers that may be derived from the transalkylation reactions and satisfactorily account for the observed results.

Starting with the *meta* isomer, all three trisubstituted isomers may be derived from this intermediate. *o*-Xylene produces an intermediate which can yield only the 1,2,3- and the 1,2,4-trimethylbenzene, while *p*-xylene, having four equivalent unsubstituted ring positions, can yield only the 1,2,4 isomer. Similarly, the possible isomers that may be derived from a bimolecular transalkylation reaction may be tabulated for all the polymethylsubstituted benzenes. Using these limitations imposed on the transalkylated products, the following reaction scheme may be derived.









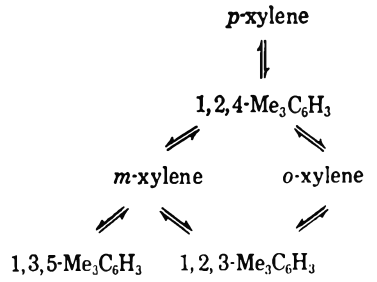
Such a scheme presents a complex interaction of various species in equilibrium. An equilibrium product distribution could be calculated if the required thermodynamic data were available for all the constituents. However, because of the lack of such data for most of

(8) H. Pines and J. T. Arrigo, *J. Amer. Chem. Soc.*, **80**, 4369 (1958).
(9) A. Streitwieser and L. Rief, *ibid.*, **86**, 1988 (1964).

TABLE IX
CALCULATED EQUILIBRIUM PRODUCT DISTRIBUTIONS FOR XYLENE–TRIMETHYLBENZENE SYSTEM

Temp, °K	% xylene in product	% transalkylate in product	Normalized product distributions: Xylene fraction o	m	p	Trimethylbenzene fraction 1,2,3	1,2,4	1,3,5
300	45.5	59.4	16.4	59.8	23.8	5.4	57.6	36.9
350	46.1	53.8	17.6	58.3	24.1	7.1	59.4	33.5
400	46.5	53.4	18.9	56.8	24.2	8.8	60.8	30.5
450	46.5	53.6	20.1	55.7	24.2	10.0	61.6	28.3
500	46.4	53.6	21.2	54.8	24.0	11.2	62.4	26.4
550	46.5	53.6	22.0	54.0	24.0	12.6	62.1	25.4
600	46.6	53.4	22.9	53.2	23.8	13.9	61.7	24.4

the polysubstituted methylbenzenes, a modified system connecting the xylenes and trimethylbenzenes may be



used to calculate equilibrium product distributions. A computer program using a method of successive elimination was used to calculate the various equilibrium constants from available thermodynamic data[10] using standard procedures.[11] The results of these calculations at various temperatures are shown in Table IX, where the extent of transalkylation and isomerization is given together with the equilibrium product distribution in both the xylene and the trimethylbenzene fractions.

The results in Table I and Figure 1 and the calculated values in Table IX correlate well and show that in order to achieve a 95% approach to equilibrium in the xylene fraction, it is necessary to have over 50% transalkylation.

The experimental results obtained from the transalkylation of the trimethylbenzenes substantiate the proposed reaction scheme. The xylene isomers derived from the 1,2,3 isomer are predominantly *ortho* and *meta*, as required. The xylene isomer distribution from the 1,3,5 isomer is higher in *o*- and *m*-xylenes than the equilibrium values. That the xylene fraction does not tend toward 100% *m*-xylene at low conversions must indicate that the rate of the transalkylation step 1,3,5 → *meta* is significantly slower than the step *meta* → 1,2,4. The data from the 1,2,4 isomer show that the *meta* and the *ortho* isomers are formed preferentially, the concentration of the latter being far above its equilibrium value. Since it is proposed that the *para* isomer is derived from the 1,2,4-trimethylbenzene, an explanation is required of its absence in the initial products from the isomerization of *o*-xylene. The greater extent of transalkylation under nonequilibrium conditions undergone by *p*-xylene compared to the *ortho* and the *meta* isomers, as shown in Figure 2, satisfactorily accounts for this anomaly. The *para* isomer would thus require a relatively higher concentration of transalkylate than the other isomers before its formation. From a system containing 100% transalkylate, 1,2,4-trimethylbenzene, and toluene (Table VIII) the *p*-xylene is formed in high concentration at low conversion. These data also show that the transfer of a methyl group from the trimethylbenzene to the toluene occurs in a kinetic and not an equilibrium distribution. The data in Tables II, III, and IV show that the 1,2,4 isomer is the trimethylbenzene formed initially from the *o*- and *p*-xylenes and that both the 1,2,4 and the 1,3,5 isomers are initially formed from *m*-xylene. Thus, a transalkylation mechanism for the isomerization of the xylenes adequately accounts for the observed data.

It has previously been observed[5] that, unlike the $AlCl_3$ and similar catalysts systems, there are no zeolite–alkylbenzene complexes which may mask reaction mechanisms. The experimental equilibrium distribution of the trimethylbenzene fraction produced from the zeolite-catalyzed isomerization of the xylenes agrees reasonably well with the calculated values. Lien and McCauley[1] have observed that the concentration of the 1,2,4 isomer in the product from the BF_3–HF catalyzed isomerization of the trimethylbenzenes is dependent upon the catalyst concentration, and that the experimental value of its equilibrium distribution only matches the calculated value after extrapolating to zero catalyst concentration. It was also demonstrated that xylene isomerization catalyzed by high catalyst concentrations results in *m*-xylene contents greatly in excess of equilibrium distribution. It is possible that the intramolecular mechanism observed for xylene isomerization with acid catalysts is a result of the enhanced stability of the *m*-xylene and 1,3,5-trimethylbenzene σ complexes[12] compared with those of the other isomers. The principal evidence for the intramolecular isomerization of the xylenes is the apparent absence of direct conversion of the *para* isomer to the *ortho* isomer or *vice versa*. However, starting with either of these isomers, the products will be the *m*-xylene σ complex and the mesitylene σ complex until a 1:1 mole ratio of these isomers to the acid catalyst is established.[1] After this step, equilibration between the acid phase and the hydrocarbon phase will take place and the formation of equilibrium distributions of the isomers will begin in the hydrocarbon phase. Further support for a transalkylation mechanism is the measurement of second-order kinetics in the $AlCl_3$-catalyzed isomerization of the xylenes in toluene solution.[13] Thus, the transalkyla-

(10) "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," American Petroleum Institute, Research Project 44, Carnegie Press, Carnegie Institute of Technology, Pittsburgh, Pa., 1953.

(11) O. A. Hougen, K. M. Watson, and R. A. Ragatz, "Chemical Process Principles," Part II, John Wiley & Sons, Inc., New York, N. Y., 1959, pp 1001–1002.

(12) S. V. Choi and H. C. Brown, *J. Amer. Chem. Soc.*, **88**, 903 (1966).

(13) H. C. Brown and H. Jungk, *ibid.*, **77**, 5579 (1955).

tion mechanism proposed for the isomerization of the xylenes using a zeolite catalyst may also be operative in an acid-catalyzed system but obscured by hydrocarbon–catalyst complex formation.

Experimental Section

The di- and trimethylbenzenes were obtained from Matheson Coleman and Bell, Norwood, Ohio, and were used without further purification. The xylenes were all over 99.8% pure and the trimethylbenzenes were all over 96.7% pure. The crystalline catalyst was synthesized from Type Y zeolite with a SiO_2/Al_2O_3 molar ratio of 5.0 by partial rare earth cation exchange (45% rare earth) and partial decationization (50%). The balance of the cations was sodium. The preparation and pertinent properties of this material have been previously reported.[5,6]

The batch experiments were carried out in a 250-ml Hartalloy Magnadash, a magnetically stirred autoclave fitted with a dip-tube for withdrawing samples. Five grams of catalyst powder was used for 0.5 mol of xylene.

The flow experiments were carried out in a high-pressure stainless steel fixed bed reactor of conventional design. For these experiments the catalyst was used in the form of $^1/_8$ in. × $^1/_8$ in. tablets. The reaction temperature and pressure were maintained at 300° and 500 psig respectively in all experiments. The hydrogen to hydrocarbon ratio was held at 5:1 while the space velocities varied between 0.5 and 20 g of feed/g of catalyst/hr.

The analyses were made on a Perkin-Elmer 880 chromatograph equipped with 150-ft [*m*-bis(*m*-phenoxyphenoxy)benzene–Apiezon L] capillary column and a flame ionization detector.

Registry No.—*o*-Xylene, 95-47-6; *m*-xylene, 108-38-3; *p*-xylene, 106-42-3; 1,2,3-trimethylbenzene, 526-73-8; 1,3,5-trimethylbenzene, 108-67-8; 1,2,4-trimethylbenzene, 95-63-6.

The Stereochemistry of Free-Radical Additions of Thiols to Substituted Cyclohexenes[1]

Norman A. LeBel, Robert F. Czaja, and Andrew DeBoer

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received April 9, 1969

Radical chain addition of hydrogen bromide to 2-chloro-4-*t*-butylcyclohexene (**1**) gave exclusively 2^c-chloro-4^c-*t*-butylcyclohexyl bromide (**8**), the product of *trans*-diaxial addition. AIBN- and uv-initiated free-radical additions of benzyl mercaptan (A), hydrogen sulfide (B), methanethiol (C), and thiolacetic acid (D) to 1- and 2-chloro- and 1- and 2-methyl-4-*t*-butylcyclohexene (**3**, **1**, **4**, and **5**, respectively) were investigated. The relative proportions of the diastereomeric adducts produced under varying reaction conditions were determined for the following reactions: A and **1**; B and **3** and **1**; C and **3** and **1**; D and **1** and **3**–**5**. In all cases, *trans*-diaxial addition predominated, and the relative proportions of products were shown to be dependent upon the addendum to olefin ratio. Conformational energy factors associated with the transition state appear to be responsible for preferential axial attack by a thiyl radical. The lower stereoselectivity of thiol additions, as contrasted to those of hydrogen bromide, are best explained in terms of a reversal of the thiyl-radical addition step. Differences in the extent of this reversibility appear to be dependent upon the relative stabilities of the thiyl radicals and the 2-thiyl-1-substituted cyclohexyl radicals, as well as on the rate of chain transfer. Bridged thiyl radical intermediates are not considered important in these additions. The concentration and temperature effects observed for free-radical additions of thiols to 1- and 2-chloro-4-*t*-butylcyclohexene compared with those observed for additions to 1- and 2-methyl-4-*t*-butylcyclohexene are of the same order of magnitude, but in opposite directions. The energy difference between the cyclohexyl-radical intermediates arising from "equatorial" thiyl-radical attack is probably responsible for the opposing trends. The extent of reversibility of the initial radical addition step is greatest for hydrogen sulfide and thiolacetic acid, less for methanethiol, and nonexistent for hydrogen bromide.

Free-radical additions of hydrogen bromide to various 1-substituted cyclohexenes have been reported to proceed exclusively in a *trans*, anti-Markovnikov manner.[2,3] On the other hand, the addition of thiol compounds was shown to be nonstereospecific;[4,5] a mixture of isomers was obtained in which the *trans*-addition product predominated. Several explanations have been offered to account for these results.[4-6] One of the factors taken into consideration was a chair–chair interconversion of the intermediate radical formed in the addition step. The importance of such chair–chair interconversions in the nonstereospecific additions of thiols can presumably be ascertained by causing the six-membered ring to prefer a single conformation.[7] To this end, we have chosen to study the stereochemistry of the radical-chain additions of hydrogen bromide to 2-chloro-4-*t*-butylcyclohexene (**1**), and of several thiols to **1**, 1-chloro-4-*t*-butylcyclohexene (**3**), 1-methyl-(**4**), and 2-methyl-4-*t*-butylcyclohexene (**5**). The light-catalyzed addition of hydrogen bromide to **3** has been reported to give predominantly, *but not exclusively*, 2^c-chloro-5^t-*t*-butylcyclohexyl bromide,[8] and a bromine-bridged, radical intermediate nicely accommodated the data.[9] Sulfur-bridging has been invoked to rationalize the high degree of stereoselectivity observed in the addition of methanethiol to 1-chloro-4-*t*-butylcyclohexene (**3**).[10] Only two adducts were identified as products of the reaction between thiolacetic acid and 1-methyl-4-*t*-butylcyclohexene (**4**); the major isomer was that resulting from diaxial addition, namely 2^c-methyl-5^t-butylcyclohexanethiol acetate.[11] In methanethiol

(1) A preliminary communication describing a portion of the work has appeared: N. A. LeBel and A. DeBoer, *J. Amer. Chem. Soc.*, **89**, 2784 (1967).

(2) H. L. Goering, P. I. Abell, and B. F. Aycock, *ibid.*, **74**, 3588 (1952).

(3) H. L. Goering and L. L. Sims, *ibid.*, **77**, 3465 (1955).

(4) H. L. Goering, D. I. Relyea, and D. W. Larsen, *ibid.*, **78**, 348 (1956).

(5) F. G. Bordwell and W. A. Hewett, *ibid.*, **79**, 3493 (1957).

(6) B. A. Bohm and P. I. Abell, *Chem. Rev.*, **62**, 599 (1962). This article contains a comprehensive review of the stereochemistry of free radical additions.

(7) *Cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 219–227.

(8) The nomenclature system adopted by Curtin and Harder, *J. Amer. Chem. Soc.*, **82**, 2357 (1960), is utilized in this paper.

(9) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 753 (1966).

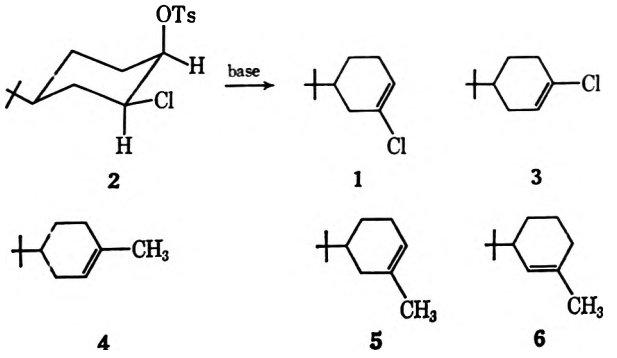
(10) P. D. Readio and P. S. Skell, *ibid.*, **31**, 759 (1966).

(11) F. G. Bordwell, P. S. Landis, and G. S. Whitney, *ibid.*, **30**, 3764 (1965).

additions to 4-*t*-butylcyclohexene and *trans*-Δ^2-octalin, the predominant adduct(s) resulted from axial attachment of the methanethiyl moiety.[12] In none of the cited recent studies[10-12] has a concentration or temperature effect upon the stereoselectivity of the thiol additions been noted, apparently contradicting the earlier observations.[4]

Starting Materials.—The vinyl chloride **1** was prepared in 85% yield by base-catalyzed elimination of 2^c-chloro-4^c-*t*-butylcyclohexyl tosylate (**2**). Both 1-chloro-4-*t*-butylcyclohexene (**3**)[9] and 1-methyl-4-*t*-butylcyclohexene (**4**)[11,13] were readily acquired. Catalytic hydrogenation of 2-methyl-4-*t*-butylphenol followed by dehydration of the mixture of cyclohexanols gave nearly equal amounts of the desired 2-methyl-4-*t*-butylcyclohexene (**5**) and the isomeric 1-methyl-3-*t*-butylcyclohexene (**6**). These compounds were separated by preparative gc. The structure of **5** was established *via* hydroboration followed by direct oxidation with chromic acid, which gave an 80:20 (*cis–trans*) mixture of the epimeric 2-methyl-4-*t*-butylcyclohexanones, as shown by gc and ir comparisons with an 85:15 mixture of authentic material.[14] The nmr spectrum of **5** very closely resembled that of **4**, and it is important to observe that the half band widths of the vinyl proton multiplets at δ 5.42 were identical in both cases (*ca.* 8.5 Hz).

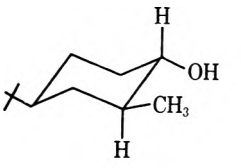
The nmr spectrum of **6** indicated the presence of one olefinic proton (δ 5.40) and one methyl group attached to a double bond (δ 1.65). The narrower half band width (4.5 Hz) of the olefinic proton multiplet agrees with the proposed structure. Hydroboration followed by oxidation gave a very low yield of a 75:25 mixture of two ketones. The low yield is most readily explained in terms of a highly hindered olefinic group in **6**.



2 **1** **3** **4** **5** **6**

Hydrogenation of **5** and **6** over palladium–charcoal catalyst in ethanol gave mixtures of the *same two* isomeric hydrocarbons, as demonstrated by gc admixture. This mixture, containing the *cis*- and *trans*-1-methyl-3-*t*-butylcyclohexanes, was different from that obtained from the reduction of **4** (which gave a mixture, 80:20, of *trans*- and *cis*-1-methyl-4-*t*-butylcyclohexane, respectively).

It is of interest to note at this point that in the dehydration of the mixture of diastereomeric alcohols to give **5** and **6**, a substantial amount of 2^t-methyl-4^t-*t*-butylcyclohexanol (**7**) was recovered unreacted. A nmr spectrum permitted assignment of the axial stereochemistry (J = 22 Hz, δ 2.95) to the hydrogen α to the hydroxyl function.[15] The methyl group was assigned the equatorial position on the basis that oxidation with aqueous chromic acid in a water–ether system gave a ketonic product which showed an identical gc retention time to that of *cis*-2-methyl-4-*t*-butylcyclohexanone. Lithium aluminum hydride reduction of 2^t-methyl-4^t-*t*-butylcyclohexyl tosylate (**7**-OTs) gave a hydrocarbon whose ir spectrum identified it as *cis*-3-methyl-*t*-butylcyclohexane, and this material was indistinguishable from the major product obtained from the catalytic hydrogenation of **5** (*vide supra*).



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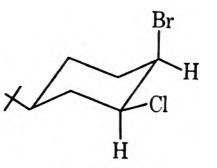

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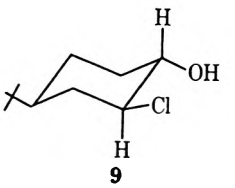


9

Radical Additions and Product Identification.—When **1** reacted with hydrogen bromide in pentane solution, using benzoyl peroxide or ultraviolet light as initiators, a single bromochloride was detected by gas chromatography. The product was identified as 2^c-chloro-4^c-*t*-butylcyclohexyl bromide (**8**), resulting from a *trans*-diaxial addition. Evidence for the structure of **8** was based on its production in the reaction of phosphorous tribromide with the *trans,trans*-chlorohydrin **9** by way of an SN2 diplacement.[16] The measured dipole moment of **8**, 3.17 ± 0.04 D, is in excellent agreement with the *cis*- as well as the *trans*-diequatorial configuration of the halogen atoms.[17] The reaction of **8** with potassium *t*-butoxide to give only **1** provides further evidence for a Br-*a*, Cl-*e* configuration, and ir bands at 680 and 736 cm^{-1} confirm this assignment.

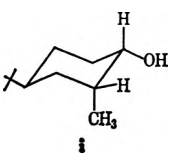
Both azobisisobutyronitrile- (AIBN) and ultraviolet light initiated additions of thiolacetic acid to **1** gave the *four* expected diastereomeric 2-chloro-4-*t*-butylcyclohexanethiol acetates **10–13**. The reactions were usually complete in 1 hr. The excess thiolacetic acid was removed by washing the reaction mixture with aqueous sodium bicarbonate solution. Control experiments in-

(12) (a) E. S. Huyser and J. R. Jeffrey, *Tetrahedron*, **21**, 3083 (1965); (b) E. S. Huyser, H. Benson, and H. J. Sinnige, *J. Org. Chem.*, **32**, 622 (1967).

(13) N. A. LeBel and G. G. Ecke, *ibid.*, **30**, 4316 (1965).

(14) N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.*, **83**, 994 (1961).

(15) The melting point of **7** has been reported as 72–73°, and that of **i** as 61–62°; F. Sipos, J. Krupicka, M. Tichy and J. Sicher, *Coll. Czech. Chem. Commun.*, **27**, 2079 (1962). The recovered alcohol, after recrystallization from pentane and sublimation at reduced pressure, had mp 61–62°, but on the basis of the chemical evidence offered it was assigned structure **7**. The reported melting points for **7** and **i** may have been inadvertently transposed, since the position of the nmr absorption band (δ 2.95) for the hydrogen α to the hydroxyl moiety in **7** agrees with that reported: E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962).



i

(16) E. L. Eliel and R. G. Haber, *J. Amer. Chem. Soc.*, **81**, 1249 (1959).

(17) P. Bender, D. L. Flowers, and H. L. Goering, *ibid.*, **77**, 3463 (1955).

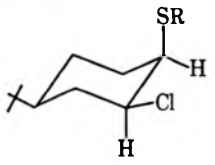
Table I

The Effect of Temperature and Acid Concentration on Product Distributions from Thiolacetic Acid Additions to 2-Chloro-4-*t*-butylcyclohexene (1).

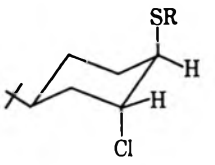
Run[a]	Molar ratio, AcSH: olefin	AcSH concn, *M*	Solvent (temp,[b] °C)	Composition, %[d] 10	11	12	13	Ratio (10 + 11): (12 + 13)	10:11	12:13
1	1:10	0.045	Hexane (5)[c]	57.9	5.1	24.8	12.2	1.7	11.4	2.0
2	1:10	0.1	Hexane (63)	47.0	7.6	30.0	15.5	1.2	6.3	1.9
3	1:1	1.0	Hexane (−60)[c]	78.7	1.6	12.8	6.9	4.1	49.2	1.9
4	1:1	0.45	Hexane (5)[c]	67.7	5.3	18.3	8.8	2.7	12.9	2.1
5	1:1	1.0	Pentane (37)	63.5	5.4	21.9	9.2	2.2	12.4	2.4
6	1:1	1.0	Hexane (63)	53.0	5.7	27.7	13.6	1.4	9.4	2.0
7	1:1	0.59	Heptane (86)	46.3	6.8	31.7	15.2	1.1	6.8	2.1
8	1:1	0.59	Heptane (106)	46.2	7.2	32.9	12.8	1.2	6.6	2.6
9	10:1	4.5	Hexane (5)[c]	74.6	5.7	13.1	6.5	4.1	13.0	2.0
10	10:1	5.9	Pentane (40)	70.8	4.6	17.4	7.3	3.1	15.5	2.4
11	10:1	5.9	Hexane (65)	60.5	7.6	20.6	11.4	2.1	8.0	1.8
12	10:1	5.9	Heptane (86)	56.8	6.9	24.9	11.3	1.8	8.2	2.2
13	10:1	5.9	Heptane (106)	53.5	6.6	28.0	11.8	1.5	8.1	2.4
14	30:1	13.5	None (5)[c]	75.8	5.4	12.0	6.8	4.3	14.0	1.8
15	30:1	10	Hexane (68)	63.7	5.1	21.5	9.6	2.2	8.2	2.0

[a] Reaction times were 1 hr. The reactions were run to 40–100% completion. Unless otherwise specified, AIBN was used as the initiator. [b] The reactions were carried out under an atmosphere of nitrogen. The temperature reported is that of the solution at reflux, except for runs 1, 4, 8, 9, 13, and 14, which were run in a sealed tube in a constant-temperature bath. Run 3 was carried out using a 2-propanol–Dry Ice bath. [c] Ultraviolet light was used as the initiator. [d] The reported percentages are normalized; the deviations observed from duplicate runs and multiple analysis were ±1.0% for 10 and 12 and ±0.5% for 11 and 13.

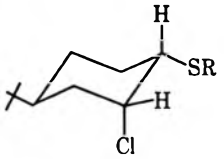
dicated that longer reaction times and the sodium bicarbonate washings did not change the relative proportions of products.



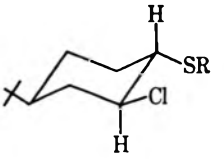
10, R = Ac
18, R = H
26, R = CH_3
34, R = CH_2Ph
38, R = Ph



11, R = Ac
19, R = H
27, R = CH_3
35, R = CH_2Ph
39, R = Ph



12, R = Ac
20, R = H
28, R = CH_3
36, R = CH_2Ph
40, R = Ph



13, R = Ac
21, R = H
29, R = CH_3
37, R = CH_2Ph
41, R = Ph

A *cis* relationship between the chloro and thiolacetoxy groups in **10** and **12** was strongly indicated by the fact that saponification and subsequent *re*acetylation of the chlorothiolacetate mixture afforded these as the sole chlorothiolacetates. The *trans* isomers **11** and **13** were expected to be converted to episulfides under these conditions, and chlorothiolacetates could not be regenerated upon reaction with acetic anhydride. When the adduct mixture was treated with a stoichiometric amount of sodium ethoxide in ethanol followed by the addition of excess methyl iodide, only two chloromethyl sulfides, **26** and **28**, were produced. These were formed in exactly the same ratio as that of **10**:**12** in the original mixture.

Additional support for the structural assignments of diastereomers **10**–**13** was obtained from the infrared and nmr spectra. Each isomer was separated by preparative gc and was examined independently. The band positions for the C–Cl stretching frequency were consistent with the respective configurations of the chloro substituents, and the observed nmr patterns unambiguously define the positions of the protons geminal to chlorine and to thiolacetoxy. For example, the distinction between **10** and **12** follows: for **12** the ir bands at 675 and 740 cm^{-1} indicated axial chlorine, and the nmr absorptions at δ 3.72 (1 H, $W_{1/2}$ = 21 Hz) and δ 4.50 (1 H, $W_{1/2}$ = 8 Hz) were consistent with an axial hydrogen α to thiolacetoxy and an equatorial hydrogen α to chlorine; the ir bands at 710 and 735 cm^{-1} in **10** are for equatorial chlorine, and the poorly resolved nmr multiplet at δ 3.78–4.58 (2 H) compared with the well-separated resonances in **12** results from upfield shift of the axial proton α to chlorine and a downfield shift of the equatorial proton α to thiolacetoxy. A 50-Hz scan of the acetyl methyl region [–$SCOCH_3$, δ 2.28–2.37] of the mixture of these chlorothiolacetates showed four distinct bands. In addition, the thiolacetate **11** was prepared by the reaction of *cis*-4-*t*-butylcyclohexene episulfide with acetyl chloride.

The radical-chain addition of thiolacetic acid to **1** was examined under varying reaction conditions, and reproducible concentration and temperature effects were observed as listed in Table I. The results of solvent dependency on the product distribution were also investigated, and these data are summarized in Table II.

The radical addition of thiolacetic acid to **3** to give the 2-chloro-5-*t*-butylcyclohexanethiol acetates **14**–**17** was also investigated in order to determine whether the position of the chlorine atom had any marked effect on the stereochemical consequences of the over-all addition process. The effects of concentration and temperature for these additions are shown in Table III.

A detailed structure proof of the chlorothiolacetates **14**–**17** was not undertaken. It was assumed that the gc elution order would be identical with that for the isomeric 2-chloro-4-*t*-butylcyclohexanethiol acetates (**10**–**13**). Saponification and subsequent methylation of the

TABLE II

PRODUCT DISTRIBUTIONS FROM THIOLACETIC ACID ADDITIONS TO 2-CHLORO-4-*t*-BUTYLCYCLOHEXENE (1) IN VARIOUS SOLVENTS

Run[a]	Molar ratio, AcSH: olefin	AcSH concn, *M*	Solvent (temp,[b] °C)	Composition, %[c] 10	11	12	13	Ratio (10 + 11): (12 + 13)	10:11	12:13
6	1:1	1.0	Hexane (63)	53.0	5.7	27.7	13.6	1.4	9.4	2.0
16	1:1	1.0	CS_2 (46)	56.4	6.6	25.0	12.0	1.7	8.6	2.1
17	1:1	1.0	Methanol (64)	49.5	7.2	27.9	15.4	1.3	6.9	1.8
18	1:1	1.0	C_6H_5Cl (67)	53.1	5.4	27.4	14.1	1.4	9.9	1.9
19	1:1	1.0	C_6H_5Cl (105)	46.4	6.7	31.5	15.3	1.1	7.1	2.1
11	10:1	5.9	Hexane (65)	60.5	7.6	20.6	11.4	2.1	8.0	1.8
20	10:1	5.9	CS_2 (45)	63.5	7.6	18.2	10.7	2.5	8.4	1.7
21	10:1	5.9	Methanol (63)	58.3	7.6	22.0	12.1	1.9	7.7	1.8
22	10:1	5.9	C_6H_5Cl (67)	64.7	5.6	19.3	10.4	2.4	11.6	1.9
23	10:1	5.9	C_6H_5Cl (98)	49.2	8.0	27.7	15.2	1.3	6.2	1.8
15	30:1	10	Hexane (68)	63.7	5.1	21.5	9.6	2.2	12.5	2.2
24	30:1	10	Methanol (66)	61.0	7.4	21.0	10.6	2.2	8.2	2.0

[a] Runs 6, 11, and 15 are from Table I and are included here for comparison. Reaction times were 1 hr. The reactions were run to 40–100% completion. AIBN was used as the initiator. [b] The reactions were carried out under an atmosphere of nitrogen. The temperature reported was that of the solution at reflux except for runs 18 and 22, which were run at an oil-bath temperature of 67°. [c] The reported percentages are normalized; the deviations observed from duplicate runs and multiple analysis were ±1.0% for 10 and 12 and ±0.5% for 11 and 13.

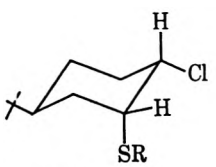
TABLE III

THE EFFECT OF TEMPERATURE AND ACID CONCENTRATION ON PRODUCT DISTRIBUTIONS FROM THIOLACETIC ACID ADDITIONS TO 1-CHLORO-4-*t*-BUTYLCYCLOHEXENE (3)

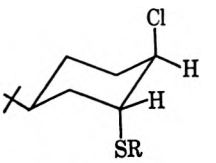
Run[a]	Molar ratio, AcSH: olefin	AcSH concn, *M*	Temp,[b] °C	Composition, %[c] 14	15	16	17	Ratio (14 + 15): (16 + 17)	14:15	16:17
25	1:1	1.0	−60	74.4	1	14.2	10.4	3.1	74	1.4
26	1:1	1.0	63	52.8	4.3	24.4	18.5	1.3	12.3	1.3
27	10:1	5.9	65	61.3	4.5	19.8	14.8	1.9	13.6	1.3

[a] Reaction times were 1 hr. Ultraviolet light was used as the initiator for run 25. AIBN was used to initiate runs 26 and 27. [b] A 2-propanol–Dry Ice bath was used to cool the reaction vessel in run 25. The temperatures reported for runs 26 and 27 were that of the solution at reflux. All runs were carried out under an atmosphere of nitrogen. Hexane was the solvent. [c] The reported percentages are normalized. The data reported for run 25 is based on one run only. Those reported for runs 26 and 27 are based on duplicate runs and multiple analysis. The observed deviations were ±1.0% for 14 and 16, and ±0.5% for 15 and 17.

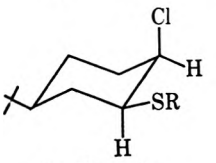
adduct mixture **14–17** gave two methyl sulfides, **30** and **32**, in the same ratio determined for **14**:**16** in the original mixture, supporting the structural assignments of the *cis* compounds.



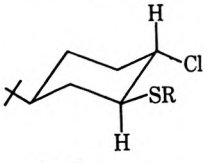
14, R = Ac
22, R = H
30, R = CH_3



15, R = Ac
23, R = H
31, R = CH_3



16, R = Ac
24, R = H
32, R = CH_3



17, R = Ac
25, R = H
33, R = CH_3

The possibility that any of the 2-chloro-5-*t*-butylcyclohexanethiol acetates **14–17** could have been formed during the addition of thiolacetic acid to 2-chloro-4-*t*-butylcyclohexene or during the analysis of the adducts **10–13** (by a molecular rearrangement process) was eliminated by gc analysis of the admixture of both series of chlorothiolacetates. Eight distinct peaks were observed.

Determination of the product distributions from the free-radical additions of hydrogen sulfide to **1** and **3**, which would give the chlorothiol adducts **18–21** and **22–25**, respectively, was complicated both by a lack of resolution and by partial decomposition on gc analysis. Therefore, these thiols were treated with acetic anhydride and a catalytic amount of pyridine; and the corresponding thiolacetates were produced in quantitative yield. Analyses of the thiolacetates permitted the quantitative results shown in Tables IV and V.

The addition of methanethiol to 1-chloro-4-*t*-butylcyclohexene (**3**) to give the mixture of adducts **30–33** has been studied by Readio and Skell, and the distribution was ascertained primarily from the results of solvolysis studies.[1c] It was found that nmr spectroscopy provided a superior method of determining the amount of each diastereomer formed. This technique was first applied to the 2-chloro-5-*t*-butylcyclohexyl methyl sulfides (**30–33**). A 50-Hz scan of the $-SCH_3$ region (δ 2.07–2.22) afforded a series of well-defined singlets, and the integrated areas beneath each band provided a measure of the relative amounts of the respective adducts. Diastereomers **30** and **32** were collected by preparative gc and their nmr spectra agreed with those already published. The diaxial chlorosulfide **31** was synthesized from *cis*-4-*t*-butylcyclohexene oxide *via* reaction with sodium thiomethoxide followed by treatment with thionyl chloride in pyridine. The nmr spectrum supported the diaxial arrangement and the infrared spec-

Table IV

Product Distributions from Thiol Additions to 2-Chloro-4-*t*-butylcyclohexene (1)

Run[a]	Temp, °C	Molar ratio	Composition, %[b]			
			Hydrogen Sulfide, R = H			
28[c]	5	12:1	**18**, 78.9	**19**, 2.2	**20**, 8.9	**21**, 10.0
			Methanethiol, R = CH_3			
33[c]	5	1:1	**26**, 77	**27**, 5	**28**, 8	**29**, 10
34[c]	5	10:1	**26**, 82	**27**, 5	**28**, 6	**29**, 7
35[d]	86	1:1	**26**, 63	**27**, 9	**28**, 15	**29**, 14
			Benzyl Mercaptan, R = CH_2Ph			
36[c]	10	1:1	**34**, 71	**35**, 10	**36**, 11	**37**, 8
37[d]	86	1:1	**34**, 61	**35**, 12	**36**, 20	**37**, 7
			Thiophenol, R = Ph			
50[e]	80	2:1	**38**, 80	**39**, 2	**40**, 14	**41**, 4

[a] Reaction times were 1 hr, except for run 50 which was allowed to proceed for 12 hr. The solvent was hexane, except in run 50 where no solvent was employed. [b] Percentages are normalized and are based on the analytical methods described in the text. [c] Uv initiation. [d] AIBN initiation. [e] Benzoyl peroxide initiation.

Table V

Product Distributions from Thiol Additions to 1-Chloro-4-*t*-butylcyclohexene (3)

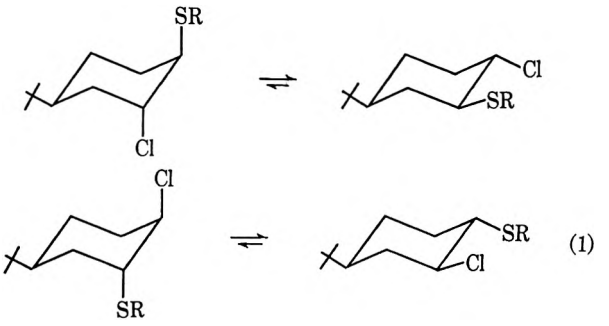
Run[a]	Temp, °C	Molar ratio	Composition, %[b]			
			Hydrogen Sulfide, R = H			
29	*ca.* −50	10:1	**22**, 71.3	**23**, 1.2	**24**, 9.3	**25**, 18.2
			Methanethiol, R = CH_3			
30[c]	−78	2.3:1	**30**, 88–91	**31**, 2.5	**32**, 2	**33**, 7–10
31	−60	*ca.* 3:1	**30**, 89	**31**, 2	**32**, 3	**33**, 6
32	10	*ca.* 3:1	**30**, 79	**31**, 4	**32**, 6	**33**, 11

[a] Reaction times were 1 hr; uv initiation was used and a nitrogen atmosphere was maintained over the solutions. [b] Percentages are normalized. [c] Data from ref 10.

trum showed a band corresponding to an axial chlorine–carbon stretching mode (685 cm^{-1}). 2-Chloro-4-*t*-butylcyclohexyl methyl sulfide (**27**) was prepared by a similar method from *trans*-4-*t*-butylcyclohexene oxide. The nmr and ir spectra again supported the assigned diaxial configuration.

Assignment of the position of the $-SCH_3$ absorption of **30**, **31**, **32**, and **27** was done by observing enhancement in the intensity of the respective nmr band upon successive addition of each component to the mixture. The position of the $-SCH_3$ resonance for the diequatorial compound **33** was based on the fact that, when the mixture of **30–33** was heated at 76° in a sealed nmr sample tube, a new band assignable to **27** appeared at the expense of **33**. The thermal equilibrium **33** ⇌ **27** is an example of the now well-established "generalized diaxial–diequatorial rearrangement" (eq 1).[18]

A similar pattern was observed in the nmr spectrum of the 2-chloro-4-*t*-butylcyclohexyl methyl sulfides **26–29** obtained from addition of methanethiol to **1**. The position of the $-SCH_3$ resonance for the two *cis* diastereomers **26** and **28** was determined from a mixture of the two sulfides obtained by saponification and methylation of the mixture of the analogous chlorothiolacetates **10–13**. The method employed for the identification of the $-SCH_3$ band of **33** was used to assign the band to **29** (*i.e.*, **29** ⇌ **31** on heating). Tables IV and V summarize the results of methanethiol additions to both 1- and 2-chloro-4-*t*-butylcyclohexene. The relative proportions reported for runs 31 and 32 were obtained by removing significant amounts of **30** by crystallization at −20° and obtaining a weight per cent of this material. Concentration of the mother liquors and nmr analysis of the remaining sulfides permitted calculation of the initial product distribution. The major *cis* isomer **34** would not crystallize, and hence it was impossible to procure any reasonable quantitative data for the addition of methanethiol to 2-chloro-4-*t*-butylcyclohexene (**1**) at −60°.



(1)

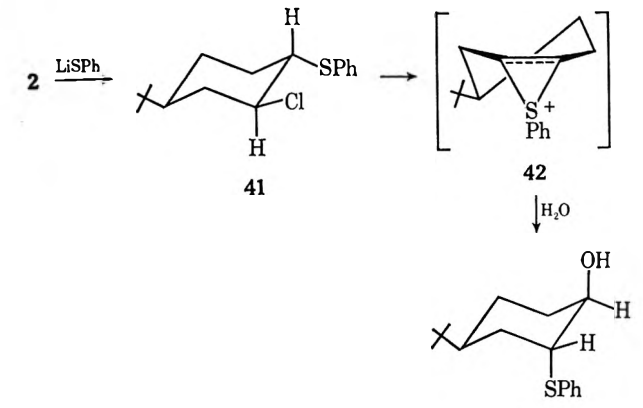
Free-radical addition of benzyl mercaptan to **1** produced the diastereomeric 2-chloro-4-*t*-butylcyclohexyl benzyl sulfides **34–37**. The relative proportion of each isomer was determined by examining the benzyl proton region (δ 3.57–3.91) of the nmr spectra. The results are also listed in Table IV. A mixture of the two *cis* isomers **34** and **36** was obtained from a chlorothiolacetate mixture (**10–13**) by saponification and subsequent treatment with benzyl iodide. The diaxial benzyl sulfide **35** was prepared by the method used for the synthesis of the diaxial methyl sulfide **27**. The nmr spectrum supported a diaxial arrangement of the chloro and benzylsulfo groups in this isomer. The position of the benzyl proton absorption of **37** (diequatorial) was determined by synthesizing 2ᵗ-chloro-5ᵗ-*t*-butylcyclohexyl benzyl sulfide. Heating this material produced a mixture containing *ca.* 70% **37**.

The benzoyl peroxide catalyzed addition of thiophenol to **1** (2:1 molar ratio) gave, after recovery of starting vinyl chloride, a 35% yield of a 1:1 adduct. The infrared spectrum of the purified adduct was very similar to that of the *cis,cis*-chlorosulfide **38** (*vide infra*). Consequently, solvolytic studies were employed for an analysis. It had been previously determined that solvolysis of pure **38** in 80% aqueous ethanol at reflux temperature for 24 hr gave no detectable chloride. Solvolysis of the adduct gave 6–7% titratable chloride, suggesting the presence of a *trans* isomer. The solvolysis product (this preparative reaction was carried out in 70% acetone) was separated from unreacted **38** by chromatography and was found to consist of a mixture of 73 ± 5% 2ᵗ-phenylsulfo-4ᶜ-*t*-butylcyclohexanol (**43**) and 27 ± 5% of 2ᵗ-phenylsulfo-5ᵗ-*t*-butylcyclohexanol by infrared analysis. The crystalline *p*-nitrobenzoate of **43** could be isolated from the mixture. The purified major adduct **38** was shown to be at least 85% homogeneous by nmr analysis—some contamination by another *cis* isomer was apparent. Similar results were obtained when the addition reaction was carried out

(18) A recent report describes such processes in steroidal systems: J. F. King, K. Abikar, D. M. Deaken, and R. G. Pews, *Can. J. Chem.*, **46**, 1 (1968).

with a 10:1 molar ratio of thiophenol to olefin, except that only 4–5% *cis* addition was detected by the solvolysis studies.

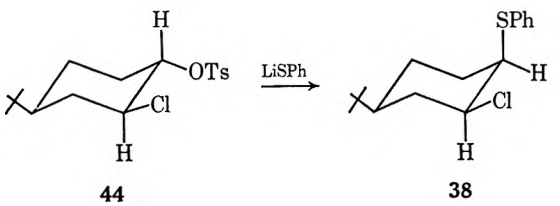
The syntheses of the thiophenol adducts **38**, **39**, and **41** were undertaken. When a suspension of lithium (or sodium) thiophenolate was stirred with the tosylate **2** in tetrahydrofuran at 40–60°, a 60% yield of 2^t-chloro-4^t-*t*-butylcyclohexylphenyl sulfide (**41**) was obtained. Substantial amounts of **1** and diphenyl disulfide were also isolated. The structure of **41** was confirmed as follows. The *trans* orientation of the chloride and sulfide groups was readily determined by the fact that **41** underwent facile solvolysis—in fact, on attempted alumina chromatography. This solvolysis, more likely than not, proceeds initially through a twist form to give the intermediate **42**. This sulfonium ion



would react with water to give 2^t-phenylsulfo-4^c-*t*-butylcyclohexanol (**43**)—the expected product of diaxial ring opening. Compound **43** was also prepared by reaction of *cis*-4-*t*-butylcyclohexene oxide with sodium thiophenolate and was desulfurized to *cis*-4-*t*-butylcyclohexanol. The nmr spectrum of **41** was consistent with its configuration assignment.

Ultimate purification of **41** is complicated by the possibility of diaxial–diequatorial rearrangement to 2^t-chloro-5^t-*t*-butylcyclohexyl phenyl sulfide. Repeated distillation of **41** did, in fact, cause increasing contamination by an isomer, determined by nmr. However, the structure of **41** was further verified by oxidation to a crystalline sulfone which underwent facile dehydrochlorination to 1-phenylsulfono-4-*t*-butylcyclohexene.

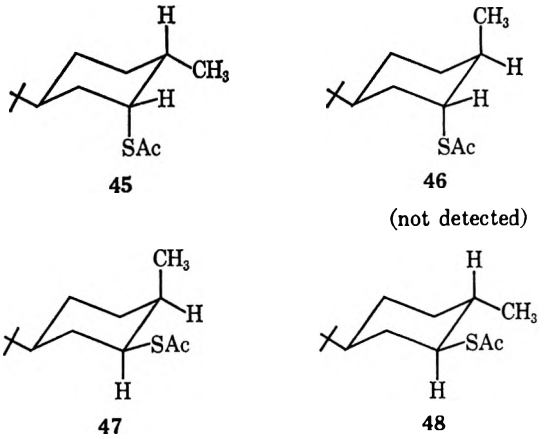
The displacement reaction with thiophenolate and the *trans,trans*-tosylate **44** led to the formation of 2^c-chloro-4^c-*t*-butylcyclohexylphenyl sulfide (**38**) in low



yield. The structure assigned to **38** is supported by the ir and nmr spectra and by its resistance to solvolysis. The chloro sulfone obtained from **38** also gave 1-phenylsulfono-4-*t*-butylcyclohexene on treatment with base.

2^t-Chloro-4^c-*t*-butylcyclohexylphenyl sulfide (**39**) was synthesized by the method analogous to that used for the preparation of **27**. The intermediate hydroxy sulfide could be desulfurized to *trans*-3-*t*-butylcyclohexanol.

The free-radical addition of thiolacetic acid to 1-methyl-4-*t*-butylcyclohexene (**4**) has been reported by Bordwell and coworkers.[11] Only two products were identified, and concentration and temperature effects were apparently not observed. The work has been repeated in this study, and *three* 2-methyl-5-*t*-butylcyclohexanethiol acetates (**45**, **47**, **48**) have been detected by



gc and nmr analysis. A 50-Hz scan of the acetyl methyl region (δ 2.20–2.30) of the nmr spectrum showed three singlets. Surprisingly, a unique concentration effect was observed, as can be seen from examination of the data in Table VI.

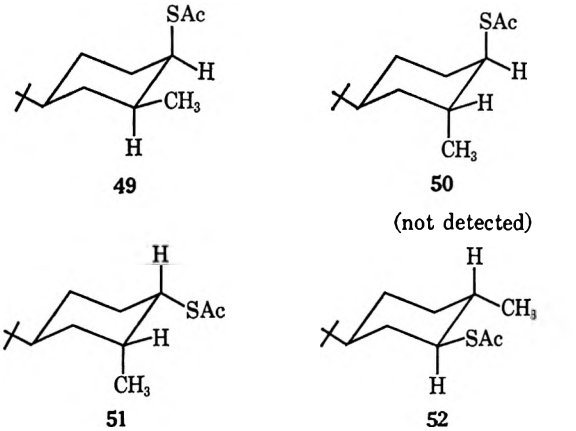
TABLE VI
PRODUCT DISTRIBUTIONS FROM THIOLACETIC ACID ADDITIONS TO 1-METHYL-4-*t*-BUTYLCYCLOHEXENE (**4**)

Run[a]	Molar ratio,[b] AcSH: olefin	Composition, %[c] 45	48	47
38	1:10	79.9	15.9	4.2
39	1:1	80.4	17.5	2.1
40	10:1	74.0	22.4	4.2
41	30:1	71.6	23.4	5.0

[a] Reaction times were 1 hr. The reactions were run in hexane at 86° in sealed tubes. AIBN was used as the initiator. [b] The olefin concentration was 0.45 *M* in all cases. [c] The reported percentages are normalized, and are the average of two runs.

Structure proof of the major products **45** and **48** was reported.[11] Structure **47** is suggested for the minor adduct (*vide infra*).

The free-radical addition of thiolacetic acid to 2 methyl-4-*t*-butylcyclohexene (**5**) was also investigated. Only three 2-methyl-4-*t*-butylcyclohexanethiol acetates (**49**, **51**, **52**) were observed by gc and nmr analysis.



A concentration effect similar to that observed for the thiolacetic acid addition to **4** was noted. The effect of reaction temperature was studied, and both sets of data are shown in Table VII.

Table VII

Product Distributions from Thiolacetic Acid Additions to 2-Methyl-4-*t*-butylcyclohexene (5)

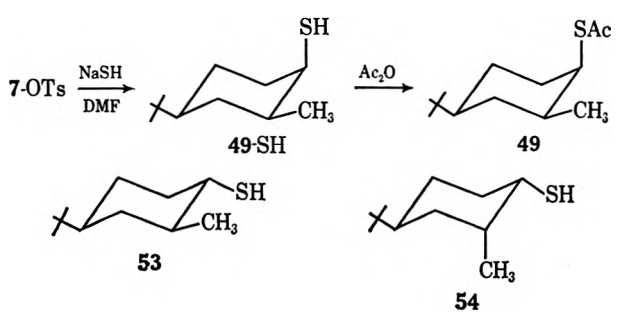
Run[a]	Temp, °C	Molar ratio,[b] AcSH: olefin	Composition, %[c] 49	52	51
42	86	1:10	84.2	14.0	1.8
43	−60	1:1	63.8	32.7	3.5
44	5	1:1	79.3	18.1	2.7
45	86	1:1	79.7	17.9	2.4
46	5	10:1	66.5	28.3	4.7
47	86	10:1	73.9	20.7	5.5
48	5	30:1	64.7	28.9	6.4
49	86	30:1	71.4	23.3	5.4

[a] Reaction times were 1 hr. Hexane was the solvent, and the reactions were run in sealed tubes. AIBN initiation was used for the runs at 86°, and ultraviolet light initiation for the remaining runs. [b] Solutions were 0.45 *M* in olefin in all cases. [c] Reported percentages are normalized, and runs 42, 45, 47, and 49 are averages of two or more reactions.

Since the amounts of *trans*-diaxial products resulting from thiolacetic acid additions to the chloro olefins **1** and **3** remained fairly constant over a wide range of thiol/olefin ratios, and since the minor product from thiolacetic acid addition to **5** showed a general tendency to be formed in increasing amounts with higher ratios of thiol:olefin, **51** was assigned the *cis* (*e*-SAc, *a*-CH_3) structure. Even though a sufficient number of reactions with thiolacetic acid and **4** were not carried out so that a similar trend for the minor product could be established, **47** was assigned the *cis* (*e*-SAc, *a*-CH_3) structure because of the similarity between the two systems. Evidence for the presence of a fourth adduct (*e.g.*, **46** and **50**) could not be found.

The minor adduct may have resulted from ionic addition of thiolacetic acid to **5**. However, examination of the literature indicated that such reactions are unusual and occur in a few special cases only if oxygen has been rigorously excluded from the reaction mixture. Attempts to promote ionic addition of thiolacetic acid to **5**, *i.e.*, addition of a radical inhibitor or addition of *p*-toluenesulfonic acid, produced small amounts of two products, presumably adducts resulting from ionic addition, in addition to the adducts **49**, **51**, and **52**. The proportion **51**:(**49** + **52**) did not increase under conditions that should promote ionic additions, which suggests that **51** is formed by a free-radical process.

An authentic sample of diastereomer **49** was prepared by a Sn2 displacement reaction of the diequatorial tosylate **7**-OTs with sodium hydrosulfide in dimethylformamide followed by acetylation of the thiol with acetic anhydride. The nmr spectrum of **49** showed the presence of an equatorial hydrogen geminal to the –SAc group ($W_{1/2}$ = 8 Hz, δ 3.83). The synthesized material showed the same gc retention time and infrared spectrum as the sample of **49** separated from the mixture by preparative gc.



The stereochemistry at the carbon atom bearing the thiolacetoxy moiety in **52** was assigned on the basis of the nmr spectrum ($W_{1/2}$ = 25 Hz, δ 2.93) of a sample obtained by preparative gc. The equatorial position of the methyl groups in both **49** and **52** was established by Raney nickel disulfurization of a mixture of **49**, **51**, and **52** (in the proportions described in run 45, Table VII). A mixture of the thiols **49**-SH, **53**, and **54** was obtained from saponification of the corresponding thiolacetates (**49**:**52**:**51** = 73.3:20.8:5.7), and these were also desulfurized. Both reductions showed a 90:10 ratio (based on gc) of *cis*- and *trans*-1-methyl-3-*t*-butylcyclohexane, respectively. Obviously the *cis* hydrocarbon could only have arisen from **49** and **52** and **49**-SH and **53**; and, therefore, the two isomers **49** and **52** *must have been present* to the extent of at least 90% in the original adduct.

The relative rates of addition of thiolacetic acid to 2-chloro- and 2-methyl-4-*t*-butylcyclohexene (**1**, **5**) were calculated on the basis of results obtained from a competition experiment. A hexane solution of **1**, **5**, and thiolacetic acid in the proportion 1:1:0.9, respectively, was irradiated at 10° for 1 hr. Analysis of the starting olefins by gc, after compensating for differences in thermal response factors, and calculation showed that **5** reacted 34 times faster than did **2**.

Discussion

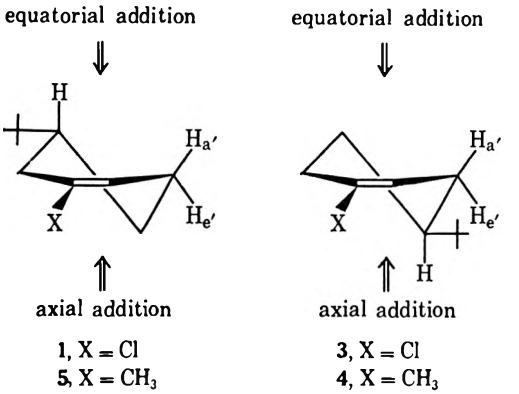
The radical-chain addition of hydrogen bromide to 2-chloro-4-*t*-butylcyclohexene (**1**) proceeds to give exclusively the product **8** from *trans*-diaxial, *anti*-Markovnikov addition. Similarly, addition to the isomeric vinyl chloride **3** gave predominantly the analogous type of product,[9] and we find no compelling reason not to accept the bridged bromoalkyl radical hypothesis[9] to account for the results in both systems. Significantly, the higher stereoselectivity for axial attachment of the addendum radical (Br· in the case of hydrogen bromide) in additions to the 2-halo-4-*t*-butylcyclohexenes as compared to the 1-halo analogs appears to be a general phenomenon, since it is also observed with thiol additions to **1** and **3**. Some subtle conformational factor is probably responsible.

As is apparent from the tabulated results, thiol concentration and temperature significantly affect the relative proportions of products formed in the additions of thiols to the four olefins used in this study. The concentration dependence is dramatically demonstrated by comparison of runs 1, 4, 9, and 14 in Table I, runs 44, 46, and 48 in Table VII, and runs 33 and 34 in Table IV.

The previous report of the dependence of the *cis*:*trans* adduct ratio upon thiolacetic acid concentration in free-radical additions to 1-chlorocyclohexene has been attributed to the effective competition between chair–chair interconversion of the intermediate radical and chain transfer.[4] It was rationalized that increasing the

thiol concentration would shorten the lifetime of the initially formed 2-axial thiyl-1-chlorocyclohexyl radical (which was assumed to undergo chain transfer to give only *cis* adduct), thereby slowing its rate of conversion into the 2-equatorial thiyl-1-chlorocyclohexyl radical (which was said to undergo chain transfer to give both *cis* and *trans* adducts).[4] *This explanation cannot be valid for a t-butylcyclohexyl system.*

An alternative explanation must be sought for the effects delineated in this work. The *t*-butyl groups in olefins **1**, **3**, **4**, and **5** should not directly interfere with the direction of approach (top or bottom) of the thiyl radical to the double bond, and exclusive *anti*-Markovnikov orientation is observed in the additions.

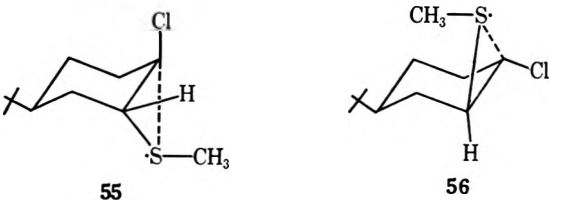


1, X = Cl
5, X = CH_3

3, X = Cl
4, X = CH_3

Over-all preference for axial orientation of the attacking thiyl group is observed in all addition reactions studied. One explanation for this prevalence for axial attack[19] by a thiyl radical is that the pseudoaxial hydrogens ($H_{a'}$) hinder the approach of the incoming group. In fact, steric approach control has been suggested as being partially responsible for the direction of thiyl-radical attack in the addition of thiolacetic acid to 1-methyl-4-*t*-butylcyclohexene.[11] However, there is a marked preference for axial addition of the thiolacetoxy radical to the Δ^5 double bonds of steroids.[20] Approach from the β side (axial attack) is generally regarded as sterically prohibitive, and thus it appears that steric hindrance is not the dominating factor in controlling the direction of radical addition to a cyclohexene.

An asymmetric sulfur-bridged radical **55** (R = CH_3) has been invoked to explain the high degree of stereoselectivity obtained in methanethiol additions to 1-chloro-4-*t*-butylcyclohexene (**3**).[10] The chloromethyl sulfide **30** (*a*-SCH_3, *e*-Cl; *trans* addition) comprised 86% of the adduct. The preponderance of axial over equatorial methylsulfo groups in the adduct was attributed to the difference in the activation energies required to produce intermediate **55** (axial thiyl-radical attack) and the bridged species **56** (equatorial thiyl-radical attack). It was suggested that *most* of the product **30** arises by direct chain-transfer with **55**. However, the presence of the three remaining 2-chloro-5-*t*-butylcyclohexyl methyl sulfides (**31**, **32**, and **33**) in the product mixture was rationalized by postulating an equilibration of the bridged-radical intermediates **55** and **56** with classical



55 **56**

open-chain radicals which, when followed by axial and equatorial chain transfer, would form a mixture of all four diastereomeric adducts **30**–**33**. These investigators also reported that no observable effect of concentration on product ratio was detected by varying the methanethiol concentration from 2.8 *M* to 14 *M*.[10]

Even if, as suggested,[10] bridged radicals are formed initially during radical additions of thiols to olefins, available evidence overwhelmingly points to the fact that such intermediates are not involved in the product-determining steps. For example, the highly stereoselective processes of *cis* additions of *p*-thiocresol to norbornene and to substituted norbornenes prohibit the intervention of a bridged species in the chain-transfer step.[21] Additionally, if a bridged radical such as **55** contributed significantly to the relative proportions of final products, then a change in the electron-donating or electron-withdrawing ability of the R group on the sulfur atom should have resulted in a noticeable effect on the stereochemical outcome of the reaction. An increasing interaction between the sulfur atom and the radical center due to the greater electron-donating capability of the R group should generate a proportionate increase in *trans*-diaxial addition.

The present work supplies data on the basis of an anticipated increasing electron-donating ability by the RS– group in the order thiolacetyl < thiyl < methanethiyl, and a bridged thiyl radical is not supported. From additions to 1-chloro-4-*t*-butylcyclohexene (**3**) at −60° (run 25 in Table III, runs 29 and 31 in Table V), the ratio of *cis* products (*a*-SR, *e*-Cl) to diaxial *trans* products is constant within experimental error (**14**:**15** = 74, **22**:**23** = 59, **30**:**31** = 45). Free radical additions of thiolacetic acid *and* of methanethiol to 2-chloro-4-*t*-butylcyclohexene at 5° (run 4 in Table I and run 33 in Table IV) also gave similar ratios of *cis* products to diaxial *trans* products (**10**:**11** = 13, and **26**:**27** = 15).

If bridged radicals are not important, other factors must be responsible for the high stereoselectivity. The marked preference for formation of *cis* product relative to *trans* product can best be explained—ignoring temporarily the high incidence of axial attack—by formation of the intermediate axial radical **57**. The steric shielding and possible dipolar repulsion provided by the axial –SR substituent located adjacent to the radical center should force the incoming thiol chain-transfer agent to approach in the direction opposite to this group. If this directive effect is superimposed on the established[11,22] preferential axial chain transfer which

(19) "Axial" and "equatorial" attack are technically misnomers. The axial or equatorial position of the thiyl radical is not known until after addition is complete. The term "parallel attack" has been suggested for approach to the cyclohexene double bond from the same side as the pseudoaxial hydrogen ($H_{a'}$). "Antiparallel attack" would then describe the approach from the other side: J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 758 (1961).

(20) R. M. Dodson, P. B. Sollman, and J. R. Deason, *J. Org. Chem.*, **30**, 2009 (1965); C. W. Shoppee, M. I. Akhtar, and R. E. Lack, *J. Chem. Soc.*, 877 (1964).

(21) A good summary is given by D. I. Davies and S. J. Cristol in "Advances in Free Radical Chemistry," Vol. I, G. H. Williams, Ed., Academic Press, Inc., New York, N. Y., 1965, Chapter 5.

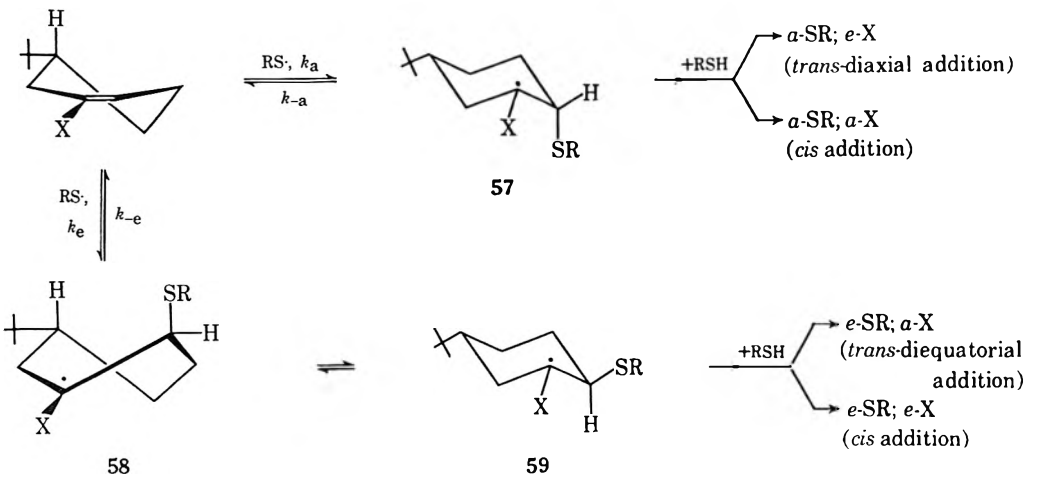
(22) F. D. Greene, C. C. Chu, and J. Walia, *J. Org. Chem.*, **29**, 1285 (1964). See also F. R. Jensen, L. H. Gale, and J. E. Rogers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968).

other cyclohexyl radicals undergo, the formation of substantial amounts of *cis* product from diaxial addition is not at all surprising.

As noted above, the ultraviolet light and AIBN-initiated additions of thiolacetic acid, hydrogen sulfide, and methanethiol to **1** and **3**–**5** led to products in which the relative proportions of adducts having the thiyl group in an axial position was greater than that with the thiyl group in an equatorial position. The initial preference is at least 9:1 and may be greater. A simple rationale is available to account for this type of "stereoelectronic control" of addition. Axial attack by a thiyl radical on 2-chloro-4-*t*-butylcyclohexene (**1**) will lead directly to a cyclohexyl radical having the chair conformation. Attack from the other side, the "equatorial direction," must give a twist-boat radical intermediate (**58**, X = Cl). The difference between the chair and twist-boat forms of cyclohexanone has been calculated as 3.205 kcal/mol.[23] If we assume that there is a similar energy difference between the two radical intermediates **57** and **58** (X = Cl), the rate of formation of **57** should be faster than that of **58**. Since the activation energy difference between chain transfer from the two intermediates is probably small, the preference for axial addition is best explained in terms of the lower energy transition state required to form the chair intermediate **57**. The magnitude of the difference also depends on the position of the transition state on the reaction coordinate. For an exothermic reaction, *e.g.*, **1** + RS· → **57**, the transition state undoubtedly more closely resembles starting material than products.

It is generally agreed that the rate-determining step in free-radical additions of thiols to alkenes is chain transfer, and that the addition of thiyl radicals to olefins is reversible. The extent of reversal is a function of both olefin and radical stability, because both are associated with the relative free energies of the intermediate states. However, elimination of thiyl radical requires a geometry in which the p orbital of the trigonal radical center is colinear with the appropriate orbital of the developing adjacent trigonal center. This requirement is met in the initially formed intermediates **57** and **58**, but, for elimination of a thiyl radical to occur from intermediate **58**, the twist conformation must be maintained. It is very likely that **58** is converted to the lower energy chair conformation **59**. The conformational energy differences between axial and equatorial –SH and $-SCH_3$ groups are approximately 0.7 kcal/mol;[24] hence it is reasonable to expect that the intermediate **59** (*e*-SR) would be more stable than **57** (*a*-SR). The energy of activation for the reversal process **59** → **1** + RS· is thus expected to be greater than that for **57** → **1** + RS·.

At low thiol to olefin ratios, reversal of the initial axial thiyl radical attack competes favorably with chain transfer. More of the adducts with equatorial SR groups will be detected because of higher conversion to intermediate **59**. Some chain transfer may occur from **58** leading to products having the skew-boat conformation, which would then undergo conformational inversion to the more stable chair forms. However, the equilibrium **58** ⇌ **59** favors **59**, and it is not unreasonable to predict that chain transfer would occur only from **59**. At high thiol to olefin ratios, the rate of the bimolecular chain transfer reaction is increased, and a higher proportion of the kinetically formed intermediate **57** will be trapped. This increase in the relative proportion of the adducts having axial –SR groups accompanying an increase in thiol concentration can only be explained on the basis that the lifetime of intermediate **57** is shortened, slowing down the competing process of elimination to olefin and thiyl radical. It is by this inhibition of reversibility of the addition step that high thiol concentration exerts its dominant control over the overall stereoselectivity of the reaction. Chain transfer from the axial thiyl radical intermediate **57** is much more highly selective in giving *trans* addition than is transfer from **59**. We are inclined to believe that the influence of low thiol concentration in reducing the *trans:cis* addition ratio *via* **57** is only of secondary importance.



One fact that has not been accounted for as yet is that additions of methanethiol are more highly stereoselective than free-radical additions of thiolacetic acid. It was pointed out earlier that the extent of reversal in the addition step is a function of both olefin stability and radical stability. In the system under study, the olefin is the same but the relative stabilities of the thiolacetoxy and methanethiyl radicals differ. The stabilities of the intermediates **57** should be the same whether R = Ac or R = CH_3. Because of the greater stability of the thiolacetoxy radical (relative to the methane-

(23) Personal communication from Professor N. L. Allinger.

(24) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 438.

thiyl radical), the reversal process, **57** → **1** + RS· (R = Ac), is more facile than if R = CH_3. This difference in the degree of reversibility of the addition step must be responsible for the observed variation in the degree of stereoselectivity. If the chain-transfer rate had been the determining factor ($CH_3COSH > CH_3SH$), then the opposite order of stereoselectivity would have been noted. The stereospecificity of hydrogen bromide additions can also be included in the over-all scheme if one considers that no reversibility of the addition step occurs because of the very high rate of chain transfer for HBr.

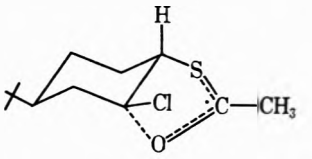
The decrease in stereoselectivity observed with an increase in temperature is also consistent with the scheme presented for additions of thiols to **1**. A higher temperature increases the probability that reaction will occur *via* the higher energy process (**1** → **58**) as well as favoring reversal from **57**. Both effects result in an over-all accumulation of products from the thermodynamically more stable intermediate **59**.

Special solvent effects could have been responsible for controlling the stereochemical outcome of the thiol-addition reactions. However, the data in Table II indicate that each of the observed trends—such as preferred direction of chain transfer from the intermediate cyclohexyl radical, thiol concentration effects, and the effect of temperature—cannot be attributed solely to the nature of the solvent, since these trends are in the same direction and are about the order of magnitude in solvents of widely different polarity.

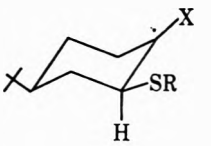
Displacement with the 2-equatorial thiyl-substituted cyclohexyl radical (**59**, X = Cl) is apparently not a very selective process. Chain transfer from **59** (chair conformation) will proceed through transition states in which the stereochemical relationship between the equatorial thiyl substituent, the chlorine group, and the chain-transfer agent HSR is approximately the same. Although the conformational free-energy difference between the developing axial and equatorial orientations of chlorine cannot be neglected, this is only 0.4 kcal/mol in the fully developed product,[24] and is not large enough to cause one transition state to be greatly favored over the other.

There is one intriguing aspect of the stereoselectivity in chain transfer from intermediate **59** (X = Cl). A rather surprising change was noted in the ratio of *trans* addition (*e*-SR, *a*-Cl) to *cis* addition (*e*-SR, *e*-Cl) on variation of the addendum from thiolacetic acid to hydrogen sulfide and methanethiol, although in none of the examples cited was the process very stereoselective. The ratio of equatorial to axial chain transfer from **59** (*e*-SR, R = Ac) during the free-radical addition of thiolacetic acid to **1** was fairly constant at 2:1 throughout the range of acid concentrations and temperatures investigated (**12**:**13** in Table I). This stereoselectivity observed in chain transfer from **59** has virtually disappeared in additions of hydrogen sulfide and methanethiol. A similar change in stereoselectivity with different thiols was noticed in free-radical additions to 1-chloro-4-*t*-butylcyclohexene (**3**) (run 26 in Table III, **16**:**17** = 1.3 for thiolacetic acid addition; run 29, **24**:**25** = 0.5 for hydrogen sulfide addition; and run 32, **23**:**33** = 0.5 for methanethiol addition in Table V).

Electrostatic repulsion or steric compression between the equatorial thiyl substituent at C-2 and the incoming transfer agent might account for the variation. Another alternative involves interaction of the equatorial thiol–acetoxy substituent with the radical center, possibly *via* a bridged intermediate such as **60**. This type of interaction is not available to thiols. Approach of the transfer agent from the bottom (axial direction) is not possible. We do not favor this type of interaction, because no significant increase in the **12**:**13** ratio is observed at high thiolacetic acid concentration or low temperatures. It may well be that other factors are involved, but these are not discernible at present.



60



61

In every case where direct comparison can be made, the ratio of axial to equatorial chain transfer is lower from intermediate **59** (X = Cl) than from the positional isomer **61**. This undoubtedly reflects the fact that, for a *t*-butylcyclohexane derivative, the 1,3-diaxial interactions of the hydrogen geminal to the *t*-butyl group are larger than those of the axial hydrogen vicinal to the *t*-butyl.

Free-radical additions of thiolacetic acid to 1- and 2-methyl-4-*t*-butylcyclohexenes (**4**, **5**) also show a preference for axial thiyl-radical attack. This preference increases from 2:1 to at least 6:1 (*cf.* runs 42 and 43 in Table VII). Reactions carried out with varying acid to olefin ratios again resulted in changes of the relative proportions of axial and equatorial thiyl-radical attack.

The differences in the stereochemistry of thiolacetic acid additions between the chloro olefins **1** and **3** and the methyl olefins **4** and **5** are striking. First of all, the concentration effect is *opposite*. Also, the amount of product with axial attachment of –SAc *increases* with increasing temperature in the methyl olefin series. Additionally, no diaxial adduct (*e.g.*, **46** or **50**) is observed with the methyl olefins, and, for the adducts with equatorial –SAc, *cis* addition producing diequatorial adduct is much more dominant with the methyl olefins **4** and **5**. These remarkable variations prompt us to propose that, for additions to the methyl-4-*t*-butylcyclohexenes, reversibility from the twist-boat radical **58**, X = CH_3 (Scheme I) is important and is inhibited by high thiolacetic acid concentrations and that chain transfer to give products with equatorial –SAc groups takes place with **58**, X = CH_3, rather than with the chair conformer **59**, X = CH_3.

As before, the kinetic addition process favors higher production of the 2-axial thiyl intermediate **57**, X = CH_3, over the twist-boat intermediate **58**, X = CH_3. However, the conformational inversion **58** ⇌ **59** no longer favors the chair form **59** when X = CH_3. There appears to be a substantial amount of bond opposition strain between the methyl group and the vicinal equatorial –SAc group in **59** (X = CH_3) that is relieved in the twist form **58**. Since the energy difference between **58** and **59**, X = CH_3, is lowered and probably favors **58**, and, since **58**, X = CH_3, is of higher energy than **57**, X = CH_3, the reverse process **58** → **5** + AcS· is facilitated. At high thiol concentration, the lifetime of **58**,

X = CH_3, is shortened and chain transfer gives greater amounts of **51** + **52**.

Although chain transfer can occur from either **58** or **59** (X = CH_3), chain transfer from the flexible form **58**, X = CH_3, is supported by the observation of an increase in the amounts of products **52** and **51** with a decrease in reaction temperature (runs 43, 44; 46, 47; 48, 49 in Table VII).

An examination of Dreiding models indicates that chain transfer from **58**, X = CH_3, *cis* to the thiol acetoxy moiety is less sterically hindered than chain transfer from the opposite direction. The transition state for equatorial chain transfer from **59**, X = CH_3, requires that the methyl group begin to assume an axial position, and, owing to the rather large conformational energy of an axial methyl substituent, the activation energy for this process will be greater than that for axial chain transfer. In any case, either **58** or **59** (X = CH_3) is predicted to give the diequatorial diastereomer **52** as the major product.

The *cis* (*e*-SAc, *a*-Cl) (12) product predominated in the chloro analogue. This reversal in the preferred direction of chain transfer with the two intermediates derived from equatorial thiolacetoxy-radical addition to 2-chloro- and 2-methyl-4-*t*-butylcyclohexene (**1** and **5**) lends support to the suggestion that the nature of the product-determining intermediates is different in each case.

All reference to geometry at the radical center has been purposely avoided in the above discussion. At low temperature and high concentration of chain-transfer agent, the 9-decalyl radicals appear to maintain a large degree of configurational or conformational integrity.[25,26] Esr measurements support a planar cyclohexyl radical.[27] Based on the above observations, there is no reason to assume that the radical intermediates are capable of configurational stability. Whether the intermediates are best represented by a sp^2-hybridized carbon atom or by a rapidly equilibrating sp^3 species, is for the moment a moot point. In the transition state of chain transfer, the carbon atom has undoubtedly acquired sp^3 character.

Conclusion

The previously reported[4] finding that the degree of stereoselectivity of free-radical thiol additions to 1-chlorocyclohexene depended on the thiol to olefin ratio has not been observed in studies of such additions to several other substituted cyclohexenes,[10-12] although in all cases investigated, the major products of the reactions resulted from *trans* addition. The studies described in this work have demonstrated that *trans*-diaxial addition predominates in free-radical additions of thiols to "rigid" cyclohexenes, and that the relative proportions of products are *indeed* dependent on the addendum to olefin ratio.

Unlike the stereospecific free-radical additions of hydrogen bromide to certain cyclic olefins,[3,9] the additions of thiols were only stereoselective. The decrease in stereoselectivity with thiols can best be explained in terms of the reversal of the thiyl-radical addition step. Differences in the extent of reversibility appear to be dependent upon the relative stabilities of the thiyl radicals and the 2-thiyl-1-substituted cyclohexyl radicals, and the rate of chain transfer. The concentration and temperature effects observed for free-radical additions of thiols to 1- and 2-chloro-4-*t*-butylcyclohexene (**3**, **1**) relative to those for 1- and 2-methyl-4-*t*-butylcyclohexene (**4**, **5**) are of the same order of magnitude but in opposite directions. The different conformations of the cyclohexyl-radical intermediates arising from equatorial thiyl-radical addition is thought to be responsible for the opposing trends. Free-radical additions with thiolacetic acid and hydrogen sulfide displayed the greatest degree of reversibility in the initial thiyl-radical addition step.

Experimental Section[28]

Materials.—Unless otherwise stated, reagents were obtained from commercial sources. The Dow Chemical Co., Midland, Mich., supplied a generous gift of 4-*t*-butylcyclohexanone. Thiolacetic acid was distilled twice. The center fraction of the second distillation was used for the free-radical additions. Methanethiol was passed through Drierite before it was condensed in the reaction vessel. Hydrogen sulfide was first passed through Drierite and phosphorus pentoxide before it was condensed. Benzyl mercaptan was used without further purification. Anhydrous magnesium sulfate was the drying agent.

1-Chloro-4-*t*-butylcyclohexene (3).—A procedure outlined by Mousseron and Jacquier[29] for the preparation of 1-chlorocyclohexene and recently reported by Readio and Skell[10] for the synthesis of **3** was used, bp 71.5–72° (4.3 mm) [lit.[10] bp 82.5–83° (7 mm)].

2-Chloro-4-*t*-butylcyclohexene (1).—A mixture of 20 g (0.06 mol) of 2^c-chloro-4^c-*t*-butylcyclohexyl tosylate (**2**)[30] and 300 ml of 5% potassium hydroxide in isopropyl alcohol was heated at 45–50° for 2 hr. The mixture was poured onto a mixture of ice and dilute hydrochloric acid, and the product was extracted with pentane. The extract was washed with 5% sodium bicarbonate solution and with water, and was dried and concentrated to give 11.0 g of crude vinyl halide, which was distilled to yield 8.5 g (85%) of 2-chloro-4-*t*-butylcyclohexene (**1**), bp 51–52° (1 mm), $n^{25}D$ 1.4802. The product gave only one peak on gc with a column containing 30% by weight of silicone 550 fluid on Chromosorb P at 182°.

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.55; H, 9.92; Cl, 20.53. Found: C, 70.02; H, 9.87; Cl, 20.15.

The ir spectrum of the vinyl chloride was characterized by bands at 1662 and 826 cm^{-1}.

1-Methyl-4-*t*-butylcyclohexene (4).—The method of LeBel and Ecke[13] was employed; the compound had bp 43–44° (4.5 mm) [lit. bp 60–62° (6 mm)].

2-Methyl-4-*t*-butylcyclohexanols.—A solution of 80 g (0.49 mol) of 2-methyl-4-*t*-butylphenol in 300 ml of glacial acetic acid was hydrogenated employing 6 g of platinum oxide catalyst. The solution was filtered, diluted with an equal volume of water, and continuously extracted with pentane for 12 hr. The pentane extract was washed with sodium bicarbonate solution until the

(25) P. D. Bartlett, R. E. Pincock, J. H. Rolston, W. G. Schindel, and L. A. Singer, *J. Amer. Chem. Soc.*, **87**, 2590 (1965).

(26) F. D. Greene and N. N. Lowry, *J. Org. Chem.*, **32**, 875 (1967).

(27) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

(28) Melting points are corrected and boiling points are uncorrected. The microanalyses were by Midwest Microlabs, Inc., Indianapolis, Ind. Perkin-Elmer grating spectrophotometers, Models 237B and 621, were used for the determination of the ir spectra. Liquids were run as films between sodium chloride plates, and solids were run in carbon disulfide in 0.1-mm sodium chloride cells. A Varian Associates A-60A spectrometer was used for the nmr spectra, deuteriochloroform or carbon tetrachloride were the solvents, and tetramethylsilane was the internal standard. F and M Gas Chromatographs, Models 775 and 810, equipped with thermal conductivity cells, were used for gc. The following gc columns were employed: column A was an 8 ft × 0.25 in. o.d. aluminum tube, packed with 15% LAC-728 on 60–80 mesh Gas-Chrom S; column B was an 8 ft × 0.375 in. o.d. aluminum tube packed with the same material as column A; columns C and D were 8 ft × 0.25 in. o.d. and 8 ft × 0.375 in. o.d. aluminum tubes, respectively, both packed with 20% E-20,000 on 60–80 mesh Gas-Chrom S; column E was an 80 × 0.75 in. o.d. stainless-steel tube packed with 20% E-20,000 on 60–80 mesh Chromosorb P. Helium was the carrier gas.

(29) M. Mousseron and R. Jacquier, *Bull. Soc. Chim. Fr.*, 648 (1950).

(30) N. A. LeBel and R. F. Czaja, *J. Org. Chem.*, **26**, 4768 (1961).

washings remained basic, and then washed twice with water. The solution was dried and concentrated to give a crude yield of 74 g. Distillation yielded a volatile forerun of 9 g, bp 28–29° (0.5 mm). Continued distillation afforded 57 g (69%), bp 58–62° (0.2 mm), of the alcohols.

Dehydration of the 2-Methyl-4-*t*-butylcyclohexanols.—To a solution of 69 g (0.41 mol) of the mixture of alcohols in 150 ml of toluene contained in a flask fitted with a Barrett water trap was added 1 g of *p*-toluenesulfonic acid. The solution was heated to reflux. When, after 2 hr at reflux, no water had collected in the trap, 1 ml of concentrated sulfuric acid was added. After 24 hr, 5.3 ml (*ca.* 70% of theory) of water had been removed. The solution was cooled to room temperature, and was washed with sodium bicarbonate solution and water. The toluene was removed by distillation at reduced pressure. Further distillation gave the following fractions: (1) 32 g, bp 95° (35 mm); (2) 20 g, bp 60° (0.5 mm). Gc analysis of fraction 1 on column C at 80° showed 3 minor and 2 major products. The major products (**5**, **6**) were present in equal proportion and comprised 90% of the product mixture. Preparative gc employing column E at 100° permitted separation of 2-methyl-4-*t*-butylcyclohexene (**5**) and 1-methyl-3-*t*-butylcyclohexene (**6**). An analytical sample of **5** had bp 82–82.5° (18 mm), n^{24}D 1.4640.

Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.72; H, 13.6.

Fraction 2 was shown to be homogeneous by gc employing column C at 160°. The material solidified on standing. Recrystallization from pentane followed by sublimation (45°, 1 mm) afforded a pure sample of 2^t-methyl-4^t-*t*-butyl-cyclohexanol (**7**), mp 61–62°.

Conversion of 2-Methyl-4-*t*-butylcyclohexene (5) to a Mixture of *cis*- and *trans*-2-Methyl-4-*t*-butylcyclohexanones.—The method of Brown and Garg[31] was used for the hydroboration and oxidation of **5**. Distillation of the crude product mixture afforded 0.2 g of product, bp 60° (oil bath, 0.5 mm). Analysis by gc (column C at 150°) showed that some starting olefin contaminated the product. Elution chromatography on a 70 × 6 mm neutral alumina column using pentane as the eluent gave an 80:20 mixture of *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanones, respectively, as shown by gc and ir spectrum comparisons with an 85:15 mixture of authentic material.[15]

Catalytic Hydrogenation of the Methyl-*t*-butylcyclohexenes.—A solution of 0.152 g (0.001 mol) of 2-methyl-4-*t*-butylcyclohexene (**5**) in 5 ml of absolute ethanol was hydrogenated employing 0.020 g of 10% palladium on carbon as the catalyst. After work-up, gc analyses on column C at 80° indicated that the isomeric *cis*- and *trans*-1-methyl-3-*t*-butylcyclohexanes were formed in 86:14 proportion, respectively. 1-Methyl-3-*t*-butylcyclohexene (**6**) was reduced and analyzed in a similar manner. Two products in a ratio 84:16 were observed. Gc and ir analysis indicated that the hydrocarbon mixtures obtained from reduction of **5** and **6** were identical. Two products in the ratio 80:20 were formed on reduction of 1-methyl-4-*t*-butylcyclohexene (**4**). The two components were assumed to be *trans*- and *cis*-1-methyl-4-*t*-butylcyclohexane, respectively. The reduction products from **4** were shown to be different from those obtained from the reduction of **5** and **6** by ir and gc analysis.

2^t-Methyl-4^t-*t*-butylcyclohexyl Tosylate (7-OTs).—The alcohol **7** (12.6 g) was converted to the tosylate by way of the usual low-temperature reaction with *p*-toluenesulfonyl chloride and pyridine.[32] After work-up, there was obtained 22 g (92%) of viscous yellow oil which solidified on standing at room temperature. The tosylate was used without further purification. Recrystallization of a sample from pentane gave white needles, mp 62.0–62.5°.

***cis*-1-Methyl-3-*t*-butylcyclohexane.**—A solution of 2.0 g (0.0062 mol) of the crude tosylate (7-OTs) in 10 ml of anhydrous ether was added drowpise to a stirred suspension of 0.470 g (0.013 mol) of lithium aluminum hydride in 25 ml of anhydrous ether over a period of 0.5 hr, while the temperature was maintained at 20–25°. The mixture was refluxed for 5 hr. After the usual work-up, distillation afforded 0.61 g (65%), bp 75° (*ca.* 20 mm), of pure *cis* hydrocarbon, n^{25}D 1.4575. That this hydrocarbon was not the *trans* isomer was shown by the infrared spectrum, which did not possess a band at 620–640 cm^{-1}.[33] Gc analysis on column C at 80° showed it to have an identical retention time as the major product from the reduction of **5**.

Free-Radical Addition of Hydrogen Bromide to 2-Chloro-4-*t*-butylcyclohexene (1).—Hydrogen bromide (anhydrous) was passed through a solution containing 0.1 g (5 mol %) of benzoyl peroxide and 1.0 g (0.006 mol) of vinyl chloride **1** in 100 ml of olefin-free pentane for 2.5 hr at room temperature. The reaction mixture was further stirred for 8 hr and hydrogen bromide was again passed in for another hour. The reaction mixture was added to crushed ice, and the aqueous layer was extracted with pentane. The pentane layer was washed with sodium bicarbonate solution and water, dried, and concentrated. The crude product (1.25–1.30 g) was analyzed by gc. A sample was shown to contain 2^c-chloro-4^c-*t*-butylcyclohexyl bromide (**8**) (80%), vinyl chloride **1** (5%), and another volatile material (15%), which was not identified. The pure bromochloride (**8**) was isolated by chromatography on alumina. Recrystallization from pentane afforded a white, crystalline solid, mp 56–57°. The ir spectrum showed bands at 680 and 736 cm^{-1}, attributed to axial bromo and equatorial chloro stretching frequencies, respectively.

Anal. Calcd for $C_{10}H_{18}BrCl$: C, 47.36; H, 7.15. Found: C, 47.25; H, 7.20.

Dipole Moment Determination.—The dielectric constants were obtained using a commercial apparatus previously described.[34] The moments were calculated by essentially the method of Halverstadt and Kumler, utilizing an IBM 650 computer. Reagent grade benzene was used as the solvent. The dielectric constants and densities of various mole fractions were measured at 25°, and the value $\mu = 3.71 \pm 0.04$ D was obtained.

The Reaction of Phosphorus Tribromide with 2^t-Chloro-4^t-*t*-butylcyclohexanol (9).—The chlorohydrin **9**[30] (4 g, 0.0021 mol) was added to an ice–salt cooled mixture of 6.0 g of phosphorus tribromide and 2 ml of pentane. The bath was allowed to warm to room temperature, and after 48 hr, water was added. The aqueous layer was extracted with pentane and the extract was washed with sodium bicarbonate solution and water and was dried. The residue after concentration (4.6 g) was chromatographed on 150 mg of Merck acid-washed alumina. The column was eluted with 650 ml of pentane and 250 ml of 10% ether–pentane. Fractions of 50 ml were collected. The pentane fractions contained 1.45 g (27%) of a colorless liquid which solidified immediately, mp 56–57°. A mixture melting point with the bromide **8** did not depress. The 10% ether–pentane fractions contained 0.5 g (16%) of starting material.

Reaction of Potassium *t*-Butoxide with 2^c-Chloro-4^c-*t*-butylcyclohexyl bromide. (8).—Potassium (*ca.* 0.2 g) was dissolved in 100 ml of dry *t*-butyl alcohol. The solution was maintained at 55° and 1.0 g of **8** was added. The mixture was stirred for 45 min, water was added, and the aqueous alcohol layer was extracted several times with pentane. The pentane layers were combined, washed, and concentrated. Approximately 0.7 g of a yellow oil remained. Rapid distillation led to the isolation of 0.60 g (90%) of a clear liquid, n^{24}D 1.4790. Gc and ir comparison with an authentic sample[30] showed it to be 2-chloro-4-*t*-butylcyclohexene (**1**).

Addition of Thiolacetic Acid to 1-Chloro- and 2-Chloro-4-*t*-butylcyclohexene (3, 1). Method A. Azobisisobutyronitrile (AIBN) Initiated Addition.—A solution of 0.500 g (0.00289 mol) of chloro olefin, **1** or **3**, and 0.024 g (5 mol %) of AIBN in the appropriate olefin-free solvent was flushed with nitrogen for 15 min at room temperature. The required amount of thiolacetic acid was added with a hypodermic syringe, and the reaction vessel was lowered into an oil bath held at the desired temperature. In the cases of reactions carried out at the reflux temperature of the solution, the oil bath was 10–15° above the boiling point of the solvent. After 1 hr, the reaction solution was cooled with an ice bath and diluted with pentane. The pentane solution was washed with sodium bicarbonate solution and water, dried, concentrated, and analyzed by gc on column A at 175° with a flow rate of 180 ml/min.

For those reactions carried out in sealed tubes, the reagents were placed in Pyrex tubes; after flushing with nitrogen, the tubes were sealed and placed in a constant-temperature bath for 1 hr. The tubes were then cooled and opened. The work up and analysis followed the above procedure.

(31) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

(32) E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5995 (1957).

(33) (a) G. N. Zhizhin *et al.*, *Neftekhimiya*, **5**, 461 (1965); *Chem. Abstr.*, **63**, 14675*a* (1965); (b) G. N. Zhizhin, Kh. E. Sterin, V. T. Alexsanyan, and A. L. Liberman, *Zh. Strukt. Khim.*, **6**, 684 (1965); *Chem. Abstr.*, **64**, 566*a* (1966).

(34) N. L. Allinger, H. M. Blatter, M. A. DaRooge, and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961).

Method B. Ultraviolet Light Initiated Addition.—The apparatus used consisted of a 2-l. vessel wrapped with aluminum foil and fitted with a water inlet tube, a water outlet tube, a Hanau S-87 quartz immersion lamp, and a quartz reaction tube which was placed about 1 cm away from the lamp. The reaction tube was equipped with a nitrogen inlet and outlet tube. Thiolacetic acid, chloro olefin **1** or **3** (0.500 g, 0.00289 mol), and the solvent were added to the reaction tube. The tube was flushed with nitrogen for 15 min, and then was irradiated for 1 hr. The work-up described in method A was used.

In the ultraviolet light induced reactions at −60°, the water bath was replaced by a 2-propanol–Dry Ice bath. In the case of sealed tube reactions, the reagents were placed in Pyrex tubes, flushed with nitrogen, sealed, and mounted 1 cm away from the light source. The results are shown in Tables I, II, and III.

Separation of the 2-Chloro-4-*t*-butylcyclohexanethiol Acetates (10–13).—Gc analysis on column A at a flow rate of 180 ml/min at 175° showed four components with retention times of 7.5, 9.2, 10.9, and 13.4 min, respectively. Products from several free-radical additions of thiolacetic acid to **1** were combined and distilled, bp 80–82° (0.03 mm). The compounds were separated by preparative gc employing column B at 180°. The two major compounds (retention times 9.2 g and 13.4 min, respectively) were separated from the somewhat volatile liquid phase by distillation. The remaining two components were purified by chromatography over silica gel using pentane as the eluent. Reexamination by gc indicated that no decomposition or rearrangement had occurred.

The component of 7.5-min retention time was identical with 2ᵗ-chloro-4ᶜ-*t*-butylcyclohexexanethiol acetate (**11**), as shown by comparison of gc retention times and ir spectra.

The second compound (9.2 min gc retention time), 2ᶜ-chloro-4ᵗ-*t*-butylcyclohexanethiol acetate (**12**), solidified on standing and was sublimed (40°, 0.02 mm) to give a product having mp 79–80°; nmr δ 3.72 (1 H, 2 = $W_{1/2}$ = 21 Hz) and 4.50 (1 H, $W_{1/2}$ = 8 Hz); ir 675 and 740 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}ClOS$: C, 57.92; H, 8.50; Cl, 14.24. Found: C, 58.22; H, 8.60; Cl, 14.35.

The structure of the compound of 10.9-min retention time, 2ᵗ-chloro-4ᵗ-*t*-butylcyclohexanethiol acetate (**13**), was assigned on the basis of its infrared and nmr spectra. The nmr had a complex multiplet at δ 3.25–3.85 (2 H); ir 725 cm^{-1}.

The component of 13.4-min retention time had an identical gc retention time and infrared spectrum as 2ᶜ-chloro-4ᶜ-*t*-butylcyclohexanethiol acetate (**10**).

***cis*-4-*t*-Butylcyclohexene Sulfide.**—Potassium thiocyanate (3.25 g, 0.033 mol) was dissolved in 4 ml of a 1:1 mixture of water and ethanol, and the solution was stirred for 30 min at room temperature. Two grams (0.013 mol) of *trans*-4-*t*-butylcyclohexene oxide[30] was added. The mixture was stirred for 36 hr, poured into water, and extracted with pentane. The pentane layers were combined, washed with water, dried, and concentrated. The crude product was rapidly distilled to yield 1.80 g (81%) of a colorless liquid, oil-bath temperature 85–90° (0.5 mm), n^{24}D 1.5087. The infrared spectrum indicated the absence of *trans*-4-*t*-butylcyclohexene oxide.

Anal. Calcd for $C_{10}H_{18}S$: C, 70.52; H, 10.65; S, 18.82. Found: C, 70.80; H, 10.71; S, 18.59.

2ᵗ-Chloro-4ᶜ-*t*-butylcyclohexanethiol Acetate (11).—*cis*-4-*t*-Butylcyclohexene sulfide (0.30 g, 0.0017 mol) was added to an excess of acetyl chloride (3 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was added to crushed ice and extracted with pentane, and the pentane layers were combined and washed with sodium bicarbonate solution and water. After drying and concentration, a pale yellow liquid (*ca.* 0.4 g) remained, which was rapidly distilled. A colorless liquid, 0.27 g (61%), n^{24}D 1.5062, was isolated, which solidified after standing. Recrystallization from pentane afforded the thiol acetate **11**: mp 50–51°; nmr δ 4.00 (1 H, $W_{1/2}$ = 8 Hz) and 4.40 (1 H, $W_{1/2}$ = 6 Hz); ir 680 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}OSCl$: C, 57.92; H, 8.51; Cl, 14.25. Found: C, 58.00; H, 8.45; Cl, 14.46.

2ᶜ-Chloro-4ᶜ-*t*-butylcyclohexanethiol (18).—Approximately 1.2 g of the addition product resulting from the ultraviolet light catalyzed addition of hydrogen sulfide to 2-chloro-4-*t*-butylcyclohexene (**1**) was added to 25 ml of 70% aqueous ethanol. The reaction mixture was heated for 45 min and water was added. The aqueous ethanol layer was extracted with pentane and the pentane layers were combined, washed several times with water, dried, and concentrated. The crude product was rapidly distilled and *ca.* 1.0 g of **18**, oil-bath temperature 100–110° (0.3–0.5 mm), n^{25}D 1.5078, was obtained.

Anal. Calcd for $C_{10}H_{19}SCl$: C, 58.09; H, 9.26; Cl, 17.15. Found: C, 58.24; H, 9.36; Cl, 17.26.

2ᶜ-Chloro-4ᶜ-*t*-butylcyclohexanethiol Acetate (10).—Acetic anhydride (2 ml) was added to 0.250 g of 2ᶜ-chloro-4ᶜ-*t*-butylcyclohexanethiol (**18**) in 6 ml of anhydrous pyridine. The mixture was refluxed for 20 min and then was added to a mixture of dilute hydrochloric acid and crushed ice. The aqueous layer was extracted several times with pentane. The pentane layers were combined, washed with sodium bicarbonate solution and water, dried, and concentrated. The crude product was rapidly distilled [oil-bath temperature, 135–140° (0.2–0.3 mm)], and 0.25 g was collected, n^{25}D 1.5078. 2ᶜ-Chloro-4ᶜ-*t*-butylcyclohexanethiol acetate (**10**) was shown to give only one peak on gc, column A at 175°; nmr complex multiplet at δ 3.78–4.58 (2 H); ir 735 and 710 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}SOCl$: C, 57.92; H, 8.51; S, 12.88. Found: C, 58.27; H, 8.51; S, 13.20.

Saponification and Reacetylation of the 2-Chloro-4-*t*-butylcyclohexanethiol Acetates (10–13).—A solution of 1.0 g (0.004 mol) of the thiolacetate adducts **10–13** in 10 ml of ethanol was flushed with nitrogen for 10 min. An equivalent amount of sodium ethoxide in ethanol was added. After the solution had been stirred at 50° for 1 hr, the reaction mixture was poured into cold water, acidified to pH 1 with dilute hydrochloric acid, and extracted with ether. The extracts were washed with water, dried, and concentrated. The crude product was treated with 2 ml of acetic anhydride and 1 drop of pyridine. This mixture was heated to reflux for 15 min, cooled, and poured into cold water. After extraction with ether and the usual work-up, analysis by gc on column A at 175° showed **10** and **12** as the only chlorothiolacetate products.

Saponification and Subsequent Methylation of the 2-Chloro-4-*t*-butylcyclohexanethiol Acetates (10–13).—A solution of 0.483 g (0.0194 mol) of the thiolacetate adducts (**10–13**) in the proportion 53:8:26:14 (**10**:**11**:**12**:**13**) in 5 ml of ethanol was cooled to 0° and flushed with nitrogen for 10 min. An equivalent amount of sodium ethoxide in ethanol was added, and the solution was stirred at 0° for 10 min. An excess of methyl iodide (2 ml) was added and the mixture was stirred at 0° for 1 hr, and was allowed to stand at room temperature for 5 hr. The mixture was poured into ice and water, and was extracted with ether. The ether extract was washed twice with water, dried, and concentrated. Gc analysis of the product mixture on column A at 140° showed two chloro methyl sulfides **26** and **28** in a 68:32 proportion. The *cis*-thiol acetates **10** and **12** were present in the ratio of 67:33 in the original thiol acetate mixture.

Addition of Hydrogen Sulfide to 1-Chloro- and 2-Chloro-4-*t*-butylcyclohexene (3, 1).—The apparatus described in method B of the addition of thiolacetic acid to vinyl chlorides **3** and **1** was used. In addition, the reaction tube was equipped with a Dry Ice condenser. The olefin (**3** or **1**) (1.0 g, 0.00578 mol) was added; the tube was cooled to −80°; and 1.5–2 ml of hydrogen sulfide was condensed. In the case of addition to **1**, 6 ml of olefin-free hexane was added. The cooling bath was removed and after a short period was replaced with a water bath. The refluxing solution was irradiated for 1 hr, after which time the hydrogen sulfide was allowed to vaporize. The crude chlorothiols **18–21** and **22–25** were quantitatively acetylated at 0° with acetic anhydride and pyridine as the catalyst. Analysis was performed by gc at 175° on column A, and the data is summarized in Tables IV and V.

Addition of Methanethiol to 1-Chloro- and 2-Chloro-4-*t*-butylcyclohexene. Method A. AIBN-Initiated Addition.—Methanethiol (*ca.* 1 ml) was condensed in a Pyrex tube at 0°. The tube was warmed to room temperature to remove some of the thiol, stoppered, cooled, and weighed. This process was repeated until 0.070 g (0.00145 mol) of methanethiol remained. After cooling, 0.012 g of AIBN (5 mol %), 0.250 g (0.00145 mol) of **1**, and 2.9 ml of hexane were added. The tube was sealed and placed in an oil bath at 86° for 1 hr, cooled, and opened. The mixture was concentrated and placed under vacuum at room temperature for 2 hr. Analysis was by nmr.

Method B. Ultraviolet Light Initiation.—The apparatus described for the additions of hydrogen sulfide was used for the additions of methanethiol to **3**. The chloro olefin **3** (4.93 g, 0.0287 mol) and 5 ml of methanethiol were added, and the mixture was irradiated for 2 hr. Hexane (6 ml) was used as the solvent for the reaction carried out at −60°. The reaction mixture was

concentrated, and crystallization from pentane at −20° usually afforded about 3 g of the major *cis* adduct **30**. Recrystallization yielded 2 g of pure 2^{c}-chloro-5^{t}-*t*-butylcyclohexyl methyl sulfide (**30**). The mother liquors were combined, concentrated, and analyzed by nmr. Preparative gc afforded a pure sample of 2^{c}-chloro-5^{c}-*t*-butylcyclohexyl methyl sulfide (**32**). The nmr spectra of **30** and **32** agreed with those published.[10]

The procedure of method A, except that AIBN was omitted, was used to prepare hexane solutions of 0.250 g (0.00145 mol) of **1** and the required amount of methanethiol in sealed tubes. The solutions were irradiated at 5° for 1 hr. After removing and concentrating the samples, the relative proportions of adducts were obtained by nmr and are listed in Table IV.

Synthesis of the Diaxial Chlorocyclohexyl Alkyl and Aryl Sulfides (27, 31, 35, 39).—A slight excess of the appropriate thiol was added to a solution of sodium ethoxide in ethanol. After stirring for 15 min, an equivalent amount of the required 4-*t*-butylcyclohexene oxide[30] was added. The mixture was heated under reflux for 3 hr and was then stirred at room temperature overnight. The mixture was then poured into cold water and acidified with dilute acetic acid, and the product was extracted with ether. The ether extract was washed with sodium bicarbonate solution and water, dried, and concentrated to give the diaxial hydroxy sulfide.

The hydroxy sulfide was converted to the corresponding chlorides using thionyl chloride in a mixture of benzene and pyridine at 0°. After the mixture had been stirred overnight at room temperature, it was poured onto crushed ice and extracted with pentane. The extract was washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water. The solution was dried and concentrated. Distillation afforded about a 70% yield (based on epoxide) of the desired diaxial chlorosulfides.

2^{t}-Chloro-5^{t}-*t*-butylcyclohexyl methyl sulfide (31) had bp 75° (oil bath, 0.07 mm), n^{24}D 1.5048.

Anal. Calcd for $C_{11}H_{21}ClS$: C, 59.83; H, 9.58; Cl, 16.05. Found: C, 60.10; H, 9.39; Cl, 15.87.

2^{t}-Chloro-4^{c}-*t*-butylcyclohexyl methyl sulfide (27) had bp 65° (oil bath, 0.07 mm), n^{24}D 1.5045.

Anal. Calcd for $C_{11}H_{21}ClS$: C, 59.83; H, 9.58; Cl, 16.05. Found: C, 60.06; H, 9.68; Cl, 15.70.

2^{t}-Chloro-4^{c}-*t*-butylcyclohexyl benzyl sulfide (35) and 2^{t}-Chloro-5^{t}-*t*-butylcyclohexyl benzyl sulfide could not be distilled without significant amounts of rearrangement. The nmr and ir were consistent with the assumed diaxial structures.

2^{t}-Chloro-4^{c}-*t*-butylcyclohexyl phenyl sulfide (39) had bp 140–145° (oil bath, 1.0 mm), n^{24}D 1.5531.

Anal. Calcd for $C_{16}H_{23}SCl$: C, 67.93; H, 8.18; Cl, 12.53. Found: C, 68.09; H, 8.21; Cl, 12.33.

Addition of Benzyl Mercaptan to 2-Chloro-4-*t*-butylcyclohexene. Method A. AIBN-Initiated Addition.—The procedure employed was essentially that used for the additions of thiolacetic acid to **1**. The olefin **1** (0.250 g, 0.00145 mol), 0.170 ml (0.00145 mol) of benzyl mercaptan, 2.8 ml of hexane, and 0.012 g (5 mol %) of AIBN were placed in a Pyrex tube and flushed with nitrogen. After sealing, the tube was placed in an oil bath at 86° for 1 hr. The tube was cooled in an ice–water bath and opened. The sample was concentrated by removing all volatiles *in vacuo*. Relative proportions of the benzyl sulfides were determined by nmr analysis.

Method B. Ultraviolet Light Initiated Addition.—The quantities used were identical with those used in method A, except that AIBN was omitted. The solution was irradiated in a sealed tube at 5° for 1 hr, and after concentration, the proportions of products were determined by nmr analysis. The results are summarized in Table IV.

Saponification and Subsequent Reaction with Benzyl Iodide of the 2-Chloro-4-*t*-butylcyclohexanethiol Acetates (10–13).—The procedure used for the preparation of a mixture of the two methyl sulfides **26** and **28** from the chlorothiol acetates **10–13** was employed. Benzyl iodide was used as the alkylating agent. After work-up the excess benzyl iodide was removed by distillation at 30–35° *in vacuo*. The two singlets for the benzyl protons of the *cis* compounds were separated by 10.6 Hz in the nmr spectrum; δ 3.82 for the benzyl proton resonance of **34** and δ 3.64 for the benzyl proton band of **36**.

Free-Radical Addition of Thiophenol to 2-Chloro-4-*t*-butylcyclohexene (1). Method A. Benzoyl Peroxide Initiated Addition.—Thiophenol (5.1 g, 0.047 mol) was added to a mixture of 0.28 g of benzoyl peroxide (5 mol %) and 4 g (0.023 mol) of vinyl halide **1** (2:1 molar ratio). The flask was evacuated several times to remove oxygen and then the reaction was allowed to proceed at 60° for 1 week. Water was added and the mixture was extracted with pentane. The extract was washed several times with cold sodium bicarbonate solution and water, dried, and concentrated. A yellow oil (6 g) remained. Distillation under reduced pressure gave 1.95 g (49%) of starting olefin. Further distillation yielded 2.35 g (30–35%), n^{24}D 1.5704, of adduct contaminated with *ca.* 10% diphenyl disulfide. Molecular distillation afforded 0.5 g of pure adduct, n^{24}D 1.5588, which was divided into two portions and analyzed.

A typical analysis was conducted in the following manner. A weighed portion of the adduct was heated to reflux in 80% ethanol for 2 hr. Upon cooling and acidification with nitric acid, the chloride concentration (4–5%) was determined by the Volhard method.

Method B. Ultraviolet Light Initiated Addition.—The apparatus described for the additions of thiolacetic acid was used. Thiophenol (6.60 g, 0.006 mol) was added to 5.15 g (0.003 mol) of **1** (2:1 molar ratio) in a Vycor tube, and this mixture was degassed at 10^{-3}–10^{-4} mm. The tube was sealed, placed in the reaction tube, and irradiated for 48 hr, after which time excess thiophenol and olefin were distilled from the adduct.

The mixture was taken up in pentane and then was washed several times with cold aqueous hydroxide solution to remove thiophenol. The pentane layer was washed with dilute hydrochloric acid, sodium bicarbonate solution, and water, dried, and concentrated. Distillation afforded 2.5 g (55%) of **1** and 3.5 g of adduct which was contaminated with diphenyl disulfide. Upon standing, the diphenyl disulfide precipitated, and redistillation gave 3.0 g (35%) of adduct.

After solvolysis of the adduct mixture in 75% aqueous ethanol for 1 hr, Volhard analysis indicated 6–7% of titrable chloride. The organic material was recovered by extracting the mixture with carbon tetrachloride. The extracts were combined, dried, and concentrated. The residue (*ca.* 2.5 g) was placed on a chromatography column consisting of 50 g of Merck acid-washed alumina, and 40-ml fractions were taken. It required 400 ml of pentane to remove 2^{c}-chloro-4^{c}-*t*-butylcyclohexyl phenyl sulfide (**38**). The column was then washed with anhydrous ether and 0.20 g of a highly viscous residue was collected. An infrared spectrum of the crude residue showed bands at 3300 and 960 cm^{-1} (axial OH).

A quantitative infrared comparison showed that this product consisted of approximately 73% 2^{t}-phenylsulfo-4^{c}-*t*-butylcyclohexanol (**43**) and 27% 2^{t}-phenylsulfo-5^{t}-*t*-butylcyclohexanol. The mixture was treated with *p*-nitrobenzoyl chloride, and a crystalline derivative was obtained which corresponded to the *p*-nitrobenzoate of **43**, mp 99–101°, mmp 99–101°. A mixture melting point with the *p*-nitrobenzoate of 2^{t}-phenylsulfo-5^{t}-*t*-butylcyclohexanol (mp 100–101°) was 86–91°.

2^{t}-Chloro-4^{t}-*t*-butylcyclohexyl Phenyl Sulfide (41).—Lithium thiophenolate (3.0 g) was added to a solution of 8.0 g (0.022 mol) of **2**[30] in 300 ml of dry THF. The heterogeneous reaction mixture was heated at 65° for a period of 3 days. After filtration through Hyflo Supercel and concentration at reduced pressure, 6.6 g of crude material remained. Pentane was added and 1 g of starting material precipitated. Distillation of the mother liquors led to the isolation of 0.8 g (20%) of 2-chloro-4-*t*-butylcyclohexene (**1**). The residue from this distillation was sublimed and *ca.* 1 g of diphenyl disulfide was collected. The residue was distilled [oil-bath temperature 120° (0.05–0.10 mm)]. A pale yellow liquid, 2.7 g (40%), n^{21}D 1.5600, was isolated.

Anal. Calcd for $C_{16}H_{23}SCl$: C, 67.93; H, 8.18; Cl, 12.53. Found: C, 67.75; H, 7.99; Cl, 12.26.

Slight contamination with 2^{t}-phenylsulfo-4^{c}-*t*-butylcyclohexyl chloride—the isomer from diaxial–diequatorial rearrangement—was noted in the nmr spectrum.

Attempted chromatography of the reaction mixture led to solvolysis of the sulfide. The product from the solvolysis was tentatively assigned as 2^{t}-phenylsulfo-4^{c}-*t*-butylcyclohexanol (**43**). The infrared spectrum showed bands at 3330 and 950 cm^{-1}.

2^{c}-Chloro-4^{c}-*t*-butylcyclohexyl Phenyl Sulfide (38).—Lithium thiophenolate (7.2 g) was added to a solution of 8 g (0.0021 mol) of 2^{t}-chloro-4^{t}-*t*-butylcyclohexyl tosylate (**44**) in 200 ml of dry THF. The heterogeneous reaction mixture was heated at 60° for a period of 4 weeks and was then worked up in the usual manner. The residue was chromatographed on 120 g of Merck acid-washed alumina. The column was initially eluted with 540 ml of pentane and then with anhydrous ether. Fractions of 10 ml were

taken for the first 20 fractions, after which 25-ml fractions were taken. Fractions 1–14 yielded diphenyl disulfide. Fractions 15–31 afforded 1.10 g of yellow oil. The ether fractions gave 5.6 g (70%) of starting material. The yellow oil was chromatographed a second time, and 1.05 g (16%) of **38** was collected, n^{25}D 1.5562.

Anal. Calcd for $C_{16}H_{23}SCl$: C, 67.93; H, 8.18; Cl, 12.53. Found: C, 68.15; H, 8.20; Cl, 12.70.

Reaction of 2^t-Phenylsulfo-4^c-*t*-butylcyclohexanol (43) with Raney Nickel.—Raney nickel W-2 (*ca.* 5 g) was heated with 0.5 g (0.002 mol) of the hydroxyphenylsulfide **43** in 40 ml of 95% ethanol for a period of 2 days. The reaction mixture was then filtered and concentrated. A white solid remained, 0.22 g (75%), mp 76–81°. Chromatography of a portion of this compound through a column of Merck acid-washed alumina using 5% ether–pentane as eluent gave an alcohol, mp 81–82.5°. A mixture melting point determination with an authentic sample of *cis*-4-*t*-butylcyclohexanol did not depress. The infrared spectra of an authentic sample and the product were superimposable.

2^t-Phenylsulfo-4^c-*t*-butylcyclohexyl *p*-Nitrobenzoate.—*p*-Nitrobenzoyl chloride (0.15 g) was added to approximately 0.2 g of **43** dissolved in 2 ml of anhydrous pyridine. During a period of 36 hr, the reaction mixture was warmed several times on a steam bath. The mixture was then added to crushed ice, acidified with dilute hydrochloric acid, and extracted several times with ether. The ether layer was washed with dilute acid, sodium bicarbonate solution, and water, dried, and concentrated. A yellow oil remained and trituration with pentane led to the isolation of yellow crystals. Recrystallization from a mixture of 1 drop of ethyl acetate in pentane afforded pale yellow crystals, mp 102–103°.

Anal. Calcd for $C_{23}H_{27}SNO_4$: C, 66.80; H, 6.58; S, 7.75. Found: C, 67.01; H, 6.78; S, 7.52.

2^t-Phenylsulfo-5^t-*t*-butylcyclohexyl *p*-Nitrobenzoate.—The *p*-nitrobenzoate was synthesized from the hydroxy sulfide in the usual manner. Recrystallization from pentane gave yellow crystals, mp 101–102°. A mixture melting point with the *p*-nitrobenzoate of **43** was depressed.

Anal. Calcd for $C_{23}H_{27}SNO_4$: C, 66.80; H, 6.58; S, 7.75. Found: C, 67.01; H, 6.78; S, 7.52.

Desulfurization of 2^t-Phenylsulfo-5^t-*t*-butylcyclohexanol.—Employing the procedure described earlier, 0.75 g of hydroxy sulfide was desulfurized, and 0.11 g (25%) of *trans*-3-*t*-butylcyclohexanol was recovered. The compound was sublimed, mp 64.5–66°. A mixture melting point with an authentic sample did not depress, and the ir spectra were superimposable.

Free-Radical Addition of Thiolacetic Acid to 1-Methyl- and 2-Methyl-4-*t*-butylcyclohexene (4, 5). Method A. AIBN-Initiated Addition.—A hexane solution of 0.220 g (0.00145 mol) of olefin (**4** or **5**), 0.012 g (5 mol %) of AIBN, and the required amount of thiolacetic acid were placed in a Pyrex tube and flushed with nitrogen. The tube was sealed and placed in an oil bath at 86° for 1 hr. Excess thiolacetic acid was removed by washing with sodium bicarbonate solution, followed by washing with water, drying, and concentrating. The relative proportions of products were determined by gc using column C at 160°.

Method B. Ultraviolet Light Initiated Addition.—The procedure was similar to that of method A except that AIBN was omitted and the addition was initiated by means of uv light using the apparatus described for the additions of thiolacetic acid to the chloro olefins **1** and **3**. The results of thiolacetic acid additions to **4** and **5** are shown in Table VI and VII.

Analysis and Separation of the 2-Methyl-4-*t*-butylcyclohexanethiol Acetates (49, 51, 52).—Gc analysis using column C at 160° with a helium flow rate of 180 ml/min showed three thiolacetates, **49**, **51**, and **52**, with retention times of 17.9, 20.0, and 22.0 min, respectively. An analytical sample was prepared by combining the products from three reactions followed by distillation: bp 72° (0.08 mm).

Anal. Calcd for $C_{13}H_{24}OS$: C, 68.36; H, 10.59. Found: C, 68.33; H, 10.68.

The two adducts which were produced in the greatest proportion, **49** and **52**, were separated by preparative gc employing column D at 170°. The diequatorial adduct **50** was the component with a retention time of 17.9 min on column A, and diastereomer **49** had a retention time of 20.0 min under the same conditions.

2^c-Methyl-4^c-*t*-butylcyclohexanethiol Acetate (49).—To a solution of 13 g (0.04 mol) of 2^t-methyl-4^t-*t*-butylcyclohexyl tosylate (**7**-OTs) in 50 ml of DMF was added 5 g (0.089 mol) of sodium hydrosulfide under an atmosphere of nitrogen. The reaction mixture was stirred at 60° for 2 days. The mixture was poured into ice and water, and was acidified to congo red with dilute hydrochloric acid. The product was extracted with pentane, and the extract was washed with water, dried, and concentrated. Distillation afforded 5 g (67%) of 2^c-methyl-4^c-*t*-butylcyclohexanethiol (**49**-SH), bp 47° (0.2 mm).

The thiol (1 g, 0.0054 mol) was acetylated using 3 ml of acetic anhydride and two drops of pyridine. After stirring at room temperature for 24 hr, the reaction mixture was poured into cold water and extracted with pentane. The extract was washed with sodium bicarbonate solution and water, dried, and concentrated. Distillation yielded 0.950 g (78%) of thiolacetate **49**, bp 79° (0.08 mm), n^{25}D 1.4912.

Desulfurization of the 2-Methyl-4-*t*-butylcyclohexanethiol Acetates.—A mixture of 0.40 g (0.0018 mol) of thiol acetate adducts **49**, **52**, and **51** in the proportion 79:18:3, respectively, was heated under reflux in 15 ml of ethanol in the presence of 2.5 g of Raney nickel (W-2) for 1.5 hr. After filtration, the ethanol solution was diluted with water and the product was extracted with pentane. The extract was washed with water, dried, and concentrated to give 0.2 g (74%) of product, which was analyzed by gc using column C at 80°. The ratio of *cis*- to *trans*-1-methyl-3-*t*-butylcyclohexane was 90:10.

2-Methyl-4-*t*-butylcyclohexanethiols (49-SH, 53, 54).—To a solution of 0.52 g (0.0023 mol) of the thiol acetates **49**, **52**, and **51** in the proportion 73:21:6, respectively, in 3 ml of ethanol was added a solution of 0.0025 mol of sodium ethoxide in 5 ml of ethanol. After the mixture had been stirred at room temperature for 1 hr, it was diluted with water and acidified to congo red with 10% hydrochloric acid. The aqueous solution was extracted with pentane, and the extract was washed with water, dried, and concentrated. Distillation gave 0.30 g (71%) of product, bp 49° (0.2 mm). Gc analysis did not give good resolution of the thiols. However, reacetylation with acetic anhydride and pyridine gave the same thiol acetates **49**, **52**, and **51** in an identical proportion as that noted for the starting material.

Desulfurization of the 2-Methyl-4-*t*-butylcyclohexanethiols.—A mixture of 0.16 g (0.0007 mol) of thiols obtained from the corresponding thiol acetates in the previous experiment was desulfurized with 1.5 g of Raney nickel (W-2) in 5 ml of ethanol. The ethanol solution was diluted with water, dried, and concentrated. The proportion of *cis*- and *trans*-1-methyl-3-*t*-butylcyclohexane was 91:9, as determined by gc analysis.

Registry No.—**1**, 17002-25-4; **5**, 15822-50-1; **8**, 20708-94-5; **10**, 20708-95-6; **11**, 20708-96-7; **12**, 20708-97-8; *cis*-4-*t*-butylcyclohexene sulfide, 20708-98-9; **18**, 20708-99-0; **27**, 20709-00-6; **31**, 20709-01-7; **38**, 20709-02-8; **39**, 20728-48-7; **41**, 20728-49-8; **43** (*p*-nitrobenzoate), 20709-03-9; 2^t-phenylsulfo-5'-*t*-butylcyclohexyl *p*-nitrobenzoate, 20728-50-1; **49**, 20709-04-0; **49**-(SH), 20728-51-2.

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Effect of the Leaving Group on Relative Reactivity and Products in Solvolysis[1]

STANLEY G. SMITH AND DAVID J. W. GOON[2]

Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois 61801

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Phenyldimethylcarbinyl chloride, *p*-nitrobenzoate, and thionbenzoate have been found to be more reactive than the corresponding benzhydryl compounds by factors of 5.5, 23, and 4700, respectively, in ethanolysis at 50°. For the cumyl derivatives, kinetic isotope effects and solvolysis products are consistent with an ionization-type reaction for the three leaving groups. The results are interpreted in terms of an observed kinetic isotope effect containing contributions from the isotope effect on elimination from the carbonium ion because of ion-pair return. The high reactivity of cumyl thionbenzoate is attributed to a decrease in the importance of ion-pair return in this system relative to the model compounds.

The nature of the anion formed in limiting solvolysis reactions is known[3,4] to affect the partitioning of carbonium ions among possible reaction products because of the intervention of ion-pair intermediates. For example, the ratio of elimination[3] to substitution is markedly dependent on the nature of the counter ion under conditions where significant fractions of the products arise from the ion pairs. Of related interest[5] is an understanding of the factors affecting limiting solvolytic reactivity as the nature of the anionic leaving group is changed. Relative reactivities have been found to depend markedly on the leaving group when different types of reactions are compared.[6-7] For example, DePuy[6] noted that some alkyl bromides undergo bimolecular elimination at a faster rate than the corresponding *p*-toluenesulfonate although toluenesulfonate esters are often more reactive than bromides in limiting solvolysis. In addition, Hoffmann[7] has reported that the ratio k_{OTs}/k_{Br} varies from 0.36 to 5000 with changes in the character of the reactions.

In this work the solvolytic reactivities of phenyldimethylcarbinyl chloride, *p*-nitrobenzoate, and thionbenzoate are compared with the behaviors of the corresponding benzhydryl derivatives. For the cumyl derivatives, the effect of deuteration of one or both methyl groups on solvolysis rates[8] and products[9] as a function of leaving group is reported and discussed in terms of the importance of ion-pair intermediates and ion-pair return.

Results

The kinetics and products in the ethanolysis of phenyldimethylcarbinyl chloride, *p*-nitrobenzoate, and thionbenzoate have been reported.[3] To facilitate comparisons with the d_3 and d_6 derivatives, new measurements of the kinetics and products from undeuterated cumyl derivatives were made in parallel runs with the deuterated analogs. Comparison of the present data with earlier results[3] is satisfactory.

Kinetics.—The ethanolysis of cumyl chloride at 25.0° was followed by electrical conductance. Standardized hydrochloric acid solutions were used for calibration of the conductance over the concentration region used in the kinetics. At 50°, the automatic titration procedure described for thion esters was used. Calculated first-order rate constants are summarized in Table I.

TABLE I

SUMMARY OF REACTION RATE CONSTANTS FOR THE SOLVOLYSIS OF CUMYL DERIVATIVES IN ETHANOL

Leaving group	Deuteration, °C	Temp, °C	Number of runs	10^4k,[a] sec^{-1}	k_H/k_D
Chloride[b-d]	d_0	25.0	10	3.44 ± 0.04	
	d_3	25.0	5	2.83 ± 0.06	1.22
	d_6	25.0	4	2.36 ± 0.01	1.46
p-Nitrobenzoate[e]	d_0	100.0	9	1.77 ± 0.06	
	d_3	100.0	5	1.40 ± 0.05	1.27
	d_6	100.0	3	1.06 ± 0.02	1.63
	d_0	50.0		0.0058[f]	
Thionbenzoate[c,g]	d_0	50.2	14	1.46 ± 0.03	
	d_3	50.2	10	1.09 ± 0.02	1.34
	d_6	50.2	7	0.75 ± 0.02	1.94

[a] Average of indicated number of measurements. Error is average derivation. [b] Concentration: (6–10) × 10^{-3} *M*. [c] Thymol blue indicator concentration: 2.1 × 10^{-5} *M*. [d] 1% (v/v) in pentane. [e] Concentration: 1 × 10^{-2} *M*. [f] Calculated from data of R. L. Buckson and S. G. Smith.[3] [g] Concentration: (0.8–20) × 10^{-3} *M*.

The solvolysis of cumyl thionbenzoate was monitored by plotting on a strip chart recorder the volume of standardized sodium ethoxide required to maintain a thermostated sample containing thymol blue at the indicator end point. The addition of titrant from a piston buret was controlled by a servo system so that the light intensity from a filtered tungsten source passing through the stirred reaction mixture and falling on a phototransistor was constant.[10,11] Aliquots from *p*-nitrobenzoate ester solvolysis were titrated in the usual way,[3] a deuterated and undeuterated compound being solvolyzed concurrently. The derived rate constants are summarized in Table I. The observed kinetic secondary deuterium isotope effects for six

(1) Research supported by the National Science Foundation.

(2) D. J. W. Goon, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1968.

(3) R. L. Buckson and S. G. Smith, *J. Org. Chem.*, **32**, 634 (1967).

(4) (a) D. J. Cram and M. R. Sahyun, *J. Amer. Chem. Soc.*, **85**, 1257 (1963); (b) M. Cocivera and S. Winstein, *ibid.*, **85**, 1702 (1963); (c) P. S. Skell and W. L. Hall, *ibid.*, **85**, 2851 (1963); (d) T. Cohen and J. Lipowitz, *Tetrahedron Lett.*, No. 49, 3721 (1964).

(5) (a) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); (b) R. G. Pearson and J. Songstad, *J. Org. Chem.*, **32**, 2899 (1967); (c) W. S. Trahanovsky and M. P. Doyle, *J. Amer. Chem. Soc.*, **89**, 4867 (1967).

(6) C. H. DePuy and C. A. Bishop, *ibid.*, **82**, 2532 (1960).

(7) H. M. R. Hoffmann, *J. Chem. Soc.*, 6753 (1965).

(8) For reviews, see, *e.g.*, (a) W. H. Saunders, Jr., *Surv. Progr. Chem.*, **3**, 109 (1966); (b) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963); (c) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

(9) For representative examples of deuterium isotope effects on solvolytic products, see (a) V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **75**, 2925 (1953); (b) V. J. Shiner, Jr., *ibid.*, **76**, 1603 (1953); (c) M. S. Silver, *ibid.*, **83**, 3487 (1961); (d) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958); (e) A. C. Cope R. B. Kinnel, *J. Amer. Chem. Soc.*, **88**, 752 (1966); (f) C. E. Boozer and E. S. Lewis, *ibid.*, **76**, 794 (1954); (g) V. J. Shiner, Jr., and J. S. Jewett, *ibid.*, **87**, 1382 (1965); (h) G. J. Frisone and E. R. Thornton, *ibid.*, **90**, 1211 (1968).

(10) The design of this instrument will be described elsewhere.[11]

(11) R. Anderson and S. Smith, unpublished work.

deuterium atoms range from k_H/k_D of 1.46 for the chloride to 1.94 for the thionbenzoate.

The reaction rates of cumyl derivatives may be compared with the rates of corresponding benzhydryl compounds. The data reported by Winstein, Fainberg, and Grunwald[12] for the benzhydryl chloride were used in this comparison. The reaction rates of the *p*-nitrobenzoate, summarized in Table II, were obtained by titration of aliquots, and the solvolysis of the thion esters was followed by the disappearance of absorption at 436 mμ.

TABLE II

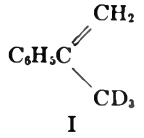
SUMMARY OF SOLVOLYSIS RATES FOR BENZHYDRYL DERIVATIVES[a] IN ETHANOL

Derivative	Temp, °C	10^5k, sec^{-1}
Chloride	50	89.0[b]
p-Nitrobenzoate	100.0	0.36 ± 0.02
	125.0	2.70 ± 0.01
	50	0.0026[c]
Thionbenzoate	75.0	0.84 ± 0.02
	100.0	14.4 ± 0.1[d]
	50	0.031[c]

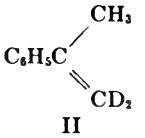
[a] *Ca.* 1×10^{-2} *M*. [b] Data from ref 12. [c] Calculated from data at higher temperatures. [d] Previously reported as 13.6×10^{-4} sec^{-1} [S. G. Smith, *Tetrahedron Lett.*, No. 21, 979 (1962)].

Products.—Product analyses were carried out by glpc with internal standards as previously described.[3] An excess of 2,6-lutidine was present in product runs involving the chloride or *p*-nitrobenzoate. With thion esters, an automatic photometric titrator[10,11] was used to neutralize continuously developed acid. The results, summarized in Table III, indicate that, as found before,[3] the fraction elimination increases in the order chloride < *p*-nitrobenzoate < thionbenzoate, with the chloride giving only 12% elimination while the thionbenzoate gives 91% elimination. Successive deuteration of the methyl groups decreases the fraction elimination and increases substitution. With the chloride, for example, elimination drops from 12 to 4% and substitution increases from 89 to 96% with six deuteriums per molecule. Similar large changes in product composition upon deuteration are noted with the other leaving groups (Table III).

The deuteration pattern of the olefin formed from the d_3 derivative is of considerable interest since elimination of a proton would form 2-phenylpropene-



I



II

3,3,3-d_3 (compound I) and elimination toward the deuterated methyl group would give 2-phenylpropene-1,1-d_2 (II). The ratio of these products, which reflects the isotope effect on the elimination step in the solvolysis, was obtained by proton nmr analysis of olefin fractions isolated by preparative glpc. The aromatic protons were used as an internal standard for the repeated integrations. Subject to the reservation of the limitation of the accuracy of the experimental method, the results summarized in Table IV indicate that with a chloride leaving group elimination discriminates between hydrogen and deuterium more than with the other leaving groups. The present data indicate that the thionbenzoate ester displays the smallest isotope effect in this competition, the observed ratio of the two products being only 1.7.

(12) S. Winstein, A. H. Fainberg and E. Grunwald, *J. Amer. Chem. Soc.*, **79**, 4146 (1957).

Discussion

Measured solvolytic characteristics of the cumyl derivatives studied in this work are summarized in Table V. These data indicate that changing the leaving group from chloride to *p*-nitrobenzoate to thionbenzoate results in a steady increase in the measured kinetic isotope effect and fraction elimination, and a decrease in ρ, m, and the discrimination between CH_3 and CD_3 in elimination. These trends suggest changes in the detailed nature of the reaction but do not seem to dictate invoking fundamentally different types of reactions for each leaving group. The large effect of the leaving group[3] on the fraction elimination in this and other similar reactions[4] suggests[3,4,13] that elimination occurs from some variety of ion pair. Substitution could also occur within the ion pair or from further stages of dissociation.[3,4] Since return from dissociated ions has not been observed in these cumyl systems,[3] the reaction may be approximated by the scheme given in eq 1, although it is clear that more than one va-

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+X^- \xrightarrow{k_S} \text{substitution} \qquad (1)$$

$$\downarrow k_E$$

elimination

riety[14,15] of ion pair may be involved and a significant portion of product may come from more dissociated species. The rate constants in eq 1 could each represent more than one kinetically important step. With these limitations, the observed rate constant is given by eq 2.

$$k^{obsd} = \frac{k_1(k_E + k_S)}{k_{-1} + k_E + k_S} \qquad (2)$$

The decrease in fraction elimination and corresponding increase in ether formation and, in the case of the thionbenzoate, thiol ester formation with deuteration of the methyl groups may be correlated[16] with the observed ratio of 2-phenylpropene-3,3,3-d_3 to 2-phenylpropene-1,1-d_2, Table IV. For example, the product from the d_3 chloride may be considered as the result of a k_S for substitution essentially the same as that for the undeuterated material and an elimination toward the CH_3 group with a rate constant of $^1/_2k_E$ and a rate constant for elimination toward the CD_3 of $^1/_2k_E$ multiplied by the measured isotope effect for this process. Such a calculation is necessarily an approximation since isotope effects on all product-forming steps but one have been neglected. However, as summarized in Table VI, this scheme predicts all of the observed products for the d_3 and d_6 compounds with considerable accuracy.

(13) H. L. Goering and K. Humski, *ibid.*, **90**, 6213 (1968).
(14) S. Winstein, P. E. Klinedinst, Jr., and G. C. Robinson, *ibid.*, **83**, 885 (1961).
(15) H. L. Goering and J. F. Levy, *ibid.*, **86**, 120 (1964).
(16) D. S. Noyce and C. A. Lane, *ibid.*, **84**, 1641 (1962).

TABLE III

PRODUCTS OF THE SOLVOLYSIS OF CUMYL DERIVATIVES IN ETHANOL

Derivative	% olefin[a]	% ether[b]	% ester[c]	Total % yield
Chloride[d,e]				
d_0	11.8 ± 2.4	89.0 ± 1.7		100.8 ± 1.6
d_2	8.6 ± 0.7	92.4 ± 2.2		101.0 ± 2.2
d_6	3.9 ± 0.3	98.1 ± 1.4		102.0 ± 2.3
p-Nitrobenzoate[e,f]				
d_0	49.6 ± 0.5	49.6 ± 0.3		99.2 ± 0.1
d_2	41.7 ± 0.1	56.9 ± 0.2		98.6 ± 0.3
d_6	31.7 ± 1.1	67.1 ± 0.4		98.8 ± 0.7
Thionbenzoate[g]				
d_0	90.6 ± 0.8	5.8 ± 0.3	2.3 ± 0.7	98.7 ± 0.9
d_2	85.6 ± 2.2	7.6 ± 0.3	3.4 ± 0.2	96.6 ± 2.3
d_6	81.6 ± 0.4	10.8 ± 0.4	6 4 ± 0.3	98.8 ± 0.6

[a] 2-Phenylpropene. [b] Ethyl cumyl ether. [c] Cumyl thiolbenzoate. [d] At 25.0°. [e] 2×10^{-2} *M*. [f] At 100.0°. [g] At 50.2°.

TABLE IV

DEUTERATION OF THE OLEFIN FROM THE ETHANOLYSIS OF d_3-CUMYL DERIVATIVES

Derivative	Temp, °C	2-Phenylpropene ratio, 3,3,3-d_3/1,1-d_2
Chloride	25	3.15 ± 0.06
	50	2.9[a]
p-Nitrobenzoate	100	2.10 ± 0.06
	50	2.4[a]
Thionbenzoate	50	1.68 ± 0.02

[a] Calculated by assuming $\Delta F^{\ddagger}_H - \Delta F^{\ddagger}_D$ is independent of temperature.

TABLE V

SUMMARY OF RESULTS FROM THE ETHANOLYSIS OF CUMYL DERIVATIVES

	Derivative		
	Chloride	*p*-Nitrobenzoate	Thionbenzoate
ρ[a]	−4.67		−2.9
m[a,b]	1.3	0.8	0.54
$k_H/k_{D(d_3)}$	1.2[c]	1.32[c]	1.34[c]
$k_H/k_{D(d_6)}$	1.42[c]	1.76[c]	1.94[c]
% substitution	89[d]	50[e]	6[c]
% elimination	12[d]	50[e]	91[c]
I/II[f]	2.9	2.4	1.7

[a] Reference 3. [b] Aqueous ethanol. [c] At 50°. [d] At 25°. [e] At 100°. [f] Product ratio: 2-phenylpropene-3,3,3-d_3 (I)/2-phenylpropene-1,1-d_2 (II).

The observed kinetic isotope effect, k_H^{obsd}/k_D^{obsd}, does not necessarily represent the isotope effect on the ionization step of these reactions. To the extent that k_{-1} is important, the isotope effect on the product forming steps such as elimination are reflected in the observed rate constant because of the competitive nature of k_{-1}, k_E, and k_S. That k_{-1} might not be negligible has been demonstrated by Goering and Chang[17] in the structurally similar system, 2-phenyl-2-butyl *p*-nitrobenzoate, where acyl–alkyl oxygen equilibration was found to occur in competition with solvolysis, and it is not clear how much return escapes detection by this method.[18-20] In the absence of ion-pair return to covalent starting material, the observed isotope effects would be expected to be cumulative,[21] with k_H/k_D being equal to the square of k_H/k_{D_3}. However, if k_{-1} is not negligible relative to k_E and k_S and a significant isotope effect exists on k_E, then, to the extent that elimination contributes to the reaction, deviation from cumulative behavior would be expected. The present data are not sufficiently accurate to provide an adequate test, although k_H/k_{D_6} tends to be larger than $(k_H/k_{D_3})^2$; *e.g.*, the thion ester gives 1.8 calculated *vs.* 1.9 observed.

If this treatment is extended further with the assumption that k_{-1} is large relative to k_E and k_S and that, as a first approximation, a cumulative isotope effect exists on k_I, then, with the observed kinetic isotope effects and the observed product isotope effects, the deuterium isotope effect of one CD_3 group on ionization, k_I, is found to be 1.15 for the chloride and *p*-nitrobenzoate and 1.10 for the thionbenzoate. These values may be closer to the actual β-deuterium isotope effects on ionization than the measured kinetic isotope effects of 1.2, 1.32, and 1.34, respectively. By this analysis, the isotope effect on proton loss from the carbonium ion makes a substantial contribution to the measured overall kinetic isotope effect.

Further understanding of the course of these reactions comes from a comparison of the reactivities of the cumyl derivatives with those of the corresponding benzhydryl compounds. The rate constants either observed at or corrected to 50° are summarized in Table VII. These data indicate that the ratios of the rate constants for cumyl chloride, *p*-nitrobenzoate, and thionbenzoate to those of the corresponding benzhydryl derivatives are 5.5, 23, and 4700. Cumyl thionbenzoate is substantially more reactive than expected on the basis of the benzhydryl system as a model. The change in the products from 50% elimination with the *p*-nitrobenzoate to 91% elimination with the thion ester does not adequately account for the observed rate increase. If the concept of approximate group additivity in linear free-energy relationships[22] is preserved, it follows that the measured rate constants do not reflect, to the same extent, the free energy of activation associated with ionization. Although a large number of other factors may be involved, a preliminary understanding of these relative rates may be obtained from

(17) H. L. Goering and S. Chang, *Tetrahedron Lett.*, **40**, 3607 (1965).

(18) A. F. Diaz, I. Lazdins, and S. Winstein, *J. Amer. Chem. Soc.*, **90**, 1904 (1968).

(19) R. Thies and H. L. Goering, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract S38.

(20) C. D. Ritchie in "Solute–Solvent Interaction," J. F. Coetzee and C. D. Ritchie, Ed., Maycel-Dekker, New York, N. Y., 1969, in press.

(21) V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, *J. Amer. Chem. Soc.*, **85**, 2413 (1963).

(22) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, p 135 ff.

TABLE VI

COMPARISON OF OBSERVED AND CALCULATED PRODUCTS IN THE ETHANOLYSIS OF CUMYL-d_3 AND -d_6 DERIVATIVES

Derivative	Deuteration	Observed products[a] Olefin[b]	Ether[c]	Ester[d]	Calculated products, % Olefin[b]	Ether[c]	Ester[d]
Chloride (25°)	d_3	8.6	91.4		8.0	92.0	
	d_6	3.8	96.2		4.1	95.9	
p-Nitrobenzoate (100°)	d_3	42.4	57.6		42.5	57.5	
	d_6	32.1	67.9		32.2	67.8	
Thionbenzoate (50°)	d_3	88.6	7.9	3.5	90	7.2	2.8
	d_6	82.6	10.9	6.5	86.8	9.5	3.8

[a] Observed product yields normalized to 100%. [b] 2-phenylpropene. [c] Ethyl phenyldimethylcarbinyl ether. [d] Phenyldimethylcarbinyl thiolbenzoate.

TABLE VII

COMPARISON OF CUMYL AND BENZHYDRYL ETHANOLYSIS RATE CONSTANTS AT 50°

	10^4k, sec^{-1} Chloride	*p*-Nitrobenzoate	Thionbenzoate
Cumyl	49	0.0058	14.6
Benzhydryl	8.9	0.00026	0.0031
Cumyl/benzhydryl	5.5	23	4700

the following considerations. The observed rate constant is clearly dependent on the magnitude of the rate constant for ionization, k_1, and, if ion-pair return is fast relative to product formation, on the value of k_{-1}, the rate constant for re-formation of starting material. Since the process corresponding to k_{-1} involves the reaction of a relatively unstable carbonium ion with a nucleophilic anion which, at least initially, is within the same solvent cage, k_{-1} might well be quite large.[20] The activation energy associated with the recombination of the ions is likely to include contributions from changes in solvation,[23,24] nonbonded repulsions,[23] and the energy required to reorganize[25,26] the structure of the cation and anion to begin to re-form a covalent bond. The importance of these effects will depend on the structures of the cation and anion as well as the nature of the solvent. Since the comparison cited above involves two cations and three anions, each with its specific reactivity modified by the proximity of the counter ion, it would not be surprising if large changes in the magnitude of k_{-1} were found. On this basis, the present results are compatible with the cumyl thionbenzoate ion pair giving substantially less return to covalent material than the other systems. Since inductive stabilization of the transition state between a covalent molecule and an ion pair is less sensitive to geometry (noncoplanarity) than is resonance stabilization,[26] the cumyl cation may contribute less to the barrier to return than the benzhydryl cation. This would increase the sensitivity of k_{-1} for the cumyl system, to the nature of the anion. Among these anions, the thionbenzoate should be relatively poor at ion-pair return, since, in the absence of the perturbing effect of the carbonium ion, it tends to be more nucleophilic at sulfur than oxygen;[27] as first formed, the sulfur is not properly positioned for covalent bonding to carbon.

The marked dependence of relative reactivity on leaving groups noted here indicates that rate comparisons involving corrections for different leaving groups may contain unknown but substantial effects resulting from the nature of the specific groups involved.

(23) E. F. Caldin, *J. Chem. Soc.*, 3345 (1965).

(24) C. D. Ritchie, G. A. Skinner, and V. G. Badding, *J. Amer. Chem. Soc.*, **89**, 2063 (1967).

(25) We are indebted to Professor C. D. Ritchie for substantial contributions to the development of these ideas.

(26) J. Hine, *J. Org. Chem.*, **31**, 1236 (1966).

(27) S. G. Smith, *Tetrahedron Lett.*, **21**, 979 (1962).

Experimental Section

Cumyl Chloride, *p*-Nitrobenzoate, and Thionbenzoate.—These materials were prepared as previously described.[3]

Acetophenone-d_3.—This compound was prepared from acetophenone by base-catalyzed exchange with D_2O (99.5% deuterated). Acetophenone (10 ml) was added to a mixture of anhydrous potassium carbonate (0.1 g) and D_2O (5 ml). After the mixture had been refluxed for 16 hr, the acetophenone was removed and placed into a fresh D_2O–base mixture. The initial D_2O mixture was refluxed with another portion of acetophenone. Ten portions of acetophenone were subjected to this procedure. The first portion was exchanged four times with fresh D_2O mixtures. The final exchanges of the other nine samples were each performed in a fresh D_2O mixture. The combined fractions were dried over magnesium sulfate and distilled to give 74.7 g (71%) of acetophenone-d_3, bp 93–95° (10 mm). Analysis by nmr indicated deuteration of the acetophenone-d_3 was *ca.* 98%.

Cumyl Alcohols.—Cumyl alcohol was commercially available from Aldrich Chemical Co. and was distilled before use. It was also prepared by the Grignard reaction between acetone and phenylmagnesium bromide. d_3-Cumyl alcohol was prepared in 86% yield after distillation from the reaction of acetophenone-d_3 and methylmagnesium iodide. The mass spectrum indicated that the product d_3-cumyl alcohol prepared was 95% d_3 and 5% d_2.

Cumyl-β-d_6 alcohol was prepared in 93% yield from acetone-d_6 (1.6 g, Merck Sharp and Dohme of Canada, Ltd.) and phenylmagnesium bromide. The mass spectrum indicated that the alcohol consisted of the following deuterated species: d_6, 92.8%; d_5, 4.4%; d_4, 0.4%; d_3, 2.4% (corresponding to 98% deuteration of the methyl groups).

Product Analysis.—Quantitative product analyses were done by glpc as previously described[3] except that the thionbenzoate product analyses were done on the same solutions used in the kinetic studies.

Isolation and Analyses of Olefin Fraction.—The products of solvolysis in ethanol of the three d_3-cumyl derivatives were concentrated as previously described.[3] The olefin was separated from the other products by preparative glpc with a 1/4-in.-diameter XF-1150 (silicone nitrile) on Chromosorb P column, 3 ft long, at 100° in an F & M Scientific 200 vapor phase chromatograph. The olefin fraction was collected, reinjected, and collected again. Carbon tetrachloride was used to rinse the olefin fractions into tubes. The ratio of 2-phenylpropene-3,3,3-d_3 to 2-phenylpropene-2,2-d_2 was determined by proton nmr analysis (Varian HA-100, unlocked for maximum sensitivity). The relative areas of the aromatic, olefinic, and methyl absorptions were determined by averaging several integrations of each peak. The area of the aromatic absorption was used as a standard of comparison. Each experiment was run two times and the results were averaged.

Product Stability.—2-Phenylpropene and ethyl cumyl ether have been shown to be stable to the conditions of ethanolysis of cumyl chloride and *p*-nitrobenzoate previously.[3] The stability of the products of ethanolysis of cumyl thionbenzoate was determined by addition of the appropriate acid (*ca.* 0.01 *M*) to ethanol containing thymol blue indicator (*ca.* 2×10^{-5} *M*), titration to a green end point with sodium ethoxide or methoxide, addition of one of the products (*ca.* 0.01 *M*), and allowing the

solution to stand at the reaction temperature for a time corresponding to 10 half-lives of the undeuterated derivative. By this method an average of 100% of the olefin, 97% of the ethyl ether, and 99% of the thiol ester were recovered.

Kinetic Procedures.—The reaction rates of d_0-, d_3-, and d_6-cumyl chloride in ethanol were determined conductometrically at 25.0°. The reactions were run in a 2.5 × 15 cm test tube into which a Radiometer electode, type CDC 140, was placed. In each run, 25 ml of ethanol was added to the test tube and equilibrated in a water bath maintained at 25.00 ± 0.01°. Then a 0.245-ml aliquot of the chloride in pentane was added and the solution was briefly agitated. Usually 90–100 resistance measurements were taken at intervals varying from 15 sec to 3 min with an Industrial Instruments, Inc., conductivity bridge, Model RC-15. The reactions were followed to at least 62%, and infinity readings were taken after 10 half-lives. At least 20 measurements selected at appropriate times were used to calculate the rate constant. A weighted, least-squares FORTRAN program for the IBM-7094 computer took the measured resistance and time data for the run, converted the resistance into concentration, and applied the first-order equation. A calibration of resistance *vs.* concentration of hydrochloric acid in ethanol was determined, and a third-order polynomial was fitted to the data. The hydrochloric acid–ethanol solutions used in the calibration were *ca.* 1% in pentane, as were the solutions used in the kinetic and product runs.

The usual sealed-ampoule technique was used for the determination of the rates of solvolysis of the cumyl *p*-nitrobenzoates.[2] For all determinations a deuterated ester and an undeuterated ester were run concurrently in the same constant-temperature bath maintained at 100.00 ± 0.02°. In an additional method, a specially constructed titration apparatus was used which electronically detected a bromthymol blue end point. This method was also used to determine the rates of solvolyses of the benzhydryl *p*-nitrobenzoates.

The rates of ethanolysis of cumyl chloride and of cumyl thionbenzoate at 50° were determined by the use of a photometric titrator.[10,11] The apparatus consisted of a light source and an optical system which collimated the light on a band pass filter (λ_{max} 600 mμ) before it passed through a stirred and thermostated reaction cell to a phototransistor.

A servo-system controlled the addition of titrant from a piston buret so that the energy falling on the sensor was constant. The reaction cell had two cavities sealed by screw-caps containing silicone rubber plugs. Syringe needles were used for the introduction of titrant, substrate, and nitrogen gas. In a kinetic run, *ca.* 20 ml of solvent containing thymol blue indicator (*ca.* 2×10^{-5} *M*) was thermostated at the reaction temperature. Dry nitrogen was bubbled through the solution very briefly and the indicator was brought to the appropriate end point. The introduction of the chlorides into the reaction cell was by injection of pentane solutions. Thionbenzoates were added as solids. The apparatus added titrant (maximum volume was *ca.* 2 ml) as necessary to maintain the selected indicator end point. Readings at appropriate times were selected from the resulting titration volume *vs.* time curve and used directly to calculate the integrated first-order rate constant.

The solvolysis of benzhydryl thionbenzoates was studied in sealed, degassed ampoules thermostated in Carbowax-400 baths maintained at 75.00 ± 0.02 and 100.00 ± 0.02°. At appropriate times the ampoules were removed from bath, cooled to room temperature, and analyzed for absorption at 436 mμ with a Beckman DU spectrophotometer.

Calculations.—First-order rate constants were calculated with a FORTRAN program and IBM-7094 and -1800 computers. The program calculated the best fit, least-square line through the points of a plot of ln *Y vs.* time. The points were weighted in proportion to the relative magnitude of the *Y* values.

Registry No.—Acetophenone-d_3, 17537-31-4.

Effect of Solvent on the Photolysis of α-Lipoic Acid[1]

PHYLLIS R. BROWN[2] AND JOHN O. EDWARDS

Metcalf Laboratory, Brown University, Providence, Rhode Island 02912

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The photolysis of α-lipoic acid in different solvents was followed by tlc and uv. It was found that a number of products are formed in each solution and the number and kind of product are dependent on the solvent. The chain length is determined by the kind of solvent; the length of the polymer chain decreased with increased availability of hydrogen atoms in the solvent. The amounts of products as well as the rate of formation of products are also solvent dependent. A mechanism is postulated in which the disulfide bond is broken homolytically in the first step. It is postulated that the reaction proceeds by chain transfer of hydrogen atoms from the solvent, causing short chains; by attack of the radicals on the other lipoic acid molecules, forming chains of longer length; or by the hydrolysis of the thio ketone formed by intramolecular abstraction of the tertiary hydrogen.

Because α-lipoic acid (1,2-dithiolane-3-valeric acid) has been found to be important biologically in the oxidative decarboxylation of α-keto acids,[3] and because it is thought to participate in photosynthesis,[4–7] several studies have been made of the photolysis of α-lipoic acid and the related compound, 1,2-dithiolane.[4,3,9]

In 1954, Barltrop, *et al.*,[4] reported that the photolysis of 1,2-dithiolane in neutral solution resulted in polymerization. They found that in acidified ethanol, the dithiolane ring was destroyed but no polymerization occurred. They suggested that the dithiyl radicals, produced by photolysis, reacted with the solvent. When Whitney and Calvin[8] photolyzed α-lipoic acid, the uv spectra indicated that a definite set of products was formed. These products were not identified. They also conducted a number of exploratory experiments on the relations between water concentration, pH, and polymerization, and concluded that polymer formation is not a simple consequence of the fission of the S–S bond. They postulated that the ultraviolet light causes slight polymerization and then inhibits it. They also felt that the failure of the biradicals to polymerize in ethanol solution was consistent with the views of Zimm and Bragg[10] that it is improbable for biradicals to form long chains. In 1956, while studying

(1) This paper is abstracted in part from the Doctoral dissertation of P. R. Brown, submitted to the Graduate School of Brown University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, June 1968.

(2) Union Carbide Fellow, 1966–1967. National Institute of Health Special Research Fellow, 1967–1968, Grant 1-F1-GM-35,937-01.

(3) L. J. Reed in "Comprehensive Biochemistry," M. Florkin and E. Stotz, Ed., **14**, Chapter II, Elsevier Publishing Co., Amsterdam, Holland, 1966.

(4) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954).

(5) M. Calvin, H. Griseback, and R. C. Fuller, *ibid.*, **77**, 2659 (1959).

(6) M. Calvin and J. A. Barltrop, *ibid.*, **74**, 6153 (1952).

(7) M. Calvin, *Fed. Proc.*, **13**, 697 (1954).

(8) R. Whitney and M. Calvin, *J. Chem. Phys.*, **23**, 1750 (1955).

(9) E. Walton, A. Wagner, F. Bachelor, L. Peterson, F. Holly, and K. Folkers, *J. Amer. Chem. Soc.*, **77**, 5144 (1955).

(10) B. Zimm and J. Bragg, *J. Polym. Sci.*, **9**, 476 (1952).

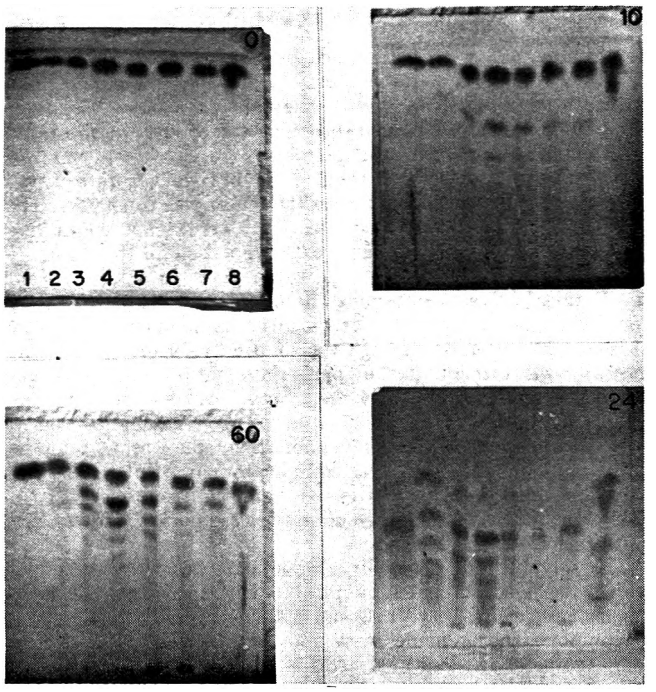


Figure 1.—Formation of products with time in photolysis of lipoic acid in different solvents as run on analytical tlc plates. The time of photolysis (in minutes except for 24 which is 24 hr) is noted on each plate. The 7×10^{-3} M solutions of lipoic acid were made up in the following solvents and applied from left to right: (1) 95% EtOH, (2) $(CH_3)_2CHOH$, (3) $CHCl_3$, (4) Et_2O, (5) C_6H_6, (6) C_6H_{12}, (7) CCl_4, (8) H_2O, OH^-.

the properties and derivatives of α-lipoic acid, Walton, *et al.*,[9] found that the ultraviolet spectra of solutions of α-lipoic acid (LA) in cyclohexane, ether, or benzene changed considerably on exposure to ordinary light for 2 days. The absorption at 3300 Å decreased and the absorption in the 2500-Å region increased. They postulated that linear disulfide polymers were formed once the cyclic disulfide bond was broken. No product studies were made, and the data collected was based on ultraviolet spectroscopy, which showed a decrease in the amount of cyclic disulfide present and an increase in absorption in the region of 2900–1900 Å. The absorption in this region is characteristic of many functional groups;[4,11] so the uv spectra provide no strong evidence for any one structure. No attempt was made to find out the effect of solvent on the course of the reaction.

Therefore, this study was made to investigate the effect of solvent on the photolysis of α-lipoic acid in order to elucidate the general mechanism of these photoreactions in various media.

Experimental Section

Materials.—The solvents used, CH_3OH, C_2H_5OH, $(CH_3)_2CHOH$, $(CH_3)_3COH$, Et_2O, C_6H_6, cyclohexane (herein referred to as C_6H_{12}), CCl_4, and C_6F_6, were spectral or reagent grade. The Et_2O, CH_3OH, C_2H_5OH, and $(CH_3)_2CHOH$ were either freshly distilled or were taken from containers that had been opened just prior to use so that peroxides would not be present. The α-lipoic acid (LA) was obtained from Sigma Chemical Co. A sample of dihydrolipoic acid (DHL), which was used as a reference compound, was also obtained from the same company.

Methods.—The photolysis reactions were followed by analytical tlc, using silical gel HR as adsorbent, $CHCl_3$–CH_3OH–HCOOH (8:1:1) as developing solution, and I_2 as visualizing agent. They were also followed by uv. The uv source was an 8-W Sylvania Blacklight Blue uv tube lamp (no. F 8T5/BLB), which radiates the major part of its energy in the ultraviolet, peaking in the 3560-Å region.

The following extinction coefficients of LA in various solvents at λ_{max} = 3330 Å were determined, using a Hitachi Perkin-Elmer 139 uv-visible spectrophotometer: 95% EtOH, 139; $(CH_3)_2CHOH$, 145; $CHCl_3$, 169; Et_2O, 158; C_6H_6, 148; C_6H_{12}, 169; CCl_4, 232; H_2O, OH^-, 121.

The products of the photolysis in Et_2O were isolated by preparative tlc, using silica gel PF 254 as adsorbent and the solvent system described for the analytical tlc. The bands were located using a "hot wire" technique.[12] The structure of the major reaction product was determined on the basis of uv, ir, DTNB sulfhydryl determinations, reaction of product with base, reaction of product with $NiCl_2$, elemental analysis, and molecular weight determinations.

Results

In following the photolysis of LA by tlc, the products were designated A, B, C, etc., until they could be identified. Product A was the product that had the highest R_f value on tlc, B was the product that had the second highest, etc. No product had an R_f value higher than LA. The product with an R_f value of 0 was designated as a polymer, because it was found that increasing molecular weights caused decreasing R_f values. It should be noted that the fact that two compounds have the same R_f value does not necessarily mean that they have identical compositions. However, because of the distinct nature of the spots on tlc, they must be similar. Therefore, the product we call product A in Et_2O may differ in detail from product A in C_6F_6. Samples of typical plates are shown in Figure 1. All reactions were followed by sampling on tlc plates the solutions which had been photolyzed for 0, 5, 10, 20, 30, 45, 60, and 120 min and 24 hr.

In order to find the effect of oxygen on the products, duplicate photolyses on solutions of LA in Et_2O and C_6F_6 were run, one in air and one under nitrogen. No differences in the products formed could be observed on tlc in either solvent. The role of water in the photolysis was investigated by comparing the photolysis products in absolute ethanol, 95% EtOH, 66% EtOH, 33% EtOH, and H_2O. It was found that, after photolysis of the LA in absolute EtOH for 2 hr, there was only a trace of H_2S (both by odor and by $Pb(Ac)_2$ paper), but in all the others H_2S was a significant product. The effect of ease of abstraction of a hydrogen atom from similar solvents was followed by photolyzing LA in CH_3OH, C_2H_5OH, $(CH_3)_2CHOH$, and $(CH_3)_3COH$. Only traces of H_2S were found after photolysis of these solutions for 2 hr; however, after 24-hr photolysis, a significant amount of H_2S was found in the CH_3OH and C_2H_5OH but not in the secondary and tertiary alcohols. DHL was not formed in $(CH_3)_3COH$ but was a major product in the other three alcohols. The tlc results of the formation of products with time in the various solvents are tabulated in Tables I–III.

From the results obtained, it is evident that photolysis of α-lipoic acid is solvent dependent. The number of products and the kind, amount, and rate of formation are dependent on the solvent in which the photolysis takes place. From tlc plus the gross observations and uv, it is apparent that the photolysis of the solutions did not proceed identically. For example, H_2S was

(11) C. Price and S. Oae, "Sulfur Bonding," Ronald Press Co., New York, N. Y., 1962.

(12) Detailed experimental procedures and results can be found in the Ph.D. Thesis of P. R. Brown, Chemistry Department, Brown University, Providence, R. I., 1968.

Table I

Products of Photolysis of α-Lipoic Acid in Various Organic Solvents[a]

Solvent	Time, min: 5	10	30	60	1440
C_2H_5OH	...	Trace A	Trace A	DHL, Traces A–C	DHL, A, smear
$(CH_3)_2CHOH$	...	Traces A, B	Traces A, B	DHL, Traces A–C	DHL, A, smear
$CHCl_3$	Trace A	A–E	A–E	A–E	A–E
$C_2H_5OC_2H_5$	Trace A	A–E	A–E	A–E	50% A–E
C_6H_6	Trace A	A–E	A–E	A–E	Trace A, rest polymer
C_6H_{12}	...	A–E	A–E	A–E	Trace A, rest polymer
CCl_4	...	A–E	A–E	A–E	Trace A, rest polymer
C_6F_6	...	A–E	A–E	A–E	Polymer

[a] The products were designated A, B, C, etc., and polymer until they could be identified. Product A had the highest R_f value of all of the products, but its R_f value was lower than that of LA. The polymer had an R_f value of 0. The term "smear" indicates that products were present as indicated by analytical tlc but that distinct separation of the spots was not obtained under the conditions used.

Table II

Products of Photolysis of α-Lipoic Acid in Various Alcohols[a]

Solvent	Time, min: 5	10	30	60	1440
CH_3OH	...	...	Trace A	Traces A–C	DHL, A, B, smear
C_2H_5OH	...	Trace A	Trace A	DHL, traces A–C	DHL, A, smear
$(CH_3)_2CHOH$	...	Traces A, B	Traces A, B	Traces A, B	DHL, A, smear
$(CH_3)_3COH$	...	A–C	A–C	A–C	A, smear

[a] See Table I, footnote a.

Table III

Products of Photolysis of α-Lipoic Acid in Ethanol–Water[a]

Solvent	Time, min: 5	10	30	60	1440
100% EtOH	...	Trace A	Trace A	DHL, trace A–C	DHL, A, smear
95% EtOH	...	...	...	Traces A–C	DHL, A, A', smear
66% EtOH	...	...	Traces A, B	Traces A, A', B, C, D	Smear
33% EtOH	...	...	Traces A, B	Traces A, A', B	Smear
H_2O	Smear	Smear	Smear	Smear	Smear

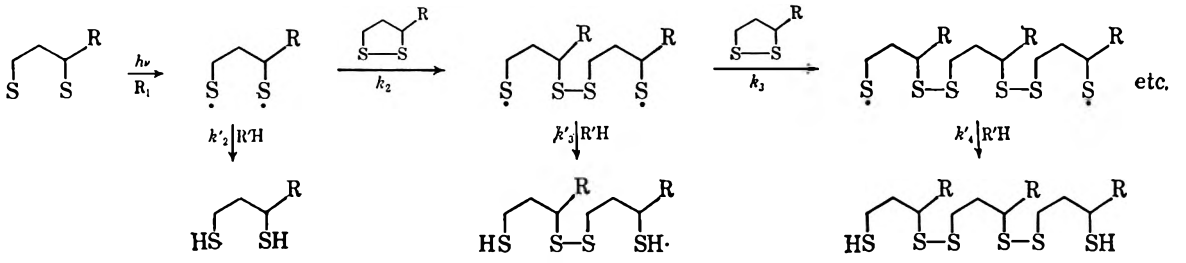
[a] See Table I, footnote a. Product A' was a product that had a higher R_f value than A but lower than LA, and was found only in certain photolyses after the initial experiments were carried out.

detected [by odor and $Pb(Ac)_2$ paper] only in the alcohol and aqueous solutions. This indicates that there was breakup of at least some of the lipoic acid molecules in these solutions, and therefore different products must have formed.

The products developed at different rates with the various solvents. For example, a definite product was seen in $CHCl_3$, Et_2O, and C_6H_6 solutions after photolysis for only 5 min, whereas in $(CH_3)_2CHOH$ a distinct product was not detected until the solution had been photolyzed for 10 min, and in CH_3OH a product was not detected for still longer. After 24-hr photolysis, traces of a compound with the R_f value of α-lipoic acid were seen in $CHCl_3$, Et_2O, and C_6H_6, but not in C_6H_{12}, C_6F_6, and CCl_4. Only in the CH_3OH, EtOH, and $(CH_3)_2CHOH$ was there a significant amount of DHL observed. The major product in Et_2O after 24-hr photolysis was product A; in no other solution was product A present in such high concentration. The spots which were detected by tlc in all the organic solvents were similar, but the intensity of each spot (indicating concentration of the product) was dependent on the particular solvent in which the LA was photolyzed. The products with the higher R_f, which appeared in the C_6H_6, C_6H_{12}, and CCl_4 solutions early in the photolysis, either disappeared completely or decreased in concentration on photolyzing for 24 hr. None of the products in the Et_2O solutions, however, either disappeared or diminished in concentration on further photolysis. In solutions of LA in Et_2O (photolyzed for 24 hr) that were allowed to stand in the dark for one month, there was no change in the amount or kind of products present; no LA re-formed nor did the concentration of product A diminish. The alcohol solutions, however, showed a significant change in 1 month. The tlc showed breakdown of the DHL that had been present immediately after photolysis. In place of the DHL, there was a spectrum of many unidentified products, some of which were not seen in other experiments. In contrast to the DHL, there was no breakdown of product A; after a month it was still present and its concentration had not decreased. Polymer formation is seen (both from the turbidity of solutions photolyzed for 24 hr and from tlc) in C_6H_6, C_6H_{12}, C_6F_6, and CCl_4, but not in the alcohols or in Et_2O. All solutions remained colorless on photolysis except the basic aqueous solution, which turned yellow. The yellow color is probably due to the depolymerization of products which takes place in basic solutions.[3,12] The C_6H_5, C_6H_{12}, CCl_4, and C_6F_6 solutions became cloudy on photolysis,

SCHEME I

POSTULATED MECHANISM FOR PHOTOLYSIS OF LIPOIC ACID

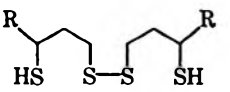


R = $(CH_2)_4COOH$

R'H = solvent

whereas the other remained clear. Since the products of the aqueous solutions were not well separated using this particular tlc procedure, no conclusions can be drawn as to the products formed in the photolysis of LA in aqueous solutions. However, from the work done on the photolysis of LA in ethanol solutions containing varying amounts of H_2O, it can be seen that H_2O has a definite effect on the formation of H_2S and hence on the breakup of LA molecules.

Using preparative tlc, small samples of product A (from photolysis of LA in Et_2O) were obtained and were characterized by several techniques.[12] Product A comprised approximately 50% of the total yield of products found in the Et_2O solution. Elemental analysis showed that no major change in atomic ratios occurred when LA is converted to product A. Experimental molecular weights were in the range of an oligomer with two LA units. The presence of sulfhydryl groups was shown by the appearance of the distinct red-brown color when nickel ion was added to product A solutions,[13] by the initial bleaching of iodine color at the product A spot in analytical tlc,[14] and by the DTNB determination for sulfhydryl content.[15] Product A depolymerized in the presence of base to form LA and DHL in equal amounts; this indicates a dimeric structure for product A. The infrared spectrum showed characteristic bands for C–H, S–H, and CO_2H groups. The ultraviolet spectrum had no bands in the area where the dithiolane ring absorbs, but adsorption was noted in the lower wavelength regions where the linear S–S and S–H groups absorb. When all the evidence is considered, it seems conclusive that product A is a linear dimer of the type where R = $(CH_2)_4CO_2H$. The



actual disposition of the R groups is not known, and indeed product A may be a mixture of structural and geometric isomers.

Product B was isolated and analyzed in similar fashion. This product has the properties generally expected for a linear timer. We presume, therefore, that the lower spots represent higher molecular weight oligomers.

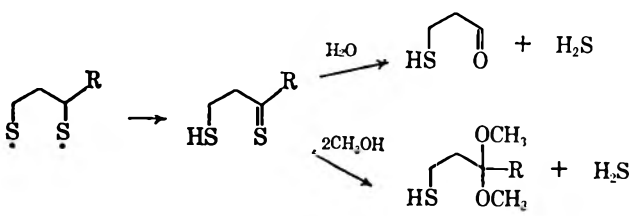
(13) P. R. Brown and J. O. Edwards, in press.

(14) P. R. Brown and J. O. Edwards, *J. Chromatog.*, **38**, 10.4, 543 (1968).

(15) G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

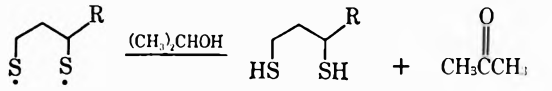
Discussion

From the results, a mechanism can be postulated for the photolysis of LA in which the disulfide linkage is broken homolytically in the first step (Scheme I). If the reaction proceeds by chain transfer of hydrogen atoms, in a type of chain transfer involving solvents that has been known for years,[16] short chains are formed. In solvents where a hydrogen atom is either not available or else not readily abstractable, the reaction can proceed by attack of the radicals on another LA molecule. If the reaction proceeds by subsequent attacks on other LA molecules, longer chains are formed. From our results, we feel that the conclusion of Whitney and Calvin[8] that light causes polymerization and then inhibits it and the conclusion of Zimm and Bragg[10] that it is improbable for diradicals to form long chains must be considered in terms of the specific system. The length of the chain of the products obtained in this particular reaction depends to a significant extent upon the solvent; the length of the polymer chain increases with decreased availability of hydrogen atoms in the solvent. In the photolysis of LA in Et_2O, the reaction proceeds primarily *via* the "chain transfer involving solvents" mechanism is which the significant products are oligomers. The results indicate that the photolysis in Et_2O and the alcohols involves hydrogen abstraction from the solvent. It is worth noting, however, that no DHL or H_2S was found in the Et_2O solution, whereas both products were found in the primary alcoholic solvents. The mechanism in these alcohols and water, therefore, is more complicated, since there is definite evidence for some breakup of the LA molecule in these photolyzed solutions. It is postulated that the mechanism of the photolysis of LA in hydroxylic solvents proceeds by one of two paths. If, as in the case of H_2O, the high bond energy of O–H prevents hydrogen abstraction from the solvent, then an intramolecular abstraction of a tertiary hydrogen may take place and a thio ketone is formed. Hydrolysis of the thio ketone leads to the formation of H_2S and a



(16) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, Chapter 4.

ketone. If the solvent is CH_3OH, H_2S and a ketal may be the end products. In a solvent such as 2-propanol, where a hydrogen is easily abstracted from the hydroxylic carbon, dihydrolipoic acid and acetone are formed along with product A and the other oligomers. Since these are only preliminary experiments, it is indicated



that a thorough product study should be made of the aqueous and alcoholic solutions. In solvents such as C_6F_6, where the products are mainly long chain polymers, it is evident that the reaction is a simple attack of the dithiyl radicals on other LA molecules. In solvents such as $CHCl_3$, CCl_4, C_6H_6, and C_6H_{12}, other products are formed as well as fair amounts of polymer. This indicates the possibility of other reactions proceeding at the same time as polymerization. Such possibilities include the abstraction of a chlorine atom from CCl_4 and formation of a chloro-LA derivative, the formation of a π-bond complex with benzene, the abstraction of a hydrogen atom from $CHCl_3$ and a subsequent coupling of the thiyl radical with the trichlorocarbon radical, etc.

Therefore it is concluded that the photolysis of LA is solvent dependent and that the final products formed are dependent on the ease of hydrogen abstraction and upon the presence or absence of water.

Registry No.—α-Lipoic acid, 62-46-4.

The Structure of Jegosapogenol (Barringtogenol C, Aescinidin) and the Configuration at C-21 and C-22 in Barringtogenol D, Aescigenin, Protoaescigenin, and Isoaescigenin[1,2]

T. NAKANO,[3] M. HASEGAWA, T. FUKUMARU, L. J. DURHAM, H. BUDZIKIEWICZ, AND CARL DJERASSI

The Department of Chemistry, Instituto Venezolano de Investigaciones Cientificas (I. V. I. C.), Apartado 1827, Caracas, Venezuela, and the Department of Chemistry, Stanford University, Stanford, California 94305

Received October 16, 1968

The structure of jegosapogenol was established as 3β,16α,21β,22α,28-pentahydroxyolean-12-ene (**1a**) on the basis of chemical as well as spectroscopic data and this triterpene was shown to be identical with barringtogenol C (aescinidin). The configuration at C-21 and C-22 in barringtogenol D, aescigenin, protoaescigenin, and isoaescigenin is discussed on the basis of nmr spectra, and their structures are revised to **12b**, **24a**, **25a**, and **26**, respectively.

The fruits of *Styrax japonica* Sieb. *et* Zucc. (Japanese name "egonoki") were once used as a substitute for soaps and as a fish poison. In 1899, Keimatsu[4] isolated from the skins of this fruit a saponin named jegosaponin. Since then, the elucidation of the chemical structure of this saponin has been the subject of a number of investigations.[5] However, in spite of these intensive studies, no structure could be proposed for this fish poison.

The earlier workers[5] reported that the acid hydrolysis of jegosaponin yielded 2 equiv each of glucuronic acid and glucose[6] as well as a sapogenin which, on digestion with alkali, was hydrolyzed to tiglic acid and jegosapogenol. For the sake of brevity, we have at the outset given the correct formula **1a** for jegosapogenol and will summarize later the relevant evidence. The nmr spectra of the acetyl derivatives (**1b**, **1c**, **1d**, **1e**, and **1f**) (see Table I) indicated that jegosapogenol has one primary hydroxyl group which was confirmed by the preparation of a monotrityl ether **1g**, and all the remaining hydroxyl groups are secondary, one of which may be more hindered than the rest. From a biogenetic point of view, one hydroxyl group is assumed to be located at C-3, and a quartet (spacings of 6 and 12 Hz) at τ 5.28 in the 100 MHz nmr spectrum (benzene) of the pentaacetate **1b** corresponds to the axially oriented proton at C-3.[7]

The mass spectrometric fragmentation patterns[8] of jegosapogenol and its tetraacetate **1c** and also the detection of seven quaternary C-methyl groups as sharp singlets in the 100-MHz nmr spectrum (benzene) of the pentaacetate **1b**[1] suggested that jegosapogenol must be a β-amyrin-type triterpene alcohol, whose one primary and three secondary hydroxyl groups are located on rings D and E.

The uv spectrum of jegosapogenol exhibited an absorption maximum at 203 mμ (ϵ 6000), which was

(1) Preliminary accounts of this work were presented in T. Nakano, M. Hasegawa, T. Fukumaru, S. Tobinaga, C. Djerassi, L. J. Durham, and H. Budzikiewicz, *Tetrahedron Lett.*, 365 (1967), and T. Nakano, M. Hasegawa, and J. B. Thomson, *ibid.*, 1675 (1967). The present paper represents part III in the series "Terpenoids" by T. Nakano and part LXIII in the series "Terpenoids" by C. Djerassi, *et al.*

(2) This work was supported by Research Grants GM-09362 and GM 06840 of the National Institutes of Health.

(3) To whom correspondence concerning this paper should be addressed.

(4) S. Keimatsu, *J. Chem. Soc. Jap.*, **20**, 1052 (1899).

(5) Y. Asahina and K. Momoya, *Arch. Pharm.*, **252**, 56 (1914); *Yakugaku Zasshi*, **34**, 105 (1914); **35**, 1 (1915); C. Sone, *Acta Phytochim.* (Tokyo), **8**, 23 (1934); **9**, 83 (1936); S. Tobinaga, *Yakugaku Zasshi*, **78**, 526, 529 (1958).

(6) Matsunami [*J. Pharm. Soc. Jap.*, **545**, 87 (1927)], however, identified glucuronic acid (1 mol), rhamnose (1 mol), and glucose (2 mol) in this hydrolysis.

(7) This proton appears as a triplet (spacing of 8 Hz) at around τ 6.5 and 5.5, respectivey, in the 60 MHz nmr spectra of the C-3-OH (β) derivatives and the acetates (see Table I). This signal constitutes the X part of an ABX pattern and its change of appearance in different solvents is consistent with a change of the relative positions of A and B. These chemical shifts are in good accordance with those of the axial proton of α- and β-amyrin and taraxerol and their acetates [see M. Shamma, R. E. Glick, and R. C. Mumma, *J. Org. Chem.*, **27**, 4512 (1962)].

(8) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 3688 (1963).

TABLE I
NUCLEAR MAGNETIC RESONANCE DATA[a]

Compd	H-3	H-21	H-22	H_2-28	H-16	H-12
1b[b]	5.28 (q, 6; 12)	4.38 (s)	4.38 (s)	6.12 (AB q, 13)	4.50 (m)	4.70 (m)
1c	5.48 (t, 8)	4.43 (d, 10)	4.60 (d, 10)	6.33 (s)	5.81 (m)	4.63 (m)
1d	5.48 (q, 7; 9)	5.97 (d, 10)	4.77 (d, 10)	6.30 (s)	5.79 (m)	4.60 (m)
1e	5.34 (m)	3.77 (d, 10)	4.02 (d, 10)[c]	5.75; 6.00 (AB q, 11)	5.34 (m)	4.54 (m)
1f	5.27 (m)	5.64 (d, 10)	4.21 (d, 10)	5.87 (diffused s)	5.56 (m)	4.62 (m)
1h	5.50 (t, 8)	4.52 (d, 11)	4.62 (d, 11)	6.33 (s)	5.77 (m)	4.62 (m)
3b	5.48 (t, 7)	4.42 (d, 10)	4.79 (d, 10)	5.54; 5.87 (AB q, 12)	...	4.20 (s)
4a	5.50 (t, 7)	4.42 (d, 11)	4.82 (d, 11)	5.50; 5.85 (AB q, 13)	...	4.50 (m)
5[d]	6.53 (t, 7)	6.48 (d, 9)	5.81 (t, 9)	...	...	4.43 (m)
8b	5.23 (t, 8)	...	3.34 (d, 3)	...	...	4.32 (m)
10	5.48 (t, 7)	5.20 (d, 10)	4.62 (d, 10)	6.23 (s)	4.25; 4.33[e] (2 H, AB q, 10)	4.60 (m)
12a	5.47 (t, 7)	6.40 (s)	4.70 (s)	5.86; 6.20 (AB q, 12)	5.72 (m)	4.70 (m)
12c	6.80 (t, 7)	6.48 (s)	5.62 (s)	6.95 (s)	5.85 (m)	4.86 (m)
13a	6.75 (t, 7)	6.27 (d, 10)	5.78 (d, 10)[c]	6.36; 6.65 (AB q, 12)	5.23 (m)	4.70 (m)
13b	5.47 (t, 8)	6.26 (d, 10)	5.77 (d, 10)[c]	6.36; 6.66 (AB q, 12)	5.20 (m)	4.70 (m)
14a[d]	6.55 (t, 8)	5.64 (d, 9)	5.30 (d, 9)[c]	5.89; 6.15 (AB q, 11)	4.65 (m)	4.31 (m)
14c	5.47 (t, 8)	4.75 (d, 9)	5.93 (d, 9)[c]	5.92 (s)	6.25 (m)	4.62 (m)
15	5.50 (t, 7)	6.53 (s)	5.84 (s)	6.35 (s)	5.22 (m)	4.79 (m)
16a	6.80 (t, 7)	5.33 (s)	4.07 (s)	5.50; 6.60 (AB q, 11)	5.65 (m)	4.63 (m)
18	...	4.82 (s)	...	5.78; 6.10 (AB q, 10)	...	4.40 (m)
20a	...	6.46 (s)	5.60 (s)	6.91 (s)	5.81 (m)	4.81 (m)
20b	...	6.51 (s)	5.79 (s)	6.37 (s)	5.53 (m)	4.75 (m)
20c	...	6.44 (s)	6.04 (s)	5.68; 6.23 (AB q, 12)	5.72 (m)	4.69 (m)
20d	...	6.42 (s)	4.72 (s)	5.89; 6.20 (AB q, 11)	5.73 (m)	4.72 (m)
21a	...	6.57 (s)	...	6.40 (s)	5.74 (m)	4.68 (m)
22b	5.48 (t, 7)	6.25 (d, 6)	4.73 (d, 6)	6.06 (s)	5.97 (m)	4.67 (m)
24b[f]	5.40 (t)	6.35 (s)	4.60 (m)	6.00 (AB q)	5.70	4.60 (m)
25b[g]	5.5 (t)	4.7	4.7	6.3 (s)		4.7
25c[g]	5.47 (t)	4.7 (m)	4.7 (m)	6.27 (s)	4.7 (m)	4.7 (m)
27[g]	5.50 (t)	4.78 (d, 9)	5.95 (d, 9)	5.93 (s)	6.24 (t)	4.65 (m)
28[g]	5.41 (t)	4.64 (d, 11)	6.18 (d, 11)	6.46 (AB q)	4.15 (m)	4.7 (m)

[a] Unless otherwise specified, the nmr spectra were taken on a Varian A-60 in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in ppm on the τ scale. Abbreviations in brackets denote singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). [b] Recorded on a Varian HR-100 in benzene. [c] In this case, the assignment of H-21 and H-22 cannot be made unequivocally and could be reversible. [d] Determined in pyridine. [e] The protons at C-15 and C-16. [f] Data from ref 23 [R. Tschesche and G. Wulff, *Tetrahedron Lett.*, 1569 (1965)]. [g] Data from ref 24 [R. Kuhn and I. Löw, *Tetrahedron*, **22**, 1899 (1966)].

shifted to 242 mμ[9] (ϵ 9900) in the oxidation product **3a**. The normal oleanene skeleton is attributed to jegosapogenol, since the selenium-dioxide oxidation of the tetraacetate **1c** led to a heteroannular diene showing triple ultraviolet absorption maxima (242, 250, and 260 mμ) characteristic of $\Delta^{11-12,13-18}$-dienes of the β-amyrin series.[10] (See Chart I).

On treatment with alkali in methanol–dioxane at 0° overnight, the keto tetraacetate **4a** underwent a retro aldol reaction[11] to furnish the nor ketone **5**,[12] which showed the absence of a primary hydroxyl group in the nmr spectrum. On titration it consumed 0.67 mol of periodic acid, indicating the presence of one α-glycol moiety. One of the two protons in the α-glycol system, H_α, exhibits a triplet signal (J = 9 Hz) at τ 5.81 due to the coupling with an adjacent newly generated proton (see A → B). Dehydration of **1c** with thionyl chloride–pyridine furnished an olefin, **10** (Chart II). In its nmr spectrum, the newly generated ethylenic protons (H-15 and H-16) appear as an AB quartet signal (J = 10 Hz) at τ 4.25 and 4.33, respectively (see C → D). The axial nature of the hydroxyl group at C-16 and the diequatorial configuration of the α-glycol system were established from nmr spectral as well as chemical evidence.[1]

On alkali treatment in methanol–dioxane at room temperature, the nor ketone **5** gave rise to a product which exhibited two absorption maxima at 247[13] and 300 mμ in the uv spectrum. This product is assumed to be a mixture of **6a** and **7a**. On refluxing with methanolic alkali, **6a** changed completely into its more stable isomer **7a**, which absorbs at 300 mμ in the uv spectrum. The mixture of compound **6a** and **7a** obtained above was oxidized with chromium trioxide–acetic acid and the resulting product was chromatographed on silica gel to afford **8a**, showing a uv absorption maximum at 250 mμ. On addition of 1 drop of alkali, this maximum was shifted to 300 mμ (**8a** → **9a**). Similar results were obtained in a retro aldol reaction of the keto tetrabenzoate **4b**. Treatment of **4b** with alkali in methanol–dioxane gave **6b**,[14] which was then oxidized with manga-

(9) This value of maximum is abnormally low compared with the value (*ca.* 250 mμ) usually observed for 11-keto-Δ^{12}-triterpenes [for leading references, see C. R. Noller, *J. Amer. Chem. Soc.*, **66**, 1269 (1944)]. This suggested the influence of some additional structural features upon this chromophore [see C. Djerassi, C. H. Robinson, and D. B. Thomas, *ibid.*, **78**, 5685 (1956)].

(10) L. Ruzicka, G. Muller, and H. Schellenberg, *Helv. Chim. Acta*, **22**, 767 (1939); D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951).

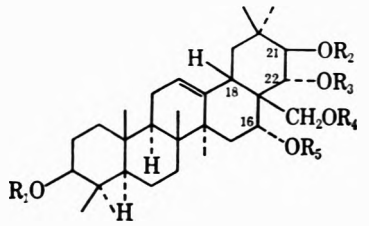
(11) D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 887 (1954).

(12) In this retro aldol reaction, no epimerization at C-17 appears to have occurred, since the ORD curve of the nor ketone **5** gave a negative Cotton effect [ORD (methanol) $[\alpha]_{589}$ −89°, $[\alpha]_{313}$ −2460° tr, $[\alpha]_{278}$ 2140° pk; see C. Djerassi, J. Osiecki, and W. Closson, *J. Amer. Chem. Soc.*, **81**, 4587 (1959)].

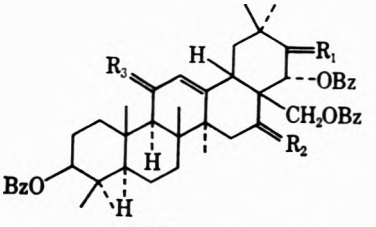
(13) The absorption maximum at 247 mμ is due to the α,β-unsaturated carbonyl chromophore in **6a**.

(14) In its uv spectrum, the benzenoid absorption at 231 mμ (ϵ 20,800), 249 (sh), 273 (sh), and 283 (sh) masks absorption due to the α,β-unsaturated carbonyl chromophore at 247 mμ.

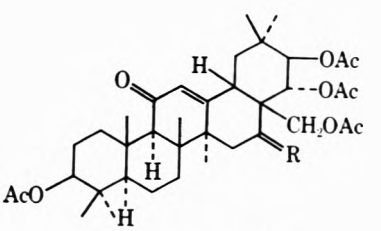
CHART I



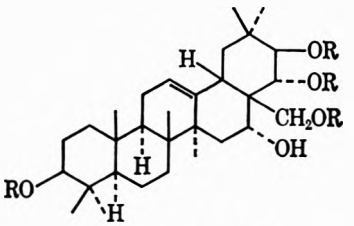
1a, $R_1 = R_2 = R_3 = R_4 = R_5 = H$
b, $R_1 = R_2 = R_3 = R_4 = R_5 = Ac$
c, $R_1 = R_2 = R_3 = R_4 = Ac$; $R_5 = H$
d, $R_1 = R_3 = R_4 = Ac$; $R_2 = R_5 = H$
e, $R_1 = R_2 = R_3 = R_4 = Bz$; $R_5 = H$
f, $R_1 = R_3 = R_4 = Bz$; $R_2 = R_5 = H$
g, $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = C(C_6H_5)_3$
h, $R_1 = R_3 = R_4 = Ac$; $R_2 = Ms$; $R_5 = H$



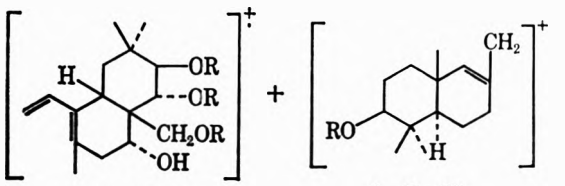
2a, $R_1 = \langle^{OH}_{H}$; $R_2 = O$; $R_3 = H_2$
b, $R_1 = R_2 = O$; $R_3 = H_2$
c, $R_1 = R_2 = R_3 = O$



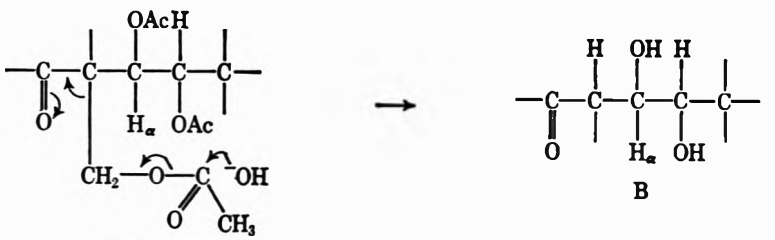
3a, $R = \langle^{H}_{OAc}$
b, $R = O$



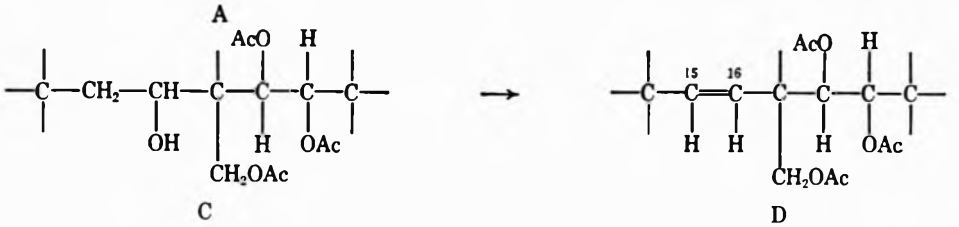
1a, R = H
c, R = Ac



a, R = H
c, R = Ac
b, R = H
d, R = Ac



A B



C D

nese dioxide in chloroform to **8b**. The uv spectrum of the latter showed a maximum at 232 mμ with shoulders at 236, 247, and 278 mμ,[15] whereas addition of alkali generated a new maximum at 300 mμ (**8b** → **9b**). The nmr spectra of **6**–**8** support the conclusions derived from the above uv spectral evidence. The ethylenic proton at C-12 found at τ 4.48 in **6b** and at τ 4.32 in **8a** and **8b** undergoes a downfield shift to τ 3.75 in **7b**.[16] Compounds **8a** and **8b** exhibited a sharp doublet signal (J = 3 Hz) at τ 3.37 and 3.34, respectively. These peaks are assignable to the proton at C-22 in coupling with the allylic proton at C-18. This large allylic coupling constant suggests that the overlap of the σ bond of C_{18} H and the π bond of C_{17} — C_{22} is maximal.[17] This is reflected in the ready double-bond migration of **6** and **8** to the corresponding isomers **7** and **9**.

On treatment with methanesulfonyl chloride–pyridine at room temperature, the triacetate **1d** was converted into a monomesylate, **1h**. Refluxing of **1h** with pyridine led to an epoxide, **12a**. The same epoxide was also obtained either by refluxing of **1d** with methanesulfonyl chloride–pyridine or reduction of **1h** with lithium aluminum hydride. In the nmr spectrum of the epoxide **12a**, the doublet signal at τ 4.77 (CHOAc at C-22) observed in the triacetate **1d** now changed to a singlet (τ 4.70),[18] and a new singlet signal (1 H) (CHO at C-21) occurred at τ 6.40 in **12a**, while the doublet at τ 5.97 (CHOH at C-21) found in **1d** disappeared. This

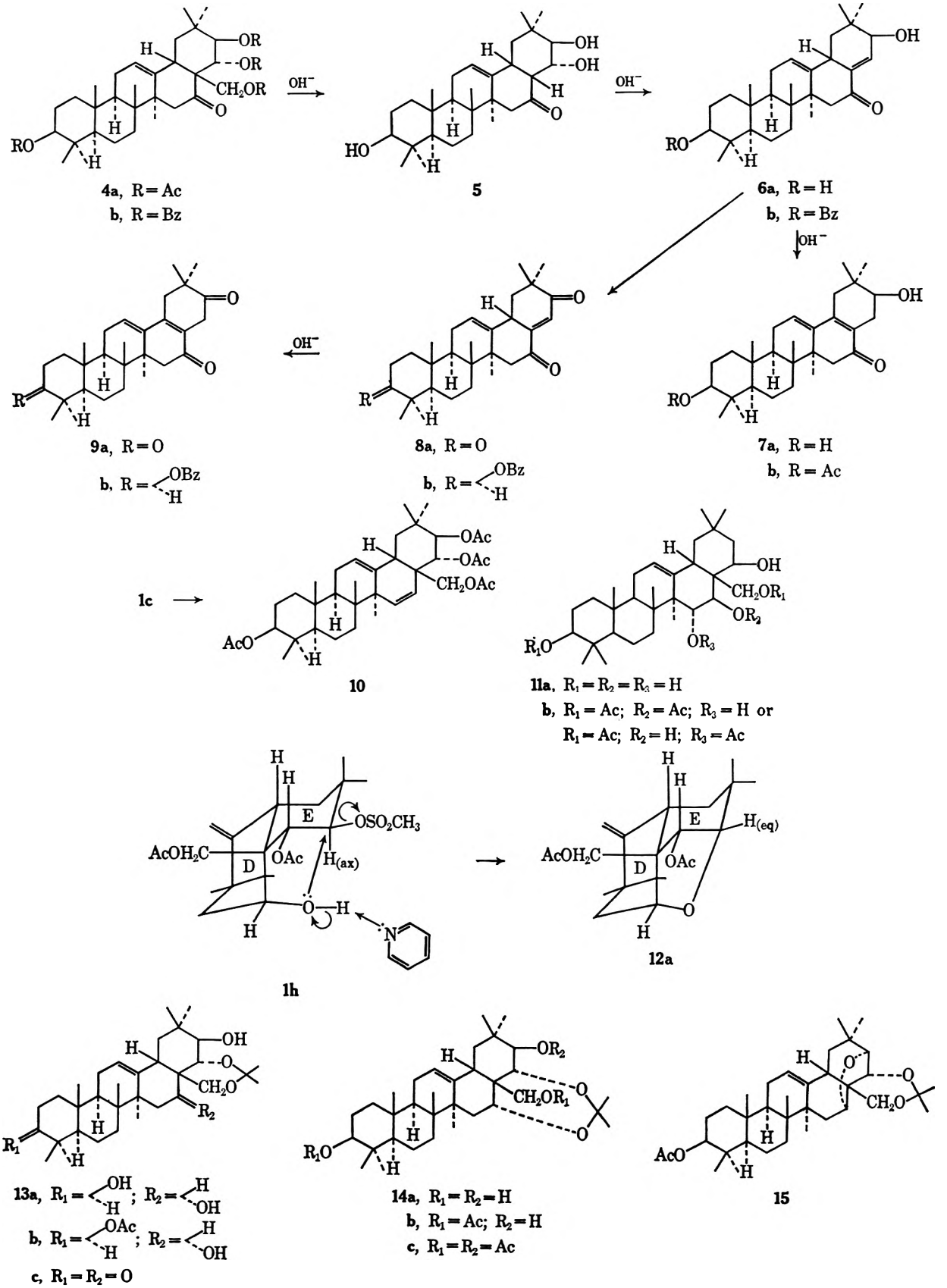
(15) Also in this case, absorption due to the α,β-unsaturated carbonyl chromophore at 250 mμ is masked by overlapping with the benzenoid absorption.

(16) For similar examples in which the introduction of the double bond conjugated to the carbonyl group causes a large downfield shift of the β proton, see N. S. Bhacca and D. H. Williams, "Application of Nmr Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 89.

(17) Inspection of Dreiding models showed that the angle (θ) between the plane of the double bond of C_{17} — C_{22} and the adjacent C_{18} H bond is approximately 90°. J_{a_1} is very small (<0.5 Hz) when θ < 20° or θ > 170°, whereas J_{a_1} lies in the range 1.3–3.1 Hz for θ = 60–110° (see p 108 of ref 16).

(18) Dreiding models of the epoxide **12a** showed that the dihedral angle of 21β-H and 22β-H is near 90°, so that $J_{21\beta\text{-H}-22\beta\text{-H}}$ must be near 0 [see M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959)].

CHART II



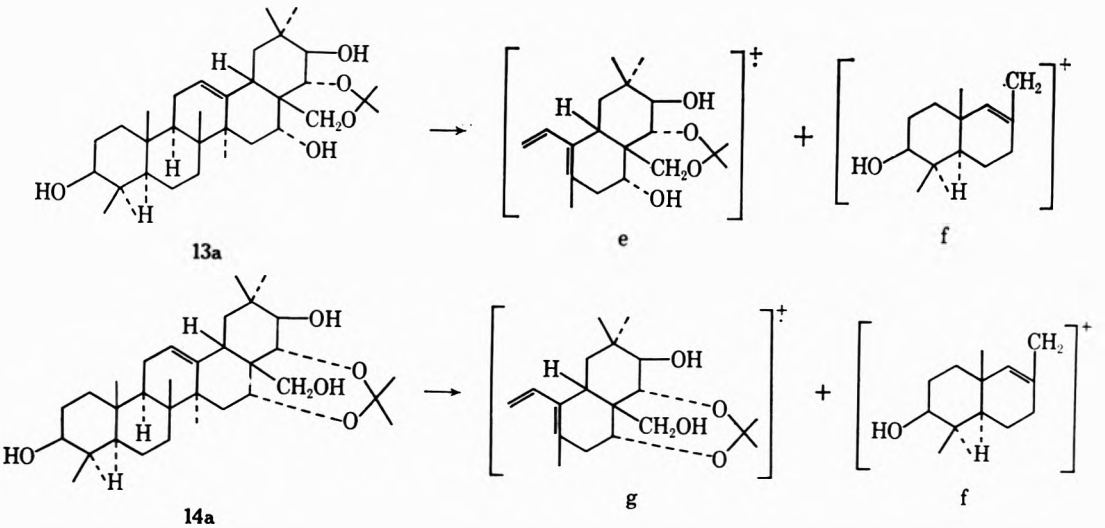
epoxide must have been formed by intramolecular SN2 displacement, as depicted by structures **1h** → **12a**.[19]

Acetonidation of jegosapogenol with *p*-toluenesulfonic acid–acetone gave two monoacetonides, **13a** and **14a** (see Experimental Section for the mass spectra and Chart III).

On acetylation with acetic anhydride–pyridine, **13a** yielded a monoacetate, **13b**, whereas **14a** furnished a mixture of a diacetate, **14b**, and a triacetate, **14c**, under

(19) If structure **11a** were the correct one for jegosapogenol, its triacetate would be **11b**, which cannot yield an epoxide analogous to **12a**.

CHART III



the same conditions. Oxidation of **13a** with the chromium trioxide–pyridine complex[20] afforded a 3,16-diketo derivative, **13c**, which showed only a six-membered carbonyl band in the infrared spectrum. On acetonidation with perchloric acid–acetone, followed by acetylation, jegosapogenol furnished a product which proved to be different from **13b**, **14b**, or **14c**. Its nmr spectrum gave peaks at τ 8.53 [s, 6 H, $OC(O)(CH_3)_2$] and 6.53 (s, 1 H). The chemical shift and shape of the latter peak is consistent with the proton at C-21 in the epoxide derivatives (see Table I), and thus this product should be considered to be 16α,21α-epoxyacetonyl acetate **15**.

Lead tetraacetate oxidation of jegosapogenol in acetic acid gave rise to **16a**, which did not exhibit an aldehyde carbonyl absorption in its infrared spectrum. On acetylation, this compound formed a triacetate, **16b**, and on methoxylation with *p*-toluenesulfonic acid–methanol, followed by acetylation, it afforded a trimethoxy monoacetate, **17**. Oxidation of **16a** with Jones reagent yielded a ketolactone, **18**, showing an infrared lactone carbonyl band at 1761 cm^{-1} in addition to a six-membered ketone absorption at 1704 cm^{-1}. This compound exhibited a signal (1 H, at C-21) at τ 4.82 in the nmr spectrum and had an absorption maximum at 203 mμ in the uv spectrum. Apparently, lead tetraacetate oxidation of jegosapogenol produced initially a dialdehyde, which underwent immediate acid-catalyzed intramolecular acetal formation to **16a**, as depicted in formula E. Sodium borohydride reduction of **18** and subsequent acetylation gave a diacetyl lactone, **19**, which showed both lactonic (1758 cm^{-1}) and ester carbonyl (1740 cm^{-1}) bands in the infrared spectrum. (See Chart IV.)

After we had proposed structure **1a**[1] for jegosapogenol, a striking similarity between this triterpene and barringtogenol C was noticed. Barua, *et al.*,[21] proposed structure **29** for barringtogenol C, a new triterpenoid sapogenin from the fruits of *Barringtonia acutangula* Gaertn, on the basis of an extensive chemical degradation.[22] However, Tschesche, *et al.*,[23] recently reported that the nmr spectrum of barringtogenol D (**30**, the 16α,21α-epoxy derivative of barringtogenol C) triacetate shows a singlet at τ 6.35 for the proton at C-21. If the acetoxyl group at C-22 were β axial, some degree of coupling between H-21 and H-22 should be observed, since the dihedral angle approximates 45° (Dreiding models). In order to confirm this point, we attempted to prepare from 16α,21α-epoxytriacetyl jegosapogenol (**12a**) 16α,21α-epoxy-3β,22β,28-triacetate (**22b**).

Alkaline hydrolysis of **12a** yielded an alcohol, **12b**, which, on tritylation, led to a trityl ether, **12c**. Oxidation with chromium trioxide–pyridine complex converted **12c** into a monoketo derivative, **20a**, and the latter was detritylated and then acetylated with acetic anhydride–pyridine at room temperature to a monoacetate, **20c**. Successive oxidation of **20c** with Jones reagent and hydrolysis yielded a diketo derivative, **21a**. Reduction of **21a** with sodium borohydride, followed by acetylation, afforded the desired compound, **22b**. This compound proved to be different from **12a** by melting point and infrared spectrum, and hence must be epimeric at C-22. The nmr spectrum of **22b** exhibited two doublets (J = 6 Hz) at τ 4.73 and 6.25, due to the protons at C-22 and C-21, respectively. Double-resonance experiments confirmed that these protons are in fact coupled to each other. These results suggested that the C-22 hydroxyl group of the barringtogenols should be α equatorial and that barringtogenol C should be jegosapogenol. Through the courtesy of Professor Tschesche, samples of barringtogenol C and D and barringtogenol D triacetate were obtained and were found to be identical with the corresponding derivatives of jegosapogenol (melting point, mixture melting point, and infrared spectrum). Thus, the structures of barringtogenol C (aescinidin)[24] and barringtogenol D should be revised to **1a** and **12b**, respectively. (See Chart V.)

The triterpene alcohol, protoaescigenin,[25] is ob-

(20) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(21) A. K. Barua, S. K. Chakraborti, P. Chakrabarti, and P. C. Maiti, *J. Indian Chem. Soc.*, **40**, 483 (1963); A. K. Barua and P. Chakrabarti, *Sci. Cult.* (Calcutta), **30**, 332 (1964); *Tetrahedron*, **21**, 381 (1965).

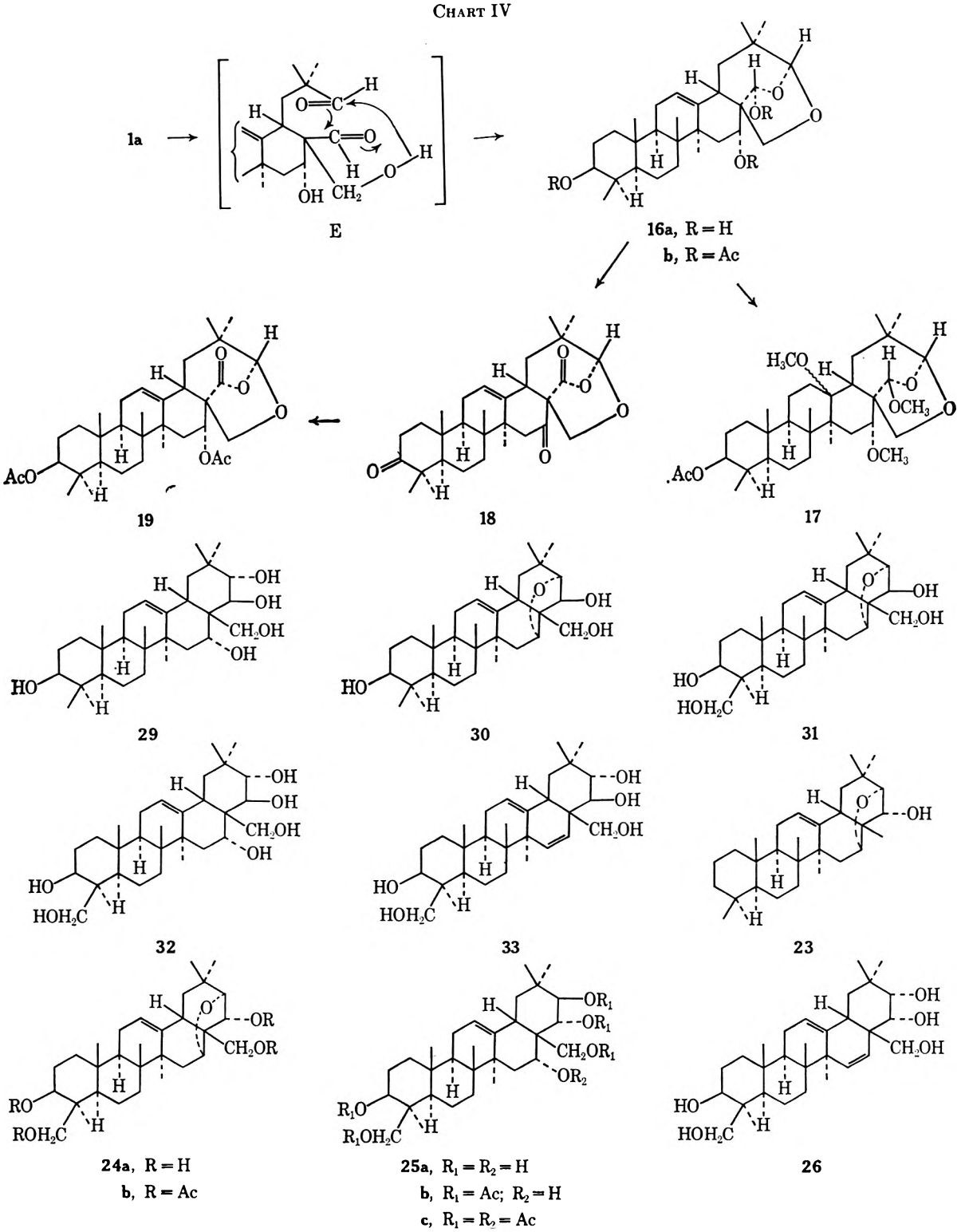
(22) The only difference between the proposed constitution of this compound and that of jegosapogenol lies in the configuration of the α-glycol system in ring E. The *trans*-diaxial (21α,22β) assignment for barringtogenol C was based mainly on the slow rate of reaction of this compound with lead tetraacetate.

(23) R. Tschesche and G. Wulff, *Tetrahedron Lett.*, 1569 (1965).

(24) R. Kuhn and I. Löw, *ibid.*, 891 (1964); *Tetrahedron*, **22**, 1899 (1966).

(25) R. Kuhn and I. Löw, *Ann.*, **669**, 183 (1963).

CHART IV



tained by the acid hydrolysis of aescin, a saponin from the seeds of the chestnut *Aesculus hippocastanum* L. On prolonged heating, aescigenin[26] is produced as an artifact. Isoaescigenin[27] is also present in the hydrolysate, and is formed when either protoaescigenin or aescigenin is refluxed with aqueous hydrochloric acid. The structures of aescigenin, protoaescigenin, and isoaescigenin were previously shown, on the basis of numerous chemical reactions, to be **31**, **32**, and **33**, respectively.[28] However, from nmr spectral as well as chemical evidence[29] presented previously, the structures of aescigenin and protoaescigenin should be revised to **24a** and

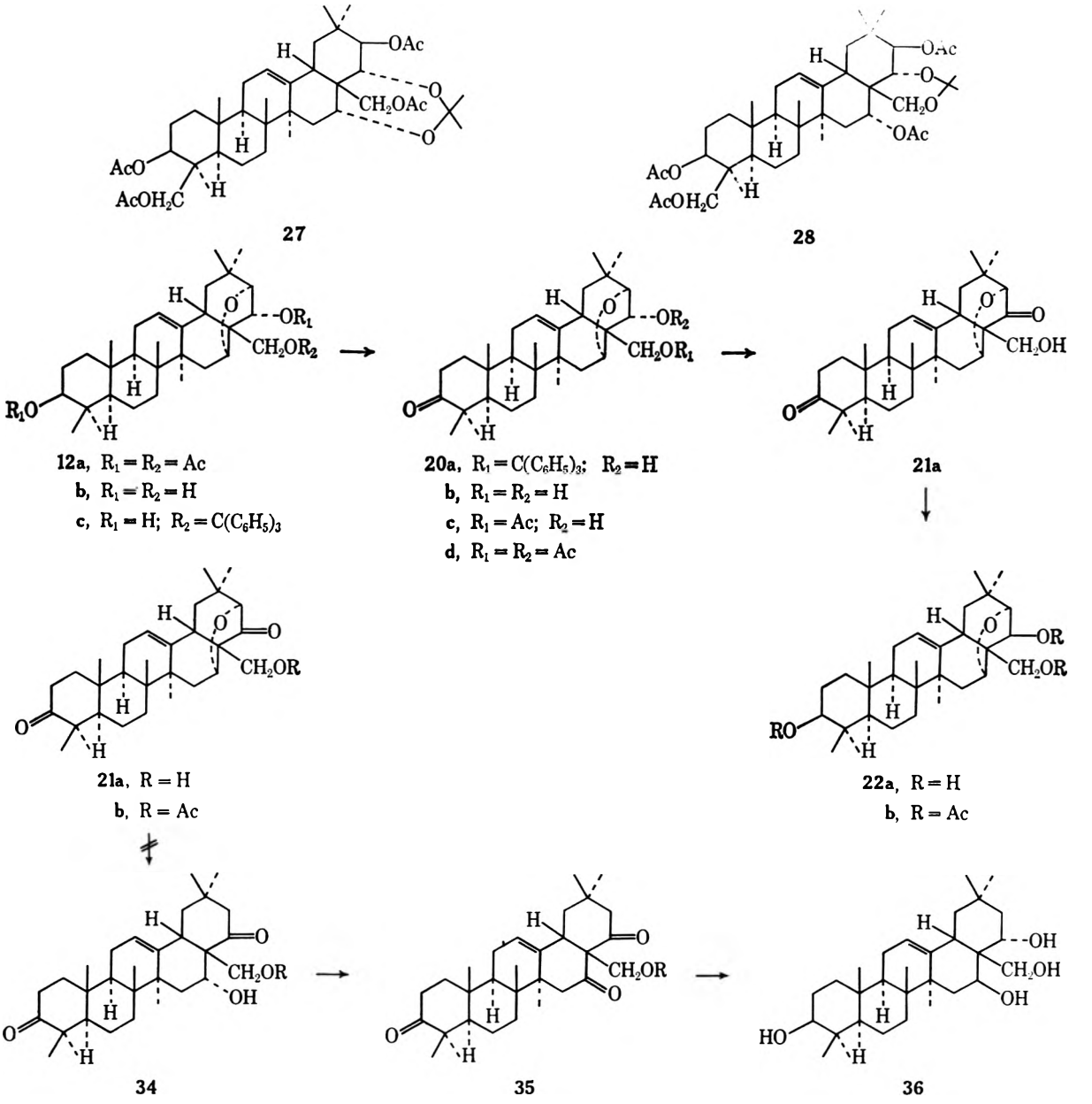
(26) G. Cainelli, A. Melera, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **40**, 2390 (1957).

(27) J. B. Thomson, *Tetrahedron*, **22**, 351 (1966).

(28) It is pertinent to note that these triterpenes, together with barringtogenol C and D, were interrelated chemically[21-27] with methyl oleanolate, whose structure has been eventually established by X-ray analysis [see C. H. Carlisle and A. M. Abd El Rahim, *Chem. Ind.* London), 279 (1954)].

(29) The original assignment of the β configuration to the 22-hydroxy group of aescigenin was based solely on molecular rotational data (see ref 26). Tschesche, *et al.*,[21] recently showed that aescigenin tetraacetate (**24b**) gives a singlet at τ 6.35 due to the proton at C-21 in the nmr spectrum, and thus H-22 must be β axial (see also discussion above). Furthermore, the epoxy alcohol **23**, derived from barringtogenol D (**12b**), was shown by Barua, *et al.*,[21] to be identical with the corresponding derivatives from aescigenin or protoaescigenin. The nmr spectra of the acetonides **27** and **28** derived from protoaescigenin show an AB quartet (see Table I) with J = 9 and 11 Hz, respectively, indicating that H-21 and H-22 are *trans* diaxial (see also ref 1).

CHART V



25a, respectively. The nmr spectra of isoaescigenin (originally assumed to be **33**) pentaacetate and its derivatives show an AB quartet in the τ 5 region. The magnitude of the small coupling constant ($J \cong 3$ Hz) between H-21 and H-22 does not enable a differentiation to be made among the three possibilities, *viz.*, (a) H-21β (equatorial) [OH-21α (axial)] and H-22α (equatorial) [OH-22β (axial)], (b) H-21β (equatorial) [OH-21α (axial)] and H-22β (axial) [OH-22α (equatorial)], and (c) H-21α (axial) [OH-21β (equatorial)] and H-22α (equatorial) [OH-22β (axial)].[30]

However, since H-22 of aescigenin was known to be α equatorial (see unrevised structure **31**), that of isoaescigenin derived from it was assumed to possess the same configuration (α equatorial).[31] However, now that the 22-OH has been established as being α equatorial (hence, the 22-H, as β axial), the only possible structure for isoaescigenin is **26**.[32,33]

Finally, we take this opportunity to report our unsuccessful attempts to convert jegosapogenol chemically into chichipegenin (**36**),[34] triterpene from the cactus *Lemaireocereus chichipe*, *via* the following route: **21** → **34** → **35** → **36**.

For the fission of the ether ring in the epoxy diketone **21**, a key step for this scheme, the following two methods were applied.

One was the reduction with zinc–acetic acid

(30) Dreiding models indicated that all these dihedral angles between H-21 and H-22 are approximately equal.

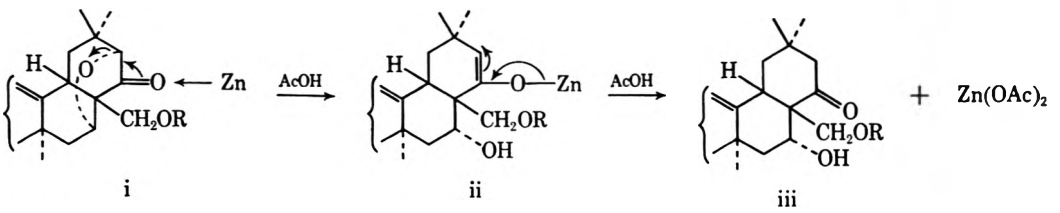
(31) The *trans*-diaxial configuration [21α-OH,22β-OH (21β-H,22α-H)] was assigned for the α-glycol system in isoaescigenin on the basis of the slow rate of its reaction with sodium metaperiodate (see ref 27).

(32) It should be noted that all the relevant structural features can be accommodated by this formula (see ref 27).

(33) Recently, a similar line of reasoning was presented to establish the identity of barringtogenol C and theasapogenol B [see I. Yoshioka, T. Nishimura, A. Matsuda, and I. Kitagawa, *Tetrahedron Lett.*, 5979 (1966); I. Yoshioka, T. Nishimura, A. Matsuda, K. Imai, and I. Kitagawa, *ibid.*, 637 (1967); N. Sugiyama, H. Aoyama, T. Sayama, and K. Yamada, *J. Chem. Soc. Jap.*, **88**, 1316 (1967)].

(34) A. Sandoval, A. Manjarrez, P. R. Leeming, G. H. Thomas, and C. Djerassi, *J. Amer. Chem. Soc.*, **79**, 4468 (1957).

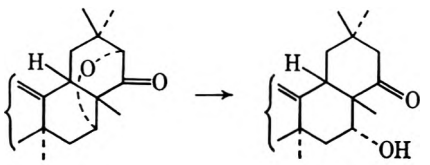
CHART VI



i ii iii

(Chart VI).[35] When **21a** was treated with zinc–acetic acid at room temperature for 13 hr, only the acetate **21b** was obtained. Refluxing of **21b** with zinc in ethanol containing a few drops of concentrated sulfuric acid yielded recovered starting material. Heating of **21b** with zinc in acetic acid with a few drops of concentrated hydrochloric acid in a sealed tube for 6 hr also resulted in the recovery of starting compound.

The other method was to reduce the epoxy diketone **21b** with aluminum amalgam.[36] However, when **21b** was allowed to react with aluminum amalgam in ether



37 **38**

saturated with water at room temperature for 1 day, only starting material was recovered. Refluxing of **21b** with aluminum amalgam in dioxane for 8 hr did not cleave the ether ring, and only a small amount of product, whose keto group at C-22 was supposed to have been reduced to the alcohol, was obtained besides the starting material.

Experimental Section

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi Model EPI-S spectrometer or a Perkin-Elmer Model 337 grating spectrophotometer in potassium bromide disks unless otherwise specified. Ultraviolet spectra were determined on a Shimazu Model SV-50 spectrophotometer in 95% ethanol solutions. Rotations were measured on a Zeiss polarimeter "0.01" in chloroform solutions. Optical rotatory dispersion was performed with a Jasco ORD/UV-5 spectropolarimeter. Unless otherwise noted, 100 mHz and 60 mHz nmr spectra were obtained in deuterochloroform solutions (about 10%) with Varian HR-100 and A-60 spectrometers, respectively, using TMS as an internal standard. Double-resonance experiments were carried out on the HR-100 after the method of L. F. Johnson, "Varian Technical Information Bulletin," Vol. III, No. 3, 1962, p 5. The mass spectra were determined at 70 eV with a CEC Model 21-103 mass spectrometer equipped with a direct inlet system.[37] Silica gel for column chromatography refers to Mallinckrodt silicic acid. For tlc, Merck silica gel G was used and the spots were identified by exposure to iodine vapor. Alumina used for column chromatography was either Woelm neutral, activity grade I, or Merck standardized, activity grade II–III. All extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate before evaporation.

Isolation of Jegosapogenol.—The dried skins (2.0 kg) of *Styrax japonica* Sieb. *et* Zucc. were ground and extracted four times each with 60 l. of hot methanol. The methanol extracts were combined, concentrated, and allowed to stand overnight. The pale green precipitates were filtered by suction and washed two times with 4 l. of ether to afford crude jegosaponin, which was heated under reflux with 8 l. of 50% ethanol containing 750 ml of concentrated hydrochloric acid for 6 hr. On cooling, crude jegosapogenin, which precipitated out, was filtered by suction and taken up in chloroform. The chloroform solution was filtered, dried, and evaporated. The residue was heated under reflux for 3 hr with 3 l. of 80% aqueous ethanol containing 180 g of sodium hydroxide. After cooling, the precipitated solid was crystallized from ethanol, yielding 100 g of jegosapogenol, mp 275° dec.

Preparation of Pure Jegosapogenol (1a).—Jegosapogenol is best purified through its acetate, followed by alkaline hydrolysis. The tetraacetate **1c** (1.361 g, see below) was refluxed with 5% methanolic sodium hydroxide (25 ml) for 3 hr. The solution was concentrated *in vacuo* and diluted with water, and the precipitate was crystallized from 95% ethanol, yielding 500 mg of pure jegosapogenol (**1a**): mp 326–330° dec; $[\alpha]_D$ 30° (*c* 0.64, pyridine); mass spectrum *m/e* (rel intensity) 490 (6, M^+), 282 (47, a), 264 (65, a − H_2O), 246 (72, a − $2H_2O$), 215 [100, a − ($2H_2O$ + CH_2OH)], 207 (35, b), and 197 [43, a − ($3H_2O$ + CH_2OH)]. Jegosapogenol was shown to be identical with barringtogenol C by direct comparison of their infrared spectra.

Anal. Calcd for $C_{30}H_{50}O_5$: C, 73.43; H, 10.27; O, 16.30. Found: C, 73.41; H, 10.18; O, 16.51.

Pentaacetate 1b.—Jegosapogenol (2.0 g) in acetic anhydride (50 ml) was heated under reflux for 1.5 hr. The solution was concentrated *in vacuo* to remove the excess acetic anhydride and extracted with chloroform. The chloroform layer was washed with water, dried, and evaporated. The oily residue (3.0 g) was chromatographed on 20 g of Woelm alumina. Elution with benzene gave 1.187 g of the pentaacetate **1b**, which was recrystallized from ethanol–water: mp 154–156°; $[\alpha]_D$ 28° (*c* 1.16); ir (Nujol) 1724 cm^{-1} (ester C=O); nmr τ (100 mHz, benzene) 7.85, 8.18, 8.21, 8.22, and 8.23 (s, 15 H, $OCOCH_3$).

Anal. Calcd for $C_{40}H_{60}O_{10}$: C, 68.54; H, 8.63; O, 22.83; 5AcO, 30.70. Found: C, 68.21; H, 8.57; O, 22.01; 5AcO, 30.78.

Tetraacetate 1c.—Jegosapogenol (10 g) in acetic anhydride (30 g) and pyridine (200 ml) was set aside at room temperature for 2 days. After removal of the solvent *in vacuo*, the product was extracted with benzene, and the benzene solution was washed successively with 1% hydrochloric acid, 5% aqueous sodium hydroxide, and water, then dried and evaporated. The crude product (11.34 g) obtained was chromatographed on 200 g of Woelm alumina, and eluted with benzene to give 5.20 g of the tetraacetate **1c**, which was recrystallized from ethanol–water: mp 234°; $[\alpha]_D$ 33° (*c* 1.13); ir ($CHCl_3$) 1739 cm^{-1} (ester C=O); nmr τ (100 mHz) 7.94 (3 H), 7.95 (3 H), and 7.98 (6 H) (s, four $OCOCH_3$), and 8.54 (3 H), 8.93 (3 H), 9.03 (3 H), and 9.11 (12 H) (s, seven C—CH_3); mass spectrum *m/e* (rel intensity) 658 (2, M^+), 390 (19, c − H_2O), 348 (20, c − AcOH), 330 [3, c − (H_2O + AcOH)], 288 (8, c − 2AcOH), 270 [16, c − (H_2O + 2AcOH)], 257 [52, c − (H_2O + AcOH + CH_2OAc)], 249 (23, d), 228 (31, c − 3AcOH), 215 [100, c − (2AcOH + CH_2-OAc)], and 197 [76, c − (H_2O + 2AcOH + CH_2OAc)].

Anal. Calcd for $C_{38}H_{58}O_9$: C, 69.27; H, 8.87; O, 21.86; 4AcO, 26.13. Found: C, 69.58; H, 8.65; O, 21.22; 4AcO, 25.84.

Triacetate 1d.—Jegosapogenol (8.0 g) in acetic anhydride (10 ml) and pyridine (80 ml) was kept at room temperature for 1 day. The solution was diluted with water and the product was

(35) We anticipated that mechanistically, this reduction proceeds as indicated above (i → ii → iii) and is similar to the reduction of α-acetoxy ketones with zinc–acetic acid to the corresponding ketones [see S. W. Pelletier, N. Adityachaudhury, M. Tomaz, J. J. Reynolds, and R. Mechoulam, *J. Org. Chem.*, **30**, 4234 (1965)].

(36) This method was used very successfully in the cleavage of the epoxy ketone **37** to the keto alcohol **38** (see ref 26).

(37) J. F. Lynch, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Experientia*, **19**, 211 (1963).

extracted with chloroform. The chloroform layer was washed with 5% hydrochloric acid and water, and evaporated. The crystalline residue was washed several times with ether to furnish 5.95 g of the triacetate **1d**: mp 245–247°; $[\alpha]_D$ 11° (*c* 1.33); ir ($CHCl_3$) 1739 cm^{-1} (ester C=O); nmr τ (100 mHz) 7.88 (3 H) and 7.94 (6 H) (s, three $OCOCH_3$), and 8.57, 8.98, 8.99, 9.02, 9.09, 9.11, and 9.12 (s, 21 H, seven C—CH_3).

Anal. Calcd for $C_{36}H_{56}O_8$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.15.

Tetrabenzoate 1e.—Jegosapogenol (10 g) was treated with 10 g of benzoyl chloride and 500 ml of pyridine at room temperature for 20 hr. After addition of methanol, the solvent was evaporated *in vacuo* and the residue was taken up in methylene chloride. The methylene chloride layer was washed successively with dilute hydrochloric acid, dilute aqueous sodium carbonate, and water, then dried and evaporated. The crude product was chromatographed on 200 g of Woelm alumina. Elution with benzene–ether (9:1) and crystallization from methanol yielded 9.24 g of the tetrabenzoate **1e**: mp >310°; $[\alpha]_D$ 21° (*c* 0.95); ir ($CHCl_3$) 1724 cm^{-1} (ester C=O); nmr τ 1.8–3.0 (m, 20 H, benzenoid protons).

Anal. Calcd for $C_{58}H_{66}O_9$: C, 76.79; H, 7.33. Found: C, 76.54; H, 7.17.

Tribenzoate 1f.—Jegosapogenol (1.0 g) in benzoyl chloride (3.0 ml) and pyridine (100 ml) was kept standing at room temperature overnight. The solution was treated with methanol, evaporated *in vacuo*, and extracted with methylene chloride. After working up in the usual way, 1.6 g of crude product was chromatographed on 45 g of Woelm alumina and eluted with ether to give 760 mg of the tribenzoate **1f**, which, after recrystallization from methanol, showed mp 271–273°; $[\alpha]_D$ 82° (c 0.22); ir ($CHCl_3$) 1724 (ester C=O) and 1605 cm^{-1} (benzenoid); nmr τ 1.8–2.8 (m, 15 H, benzenoid protons).

Anal. Calcd for $C_{51}H_{62}O_8$: C, 76.28; H, 7.78. Found: C, 76.57; H, 7.79.

Monoketomonohydroxytribenzoate 2a.—To a solution of 4 g of the tribenzoate **1f** in 500 ml of acetone was added, at 0°, 2.8 ml of Jones reagent (equivalent to 720 mg of chromium trioxide). After dilution of the solution with water, the product was extracted with methylene chloride. The methylene chloride solution was washed with aqueous sodium carbonate and water, dried, and evaporated, yielding 1.8 g of the monoketomonohydroxytribenzoate **2a**: mp 285–287° dec; ir ($CHCl_3$) 3546 (OH) 1712 (C=O), and 1608 cm^{-1} (benzenoid); nmr τ 1.8–2.8 (m, 15 H, benzenoid protons).

Anal. Calcd for $C_{51}H_{60}O_8$: C, 76.97; H, 7.55. Found: C, 76.71; H, 7.69.

Diketotribenzoate 2b.—The monoketomonohydroxytribenzoate **2a** (1.5 g) in acetone (20 ml) was treated at 0° with 0.5 ml of Jones reagent (equivalent to 125 mg of chromium trioxide) for 40 min. Usual work-up afforded 0.965 g of product which was chromatographed on 40 g of silica gel. Elution with methylene chloride gave 402 mg of the diketotribenzoate **2b**: mp 178–181°; ir ($CHCl_3$) 1712 cm^{-1} (C=O); nmr τ 1.8–2.8 (m, 15 H, benzenoid protons), 4.30 (s, 1 H, CHOBz at C-22), 4.37 (m, 1 H, double bond at C-12), and 5.30 (m, 3 H, CHOBz at C-3 and CH_2-OBz at C-28).

Anal. Calcd for $C_{51}H_{58}O_8$: C, 76.77; H, 7.32. Found: C, 76.35; H, 7.40.

Trityl Ether 1g.—Jegosapogenol (2.0 g) and trityl chloride (6.0 g) in pyridine (50 ml) were heated under reflux for 6 hr. The solvent was evaporated *in vacuo* to dryness, and the residue was taken up in chloroform. The chloroform solution was washed with water, dried, and evaporated. The product was chromatographed on 100 g of Merck alumina in benzene. Elution with chloroform–methanol (20:1) and crystallization from hexane–ether yielded 1.8 g of the trityl ether **1g**: mp 276–278°; nmr τ 2.62 (m 15 H, benzenoid protons), 4.76 (m, 1 H, double bond at C-12), 5.51 (m, 1 H, CHOH at C-16), 6.22 (s, 2 H, CH_2OCPh_3 at C-28), and 6.80 and 7.20 (AB q, 2 H, J = 9 Hz, CHOH at C-21 and C-22).

Anal. Calcd for $C_{49}H_{64}O_5$: C, 80.29; H, 8.80; O, 10.91. Found: C, 80.11; H, 8.95; O, 11.08.

Triketotribenzoate 2c.—The tribenzoate **1f** (289 mg) was treated with chromium trioxide (140 mg) in acetic acid (50 ml) and the solution was kept standing overnight. The usual work-up yielded 280 mg of crude product, which was chromatographed on 10 g of Woelm alumina. Elution with ether gave 108 mg of the triketotribenzoate **2c**, which, after recrystallization from methanol, showed mp 281°; ir ($CHCl_3$) 1721 (C=O), 1669 (conjugated C=O), and 1603 cm^{-1} (benzenoid); uv λ_{max} 232 mμ (ϵ 68,000); nmr τ 1.8–2.8 (m, 15 H, benzenoid protons), 4.16 (s 1 H, double bond at C-12), 4.32 (s, 1 H, CHOBz at C-22), 5.23 (t, 1 H, J = 7 Hz, CHOBz at C-3), and 5.18 and 5.48 (AB q, 2 H, J = 12 Hz, CH_2OBz at C-28).

Anal. Calcd for $C_{51}H_{56}O_9$: C, 75.34; H, 6.94. Found: C, 75.42; H, 7.13.

Monoketopentaacetate 3a.—The pentaacetate (569 mg) was oxidized at room temperature overnight with chromium trioxide (40 mg) in 5 ml of 85% aqueous acetic acid and 30 ml of glacial acetic acid. After decomposition of the excess chromium trioxide with methanol, the product was isolated as usual (462 mg) and then chromatographed on 14 g of Woelm alumina. Elution with benzene–ether (9:1) afforded 301 mg of an α,β-unsaturated ketone, **3a**, which, after recrystallization from water-saturated ether, had mp 233–236°; uv λ_{max} 242 mμ (ϵ 9900); ir ($CHCl_3$) 1748 (ester C=O) and 1667 cm^{-1} (conjugated C=O); nmr τ 4.30 (s, 1 H, double bond at C-12), 4.63 (s, 3 H, CHOAc at C-16, C-21, and C-22), 5.47 (t, 1 H, J = 8 Hz, CHOAc at C-3), 6.29 (s, 2 H, CH_2OAc at C-28), and 7.72, 7.92, 7.94, 7.97, and 8.04 (s, 15 H, five $OCOCH_3$).

Oxidation of the Tetraacetate with Chromium Trioxide.—The tetraacetate **1c** (1.028 g) was treated with chromium trioxide (200 mg) in glacial acetic acid (40 ml) at room temperature overnight. After dilution with water, the solution was extracted with ether and the product (994 mg) was isolated as usual. This was chromatographed on 30 g of Woelm alumina [elution with benzene–ether (9:1)] and crystallized from 95% ethanol to afford 347 mg of the keto tetraacetate **4a**: mp 283–285°; $[\alpha]_D$ −30° (*c* 1.43); ir ($CHCl_3$) 1745 (ester C=O) and 1724 cm^{-1} (C=O); nmr τ 7.94, 7.95, 7.98, and 8.01 (s, 12 H, four $OCOCH_3$); ORD (dioxane) $[\alpha]_{589}$ −30°, $[\alpha]_{324}$ −1290° tr, $[\alpha]_{275}$ +1470° pk.

Anal. Calcd for $C_{38}H_{56}O_9$: C, 69.48; H, 8.59. Found: C, 69.50; H, 8.86.

Elution with ethyl acetate gave 245 mg of crystals, which, after recrystallization from 95% ethanol, provided 40 mg of the 11,16-diketo tetraacetate **3b**: mp 295°; uv λ_{max} 241 mμ; ir ($CHCl_3$) 1739 (C=O) and 1667 cm^{-1} (conjugated C=O); nmr τ 7.93 (9 H) and 8.00 (3 H) (s, four $OCOCH_3$).

Anal. Calcd for $C_{38}H_{54}O_{10}$: C, 68.03; H, 8.11. Found: C, 68.00; H, 8.40.

Selenium Dioxide Oxidation of the Tetraacetate 1c.—A solution of 1.987 g of the tetraacetate in 100 ml of glacial acetic acid was heated under reflux with 1.3 g of selenium dioxide for 12 hr. The solution was diluted with water and the product was extracted with ether. The ether extract was washed with water, dried, and evaporated to afford 1.708 g of crude product which was chromatographed on 60 g of Woelm alumina. Elution with benzene–ether gave 0.867 g of product, which was recrystallized from hexane–ether to show mp 153–157°, identical with the pentaacetate **1b**. Elution with ether–ethyl acetate and ethyl acetate gave 749 mg of $\Delta^{11:12,13:18}$-diene as an amorphous solid, mp 147–153°, which had uv absorption maxima at 242, 250, and 260 mμ.

Reduction of the Keto Tetraacetate 4a with Sodium Borohydride.—To a solution of 740 mg of the keto tetraacetate in 25 ml of methanol and 10 ml of dioxane was added 300 mg of sodium borohydride. The solution was stirred at room temperature for 2.5 hr and diluted with water, and the product was extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to yield 740 mg of crude product, which was chromatographed on 20 g of Merck alumina. Elution with benzene–ether (4:1 to 1:1) gave 530 mg of product, which was shown to be identical with the tetraacetate **1c** by mixture melting point, ir, and nmr spectra.

Retro Aldol Reaction of the Keto Tetraacetate 4a.—To a solution of 1.0 g of the keto tetraacetate in 20 ml of dioxane was added 20 ml of ice-cooled 5% methanolic sodium hydroxide, and the solution was kept in the refrigerator overnight. The reaction mixture was poured onto aqueous sulfuric acid solution containing crushed ice. The product was extracted with chloroform, and the chloroform layer was washed with water, dried, and evaporated, leaving 650 mg of a residue which showed absorption maxima at 242 and 300 mμ in the uv spectrum. This was chromatographed on 10 g of silica gel and the chloroform fractions 4–6 (135 mg, one spot on tlc) were combined and crystallized from chloroform to give the nor ketone **5**: mp 245–246°; $[\alpha]_D$ −25° (*c* 0.78); ir 1705 cm^{-1} (C=O); nmr τ (60 MHz, pyridine)

8.71, 8.75, 8.85, 8.89, 8.94, 9.03, and 9.15 (s, 21 H, seven C—CH_3).

Anal. Calcd for $C_{29}H_{46}O_4 \cdot H_2O$: C, 73.07; H, 10.15. Found: C, 73.35; H, 10.55.

This compound consumed 0.67 equiv of periodic acid on titration.

Alkali Treatment of the Nor Ketone 5.—A solution of 600 mg of the nor ketone and 800 mg of sodium hydroxide in 40 ml of dioxane and 20 ml of methanol was left at room temperature overnight. The solution was diluted with water and the product was extracted with chloroform. Washing of the chloroform extract with water, drying, and evaporation yielded 520 mg of product, which exhibited two absorption maxima at 247 (corresponding to **6a**) and 300 mμ (corresponding to **7a**). By refluxing of this compound with 10 ml of 1% methanolic sodium hydroxide, the former band (247 mμ) was shifted to 300 mμ.

The compound **7a** (400 mg) was acetylated with acetic anhydride–pyridine (0.5–10 ml) at room temperature overnight. The product was isolated in the usual manner and chromatographed on 4 g of silica gel. Elution with chloroform and crystallization from ether–hexane afforded 52 mg of the monoacetate **7b**: mp 215°; $[\alpha]_D$ 37° (c 2.01); uv λ_{max} 300 mμ (ε 12,400); ir ($CHCl_3$) 3448 (OH), 1718 (ester C=O), 1661 (conjugated C=O), and 1629 and 1600 cm^{-1} (double bond); nmr τ 3.75 (m, 1 H, double bond at C-12), 5.47 (t, 1 H, J = 7 Hz, CHOAc at C-3), 6.48 (m, 1 H, CHOH at C-21), and 7.94 (s, 3 H, $OCOCH_3$).

Anal. Calcd for $C_{31}H_{46}O_4$: C, 77.13; H, 9.67. Found: C, 77.45; H, 9.44.

Oxidation of Compounds 6a and 7a with Chromium Trioxide–Acetic Acid.—The product (1.3 g) obtained by alkali treatment of the nor ketone **5** was dissolved in acetic acid (30 ml) and treated with 471 mg of chromium trioxide. After standing at room temperature overnight, the solution was diluted with water and extracted with chloroform. The product (490 mg) was isolated in the usual manner and chromatographed on 50 g of silica gel. Crystallization of the first chloroform effluent (65 mg) from methanol–acetone gave 27 mg of **8a** as needles: mp 188–191°; $[\alpha]_D$ 19° (c 1.10); ir ($CHCl_3$) 1706 (C=O), 1686 (conjugated C=O), and 1623 cm^{-1} (double bond); nmr τ 3.37 (d, 1 H, J = 3 Hz, at C-22), 4.33 (m, 1 H, double bond at C-12), and 6.40 (m, 1 H, allylic proton at C-18).

Anal. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23. Found: C, 79.58; H, 8.91.

The uv spectrum of this compound showed an absorption maximum at 250 mμ, which, on addition of a trace of alkali, was shifted to 300 mμ.

Keto Tetrabenzoate 4b.—The tetrabenzoate (150 mg) in pyridine (1.5 ml) was treated with chromium trioxide–pyridine (200 mg–2.0 ml) complex. The mixture was kept standing at room temperature overnight, diluted with water, and extracted with chloroform. The chloroform solution was washed with dilute hydrochloric acid and water, dried, and evaporated. The residue was taken up in acetone and filtered on alumina. The filtrate was concentrated and crystallized from methanol to give 102 mg of the keto tetrabenzoate **4b**: mp >300°; ir 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{58}H_{64}O_9$: C, 76.97; H, 7.13; O, 15.91. Found: C, 76.75; H, 7.15; O, 15.61.

Retro Aldol Reaction of the Keto Tetrabenzoate 4b.—A solution of the keto tetrabenzoate in 50 ml of dioxane was treated with 20 ml of 10% aqueous sodium hydroxide at room temperature under a nitrogen stream for 3 days. The reaction mixture was diluted with water, the product was extracted with chloroform, and the chloroform extract was washed with water, dried, and evaporated *in vacuo*. After washing several times with ether, the product was recrystallized from methanol–methylene chloride, whereupon 750 mg of **6b** was obtained: mp 277–278° dec; $[\alpha]_D$ 1°; uv λ_{max} 231 (ε 20,800), 249 (sh), 273 (sh), and 283 (sh) mμ; ir ($CHCl_3$) 3534 (OH), 1706 (C=O), and 1639 cm^{-1} (double bond); nmr τ 1.8–2.7 (m, 5 H, benzenoid protons), 3.27 (q, 1 H, J = 2 and 3 Hz at C-22), 4.48 (m, 1 H, double bond at C-12), and 5.25 (t, 1 H, J = 7 Hz, CHOBz at C-3).

Anal. Calcd for $C_{36}H_{48}O_4$: C, 79.37; H, 8.88. Found: C, 79.29; H, 9.10.

Manganese Dioxide Oxidation of Compound 6b.—A solution of 445 mg of the compound in 40 ml of chloroform was vigorously stirred with 2.0 g of active manganese dioxide at room temperature overnight. The solution was filtered, and the filtrate was washed with water and evaporated to afford 390 mg of product. Purification by chromatography on 10 g of silica gel and recrystallization from methanol yielded 194 mg of **8b**: mp 259–261°; $[\alpha]_D$ 17°; ir ($CHCl_3$) 1721 (ester C=O) and 1689 cm^{-1} (conjugated C=O).

This compound showed uv λ_{max} 232 (ε 22,800), 236 (sh), 247 (sh), and 278 (sh) mμ, and by addition of a trace of alkali, a new peak was generated at 300 mμ.

Dehydration of the Tetraacetate 1c with Thionyl Chloride–Pyridine.—The tetraacetate (6.23 g) was heated under reflux with thionyl chloride (12 ml) and pyridine (200 ml) for 3 hr. Water was added to the reaction mixture and the product was extracted with ether. The ether extract was washed with dilute hydrochloric acid and water, dried, and evaporated, yielding 6.34 g of product. This was chromatographed on 120 g of Merck alumina, and elution with benzene to benzene–ether (3:1) gave 4.99 g of product. Recrystallization from methanol yielded 2.78 g of the olefin **10**: mp 230–232°; $[\alpha]_D$ −4.6° (c 1.15); ir 1740 cm^{-1} (ester C=O); nmr τ 7.93, 7.97, 7.99, and 8.01 (s, 12 H, four $OCOCH_3$).

Anal. Calcd for $C_{38}H_{56}O_8$: C, 71.22; H, 8.81. Found: C, 71.45; H, 8.91.

Triacetylmonomesylate 1h.—The triacetate **1d** (2.0 g) in pyridine (20 ml) was treated with methanesulfonyl chloride (1.0 ml) at room temperature. After 6 hr, the solution was diluted with water and extracted with chloroform, and the chloroform layer was washed with dilute hydrochloric acid and water, dried, and evaporated. Recrystallization of the crude product from methanol gave 1.88 g of the monomesylate **1h**: mp 168–169°; $[\alpha]_D$ 46° (c 0.75); ir 1735 cm^{-1} (ester C=O); nmr τ 7.00 (s, 3 H, OSO_2CH_3 at C-21), and 7.87, 7.93, and 7.95 (s, 9 H, three $OCOCH_3$).

Anal. Calcd for $C_{37}H_{58}O_{10}S$: C, 63.94; H, 8.41. Found: C, 63.66; H, 8.58.

Epoxy Compound 12a. Method A.—The triacetylmonomesylate **1h** (212 mg) was refluxed with pyridine (10 ml) for 1.5 hr. The solution was diluted with water and extracted with chloroform, and the chloroform extract was washed with dilute hydrochloric acid and water, dried, and evaporated. The product was chromatographed on 5 g of Merck alumina. Crystallization of the benzene fractions (169 mg) from acetone gave the epoxide **12a**: mp 235–236°; $[\alpha]_D$ 58° (c 1.11); ir 1740 cm^{-1} (ester C=O); nmr τ 7.95 (s, 9 H, three $OCOCH_3$); mass spectrum[23] m/e (rel intensity) 598 (2, M^+), 538 (8), 478 (1), 348 (83), 288 (73), 249 (20), 228 (100), 215 (72), 190 (100), and 189 (46).

This compound was shown to be identical with barringtogenol D triacetate by direct comparison (melting point, mixture melting point, and infrared spectrum).

Anal. Calcd for $C_{36}H_{54}O_7$: C, 72.21; H, 9.09. Found: C, 72.18; H, 9.21.

Method B.—The triacetate **1d** (478 mg) in methanesulfonyl chloride (1 ml) and pyridine (10 ml) was heated under reflux for 2 hr. The product was worked up as above and the crude product (474 mg) was chromatographed on 10 g of Merck alumina. Elution with benzene gave 438 mg of **12a**.

Lithium Aluminum Hydride Reduction of the Triacetylmonomesylate 1h.—To a suspension of 140 mg of lithium aluminum hydride in 60 ml of dry ether was added 500 mg of the compound in 30 ml of dry dioxane, and the mixture was stirred at room temperature for 5 hr. After the excess reagent was destroyed with water-saturated ether, the complex was treated with saturated aqueous sodium sulfate solution. The ether layer was separated, dried, and evaporated to yield 362 mg of product, which, after crystallization from methanol, showed mp >300°. Identity with the epoxytriol **12b** (see below) was achieved by direct comparison (infrared spectrum). On acetylation, this compound gave rise to the epoxytriacetate **12a** (melting point and nmr spectrum).

Acetonidation of Jegosapogenol. Method A. Catalyzed with *p*-Toluenesulfonic Acid.—Jegosapogenol (1.0 g) in 140 ml of dry acetone containing 200 mg of *p*-toluenesulfonic acid was heated under reflux for 15 hr. The solution was evaporated and the product was taken up in chloroform. The chloroform solution was evaporated and the residue (1.0 g) was chromatographed on 25 g of Woelm alumina. Elution with benzene–ether [(3:1) to (1:1)] yielded, after recrystallization from acetone, 280 mg of the acetonide **13a**: mp 259–263°; $[\alpha]_D$ 101° (c 0.43); nmr τ 8.53 [s, 6 H, $OC(O)(CH_3)_2$]; mass spectrum m/e (rel intensity) 530 (4, M^+), 454 [3, M − (H_2O + Me_2C=O)], 441 [9, M − $Me_2C(OH)OCH_2$], 424 {14, M − [H_2O + $Me_2C(O)OCH_2$]}, 322 (100, e), 246 [57, e − (H_2O + Me_2C=O)], 215 {57, e − [H_2O + $Me_2C(OH)OCH_2$]}, 207 (58, f), and 197 {25, e − [$2H_2O$ + $Me_2C(OH)OCH_2$]}.

Anal. Calcd for $C_{33}H_{54}O_5$: C, 74.67; H, 10.26. Found: C, 74.85; H, 10.29.

Elution with ether–methanol (9:1) and crystallization from acetone yielded 90 mg of the acetonide **14a**: mp 206–207°; $[\alpha]D$ 102° (*c* 0.34); nmr τ 8.31 and 8.49 [s, 6 H, $OC(O)(CH_3)_2$]; mass spectrum *m/e* (rel intensity) 530 (0.6, M^+), 512 (51, M − H_2O), 454 [6, M − (H_2O + Me_2C=O)], 436 [15, M − (2H_2O + Me_2C=O)], 246 [100, g − (H_2O + Me_2C=O)], 233 [88, g − (CH_2OH + Me_2C=O)], 228 [52, g − (2H_2O + Me_2C=O)], 215 [54, g − (H_2O + CH_2OH + Me_2C=O)], 207 (57, f), and 197 [41, g − (2H_2O + CH_2OH + Me_2C=O)].

Anal. Calcd for $C_{33}H_{54}O_5 \cdot H_2O$: C, 72.22; H, 10.29. Found: C, 72.07; H, 10.39.

Acetylation of the Acetonide 13a.—The acetonide (600 mg) in acetic anhydride (1 ml) and pyridine (10 ml) was set aside at room temperature overnight. The solution was diluted with water and extracted with chloroform, and the chloroform layer was washed with dilute hydrochloric acid and water, dried, and evaporated. The product (600 mg) was chromatographed on 20 g of Woelm alumina, and elution with benzene–ether (3:1) gave 230 mg of the monoacetate **13b** as an amorphous powder: nmr τ 7.94 (s, 3 H, $OCOCH_3$).

Acetylation of the Acetonide 14a.—The acetonide (230 mg) in acetic anhydride (1.5 ml) and pyridine (8 ml) was kept standing at room temperature for 4 days. The solution was diluted with water and the product was extracted with chloroform. The chloroform layer was washed with dilute hydrochloric acid and water, dried, and evaporated, yielding 226 mg of product. This was chromatographed on 5 g of Woelm alumina and eluted with benzene to give 36 mg of the triacetate **14c** as an amorphous powder: nmr τ 7.90, 7.91, and 7.94 (s, 9 H, three $OCOCH_3$).

Elution with benzene–ether [(6:1) to (1:1)] gave 60 mg of the diacetate **14b**, which, after crystallization from ethanol, showed mp 222–225°; nmr τ 4.66 (m, 1 H, double bond at C-12), 5.47 (t, 1 H, J = 8 Hz, CHOAc at C-3), 5.82 and 6.05 (AB q, 2 H, J = 11 Hz, CH_2OAc at C-28), 6.00 and 6.10 (AB q, 2 H, J = 10 Hz, CHOH at C-21 and CHO- at C-22), 6.44 (m, 1 H, CHO- at C-16), and 7.90 and 7.95 (s, 6 H, two $OCOCH_3$).

Oxidation of the Acetonide 13a by Chromium Trioxide–Pyridine Complex.—The acetonide (235 mg) in pyridine (2.5 ml) was oxidized with chromium trioxide–pyridine (250 mg–2.5 ml) at room temperature overnight. The reaction mixture was diluted with water and extracted with chloroform. The chloroform layer was washed with dilute hydrochloric acid and water, dried, and evaporated, yielding 230 mg of product. This was filtered in chloroform on 4 g of Woelm alumina and the filtrate was concentrated to dryness. Crystallization of the residue from methanol gave 120 mg of **13c**: mp 275–277°; ir ($CHCl_3$) 1705 cm^{-1} (C=O); nmr τ 4.49 (m, 1 H, double bond at C-12), 5.64 and 6.22 (AB q, 2 H, J = 12 Hz, CH_2O- at C-28), 5.88 (d, 1 H, J = 9 Hz, CHO- at C-22), 6.42 (d, 1 H, J = 9 Hz, CHOH at C-21), 8.52 [s, 6 H, $OC(O)(CH_3)_2$], and 8.60, 8.74, 8.86, 8.89, 8.92, 8.98, and 9.04 (s, 21 H, seven C—CH_3).

Anal. Calcd for $C_{33}H_{50}O_5$: C, 75.24; H, 9.57. Found: C, 75.07; H, 9.71.

Method B. Catalyzed with Perchloric Acid.—To a solution of 2.0 g of jegosapogenol in 300 ml of dry acetone was added dropwise 30 drops of 60% perchloric acid until the solution became clear. The solution was kept at room temperature for 2 days, then concentrated *in vacuo*, diluted with water, and neutralized with aqueous sodium carbonate. The product (847 mg) was isolated by extraction with ether and chromatographed on 25 g of Woelm alumina. Elution with benzene–ether (9:1) gave 395 mg of product, which, after acetylation, was purified through chromatography. Crystallization from methanol gave the acetonide **15**: mp 227–229°; $[\alpha]D$ 26° (*c* 1.07); ir 1735 cm^{-1} (ester C=O); nmr τ 7.97 (s, 3 H, $OCOCH_3$) and 8.53 [s, 6 H, $OC(O)(CH_3)_2$].

Anal. Calcd for $C_{35}H_{54}O_5$: C, 75.77; H, 9.81. Found: C, 75.91; H, 10.01.

Lead Tetraacetate Oxidation of Jegosapogenol.—A suspension of 3 g of jegosapogenol and 7.5 g of lead tetraacetate in 180 ml of acetic acid was stirred at room temperature overnight. The resulting precipitate was collected and dissolved in ether, and the ether solution was washed with dilute aqueous sodium carbonate and water, dried, and evaporated, yielding 2.402 g of product, which was recrystallized from aqueous acetone to give 1.215 g of the hemiacetal **16a**: mp 206–207°; $[\alpha]D$ −14° (*c* 0.48).

Anal. Calcd for $C_{30}H_{48}O_5 \cdot H_2O$: C, 71.11; H, 9.95. Found: C, 71.24; H, 10.29.

Acetylation of this compound with acetic anhydride–pyridine afforded the acetate **16b**: mp 201–203°; $[\alpha]D$ −16° (*c* 0.74); ir ($CHCl_3$) 1727 cm^{-1} (ester C=O); nmr τ 3.13 [s, 1 H, O—C(O)H at C-22], 4.58 (m, 1 H, double bond at C-12), 5.30 [s, 1 H, O—C(O)H at C-21], 5.53 (m, 2 H, CHOAc at C-3 and C-16), 5.82 and 6.67 (AB q, 2 H, J = 10 Hz, CH_2O- at C-28), and 7.86, 7.97, and 7.98 (s, 9 H, three $OCOCH_3$).

Methoxylation of the Hemiacetal 16a.—A solution of 220 mg of the hemiacetal and 90 mg of *p*-toluenesulfonic acid in 100 ml of methanol was refluxed for 2 hr. The solution was concentrated and diluted with water, and the product was isolated (178 mg) by extraction with chloroform. This was chromatographed on 5 g of Woelm alumina, and the product (93 mg), eluted with ether, was acetylated with acetic anhydride (0.3 ml), and pyridine (3 ml). The acetate thus obtained was filtered in chloroform on alumina and crystallized from methanol, giving 20 mg of **17**: mp 233–234°; ir ($CHCl_3$) 1727 cm^{-1} (ester C=O); nmr τ 6.43, 6.46, and 6.47 (s, 9 H, three OCH_3), 7.96 (s, 3 H, $OCOCH_3$), and no signal corresponding to H-12 on the double bond.

Oxidation of the Hemiacetal 16a.—To a stirred solution of 100 mg of the hemiacetal in 5 ml of acetone was added dropwise 0.2 ml of Jones reagent (equivalent to 50 mg of chromium trioxide) under ice cooling. After 15 min, the solution was diluted with water and the product was extracted with chloroform, the chloroform solution was washed with aqueous sodium carbonate and water, dried, and evaporated. Recrystallization of the residue (79 mg) from acetone gave **18**: mp 290–300° dec; $[\alpha]D$ −6° (*c* 0.92); ir ($CHCl_3$) 1761 (lactone C=O) and 1704 cm^{-1} (C=O); uv λ_{max} 203 mμ (ϵ 10,800). The mass spectrum of this compound showed the molecular ion peak at *m/e* 482.

Anal. Calcd for $C_{30}H_{42}O_5$: C, 74.65; H, 8.77. Found: C, 74.62; H, 9.08.

Reduction of the Keto Lactone 18.—A solution of 173 mg of the keto lactone and 600 mg of sodium borohydride in 20 ml of methanol and 20 ml of dioxane was stirred at room temperature for 20 hr. The solution was diluted with water and the product was extracted with methylene chloride. The methylene chloride layer was washed with water, dried, and evaporated to afford 130 mg of product, which, after acetylation, was chromatographed on 5 g of Woelm alumina. Elution with methylene chloride gave 30 mg of the diacetyl lactone **19**: mp 243–245°; $[\alpha]D$ 47° (*c* 0.60); ir ($CHCl_3$) 1758 (lactone C=O), 1740 (ester C=O), and 1730 cm^{-1} (ester C=O); nmr τ 4.64 (m, 1 H, double bond at C-12), 4.83 (m, 1 H, CHOAc at C-16), 4.86 (s, 1 H, O—C(O)H at C-21), 5.50 (t, 1 H, J = 8 Hz, CHOAc at C-3), 6.06 and 6.28 (AB q, 2 H, J = 10 Hz, CH_2O at C-28), and 7.95 and 8.03 (s, 6 H, $OCOCH_3$).

Anal. Calcd for $C_{34}H_{50}O_7$: C, 71.55; H, 8.83. Found: C, 71.89; H, 8.73.

Epoxytriol 12b.—The epoxytriacetate **12a** (4.81 g) was refluxed with 5% methanolic sodium hydroxide (100 ml) for 2 hr. The solution was concentrated and diluted with water, and the resulting precipitate (3.52 g) was filtered and recrystallized from methanol to afford **12b**: mp >300°; $[\alpha]D$ 22° (*c* 0.70, dioxane).

This compound was shown to be identical with barringtogenol D by direct comparison of their infrared spectra.

Anal. Calcd for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24; O, 13.54. Found: C, 76.26; H, 10.12; O, 13.80.

Tritylation of the Epoxytriol 12b.—The epoxytriol (1.20 g) was refluxed with trityl chloride (3.60 g) and pyridine (30 ml) for 8 hr. The solution was diluted with water and the product was extracted with chloroform. The chloroform layer was washed with water, dried, and evaporated. The residue was chromatographed on 200 g of Merck alumina. Elution with ether–methanol (9:1) and crystallization from methanol gave 1.22 g of the trityl ether **12c**: mp 183–185°; $[\alpha]D$ 70° (*c* 1.40); nmr τ 2.66 (m, 15 H, benzenoid protons).

Anal. Calcd for $C_{49}H_{62}O_4$: C, 82.31; H, 8.74; O, 8.95. Found: C, 82.20; H, 8.95; O, 8.98.

Oxidation of the Epoxy Trityl Ether 12c by Chromium Trioxide–Pyridine.—The epoxy trityl ether (1.22 g) in pyridine (10 ml) was treated with chromium trioxide–pyridine (1.5 g:15 ml) complex and the mixture was stirred at room temperature overnight. The product (1.36 g) was isolated by extraction with chloroform as usual and chromatographed on 40 g of Merck alumina. The product, eluted with benzene to benzene–ether (1:1), was crystallized from methanol to yield 1.00 g of **20a**: mp 238–241°; $[\alpha]D$ 87° (*c* 0.67); ir 1700 cm^{-1} (C=O); nmr τ 2.62 (m, 15 H, benzenoid protons).

Anal. Calcd for $C_{49}H_{60}O_4$: C, 82.54; H, 8.48; O, 8.98. Found: C, 82.28; H, 8.34; O, 8.93.

Acid Hydrolysis of the Epoxyketo Trityl Ether 20a.—The epoxyketo trityl ether (925 mg) in ethanol (40 ml) was heated under reflux with 10 ml of 5% aqueous hydrochloric acid for 1.5 hr. The reaction mixture was diluted with water and the product (983 mg) was isolated by extraction with chloroform and chromatographed on 30 g of Merck alumina. Elution with chloroform to chloroform–methanol (20:1) yielded 666 mg of **20b**, which, after recrystallization from ether–chloroform, showed mp 230–233°; $[\alpha]_D$ 70° (*c* 0.59); ir 1703 cm^{-1} (C=O).

Anal. Calcd for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85; O, 13.60. Found: C, 76.73; H, 9.87; O, 13.65.

Acetylation of the Compound 20b.—A mixture of 3.2 g of the compound, 15 ml of pyridine, and 0.7 ml of acetic anhydride was set aside at room temperature overnight. After the usual work-up, the product was chromatographed in chloroform on 50 g of silica gel. The fractions 4–15 (chloroform), which were homogeneous on tlc, were combined and crystallized from methanol to yield 1.478 g of the monoacetate **20c**: mp 186–187°; $[\alpha]_D$ 24° (*c* 1.01); ir 1730 (ester C=O) and 1700 cm^{-1} (C=O); nmr τ 7.88 (s, 3 H, $OCOCH_3$).

Anal. Calcd for $C_{32}H_{48}O_5$: C, 74.96; H, 9.44; O, 15.60. Found: C, 74.74; H, 9.33; O, 15.60.

Rechromatography of the mother liquor of the fractions 4–15 and the fractions 2–3 (chloroform) gave an additional 200 mg of **20c**.

The fraction 1 (chloroform) gave the diacetate **20d**, which, after recrystallization from methanol, showed mp 218–219°; $[\alpha]_D$ −22° (*c* 2.22); ir 1740 (ester C=O) and 1700 cm^{-1} (C=O); nmr τ 7.96 (s, 6 H, two $OCOCH_3$).

Anal. Calcd for $C_{34}H_{50}O_6$: C, 73.61; H, 9.09; O, 17.31. Found: C, 73.56; H, 9.23; O, 17.25.

Oxidation of the Compound 20c.—To a solution of 165 mg of the compound in 10 ml of acetone was added, at 0°, 0.4 ml of Jones reagent (equivalent to 108 mg of chromium trioxide). The solution was stirred at room temperature for 2.5 hr and methanol was added to decompose the excess reagent. The solution was basified with dilute sodium bicarbonate and the product was extracted with chloroform. The chloroform layer was washed with water, dried, and evaporated to give 157 mg of product. This was chromatographed on 10 g of Merck alumina, and elution with benzene–ether (1:1) gave 41 mg of **21a**, which, after recrystallization from methanol, showed mp 228–230°; $[\alpha]_D$ −21° (c 1.02); ir 1753 (five-membered C=O) and 1703 cm^{-1} (C=O).

Anal. Calcd for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46; O, 13.66. Found: C, 76.56; H, 9.36; O, 13.42.

Reduction of the Compound 21a with Sodium Borohydride.—To a solution of 100 mg of the compound in 5 ml of methanol and 1 ml of chloroform was added 50 mg of sodium borohydride, and the mixture was stirred for 2 hr. The solution was diluted with water and the product was extracted with chloroform. The chloroform layer was washed with water, dried, and evaporated to afford 110 mg of product. Recrystallization from acetone gave 83 mg of **22a**: mp 258–259°; $[\alpha]_D$ 26° (*c* 0.42, dioxane).

Anal. Calcd for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24; O, 13.54. Found: C, 76.44; H, 10.16; O, 13.66.

Acetylation of Compound 22a.—The compound (74 mg) in acetic anhydride (0.2 ml) and pyridine (2 ml) was left at room temperature for 2.5 days. Usual work-up yielded 96 mg of product, which, after recrystallization from acetone, furnished 29 mg of the acetate **22b**: mp 215–216°; $[\alpha]_D$ 26° (*c* 0.92); ir 1730 cm^{-1} (ester C=O); nmr τ 7.90, 7.96, and 7.99 (s, 9 H, three $OCOCH_3$), and 8.53 (3 H), 8.94 (3 H), 9.06 (6 H), and 9.13 (9 H) (s, seven C–CH_3).

Anal. Calcd for $C_{36}H_{54}O_7$: C, 72.21; H, 9.09; O, 18.70. Found: C, 72.12; H, 8.96; O, 18.54.

Registry No.—**1a**, 13844-01-4; **1b**, 14694-67-8; **1c**, 13844-00-3; **1d**, 14257-18-2; **1e**, 20852-69-1; **1f**, 20852-70-4; **1g**, 20852-71-5; **1h**, 14162-52-8; **2a**, 20852-73-7; **2b**, 20852-74-8; **2c**, 20852-75-9; **3a**, 20852-76-0; **3b**, 20852-77-1; **4a**, 13843-99-7; **4b**, 20930-46-5; **5**, 20852-79-3; **6b**, 20852-80-6; **7b**, 20852-81-7; **8a**, 20852-82-8; **8b**, 20852-83-9; **10**, 20852-84-0; **12a**, 13862-93-6; **12b**, 19882-11-2; **12c**, 20852-86-2; **13a**, 20852-87-3; **13b**, 20852-88-4; **13c**, 20852-89-5; **14a**, 20852-90-8; **14b**, 20852-91-9; **14c**, 20852-92-0; **15**, 18178-99-9; **16a**, 20852-94-2; **16b**, 20852-95-3; **17**, 20852-96-4; **18**, 20852-97-5; **19**, 20930-47-6; **20a**, 20852-98-6; **20b**, 20852-99-7; **20c**, 20853-00-3; **20d**, 20853-01-4; **21a**, 14257-19-3; **22a**, 1258-99-7; **22b**, 864-98-2; **24a**, 17806-68-7; **24b**, 20853-06-9; **25a**, 20853-07-0; **25b**, 15914-79-1; **25c**, 20853-09-2; **26**, 20853-10-5; **27**, 20853-11-6; **28**, 20853-12-7.

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Mass Spectrometry in Structural and Stereochemical Problems. CLXXIII.[1] The Electron Impact Induced Fragmentations and Rearrangements of Trimethylsilyl Esters of ω-Phenoxyalkanoic Acids[2]

JOHN DIEKMAN,[3a] J. B. THOMSON,[3b] AND CARL DJERASSI

Department of Chemistry, Stanford University, Stanford, California 94305

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In connection with the computer-assisted interpretation of mass spectra, studies of the mass spectra of bifunctional compounds are needed in order to determine whether the electron impact induced fragmentations are characteristic of each functional group or whether they reflect some interaction of the two groups. In view of the wide applications of trimethylsilyl derivatives in combined vapor phase chromatography–mass spectrometry, the mass spectra of a series of trimethylsilyl ω-phenoxyalkanoates were investigated. These mass spectra exhibit four prominent decomposition modes (see Table I) which depend upon the interaction of the phenyl ether and silyl ester moieties. The mass spectra of some phenyl (II), benzyloxy (III), and alkoxy (IV) analogs, as well as some methyl ester analogs (V) illustrate the necessity of the presence of a heteroatom in *both* of the functional groups at the ends of the polymethylene chain in order to observe the appropriate interactions. Since these seem to be rather independent of chain length, it is suggested that charge transfer involving the heteroatoms is responsible for maintaining the heteroatoms in close proximity, thus resulting in coiling of the polymethylene chain. The cleavages characteristic of each separate functionality in these compounds (I–V) are also discussed.

Recently,[4] a program has been initiated in our laboratories on the application of artificial-intelligence computer techniques to the interpretation of mass spectra. Although the incipient stages of the program involved the establishment of rules for computer-assisted interpretation of the mass spectra of monofunctional compounds (*e.g.*, aliphatic ketones[4b]), the success to date has stimulated an anticipation of the problems involved in establishing rules for polyfunctional compounds. It is of particular importance to determine whether two functional groups in the same molecule will direct fragmentation patterns independent of one another, or whether their combination will cause unique sequences resulting from interaction of the two moieties. Obviously, the latter situation will necessitate significant variations in the "rules" for computer-assisted mass spectra interpretation. There already exist several documented instances where introduction of a second functional group into a monofunctional compound alters the independent fragmentation patterns, and there are a few striking examples of such interactions even when the functional groups are separated by long polymethylene chains.[5-10] A series of investigations into the mass spectral behavior of bifunctional compounds has been under way at Stanford[11-13] and the research described in this paper concerns still another group of such bifunctional compounds.

This study describes the electron impact induced fragmentation of a series of trimethylsilyl ω-phenoxyalkanoates (I) and some related species (II–V). Not

$C_6H_5O(CH_2)_nCO_2Si(CH_3)_3$
I (n = 1–6, 10)

$C_6H_5(CH_2)_nCO_2Si(CH_3)_3$
II (n = 2, 3)

$C_6H_5CH_2O(CH_2)_3CO_2Si(CH_3)_3$
III

$RO(CH_2)_nCO_2Si(CH_3)_3$
IV (n = 3, 4; R = CH_3)
(n = 3; R = C_2H_5)

$C_6H_5O(CH_2)_nCO_2CH_3$
V (n = 2, 3)

only are these results important for artificial intelligence studies, but there exist many other attractive reasons for investigating the mass spectra of this series. First, the ultimate intention of establishing a completely automated system capable of separating the components of a mixture by vapor phase chromatography, recording the mass spectrum of each component, and interpreting each spectrum with the aid of a computer necessitates establishing the "fragmentation rules" for derivatives particularly suited to vapor phase chromatographic separation. Trimethylsilyl derivatives have been the most popular choice as derivatives for facilitating vapor phase chromatographic separation of nonvolatile materials.[14] Second, a significant amount of research on the mass spectra of trimethylsilyl derivatives has been previously[9,15,16] accomplished at Stanford, and it is therefore attractive to investigate another type of trimethylsilyl derivative, trimethylsilyl esters. Third, these previous investigations[9,16] of

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(3) (a) National Science Foundation Predoctoral Fellow (1966–1967); National Institutes of Health Predoctoral Fellow (1967–1969). (b) National Institutes of Health International Postdoctoral Fellow (1965–1966) on leave from University College, Dublin.

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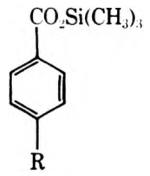
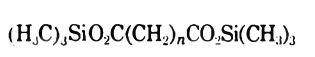
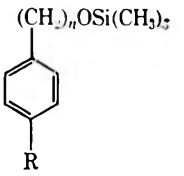
trimethylsilyl derivatives have provided a number of novel and interesting electron impact induced alkyl migrations,[17] and it was anticipated that trimethylsilyl esters would likewise exhibit new examples of these migrations. At present, there exist very few documented investigations of the mass-spectral behavior of trimethylsilyl esters.[18] Teeter[19] has reported the mass spectra of a number of substituted trimethylsilyl benzoates (VI) as well as the spectra of a number of tri-



VI



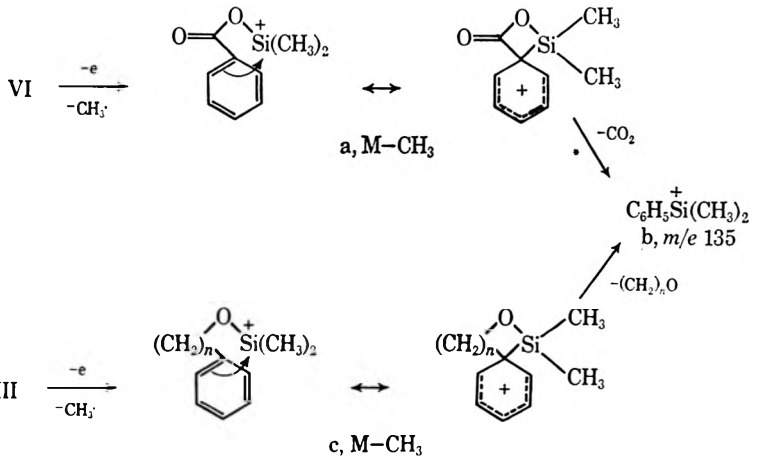
VII

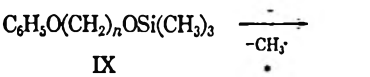


VIII

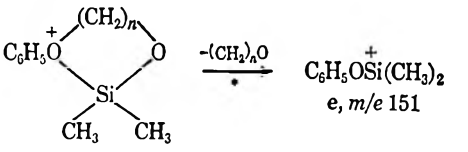
methylsilyl derivatives of amino acids. More recently, McCloskey and collaborators[7] discussed the mass spectra of some bistrimethylsilyl polymethylene esters (VII). It is important to note that both of these publications[7,19] contain interesting examples of electron impact induced alkyl migrations involving the trimethylsilyl group. McCloskey[7] presented important evidence for the coiling of chains in molecules, thus allowing the interaction of otherwise remote sites (the terminal trimethylsilyl ester functions). Teeter[19] demonstrated that the intense *m/e* 135 peak in the mass spectrum of trimethylsilyl benzoate (VI, R = H) arose by elimination of carbon dioxide from the M − CH_3 species (a → b).[20] This process (a → b) is analogous to the rearrangement c → b,[16] with elimination of formaldehyde, of the M − CH_3 species in the electron impact induced behavior of benzyl trimethylsilyl ester (VIII, n = 1). It is also similar to the abundant rearrangement ion (e) generated[9] from the M − CH_3 fragments (d) in the fragmentation of terminally substituted phenoxypolymethylene trimethylsilyl esters (IX). These three rearrangement processes (a → b, c → b, and d → e) stimulated a search for alkyl migrations in the fragmentation of terminally substituted phenoxypolymethylene trimethylsilyl esters (I). Parenthetically, it may be noted that there are a number of recent publications[6,8,21,22] which discuss the fragmentation patterns of the trimethylsilyl derivatives (ethers) of hydroxypolymethylene alkyl esters (X), but they have no important bearing on the present discussion.

The presently described investigation and elucidation of the electron impact induced fragmentations of some phenoxypolymethylene trimethylsilyl esters (I) and related compounds (II–V) employ deuterium labeling, high resolution mass measurements, and computer-assisted metastable peak evaluation[23] in order to assign fragmentation patterns.

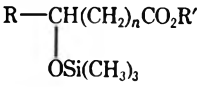




IX



d, M−CH_3



X

Discussion

As was pointed out in the introduction, the mass spectra (see for example, Figures 1–4) of a series of terminally substituted phenoxypolymethylene trimeth-

(17) For a complete review, see P. Brown and C. Djerassi, *Angew. Chem. Intern. Ed. Engl.*, **6**, 477 (1967).

(18) See ref 14, p 39.

(19) R. M. Teeter, Abstracts, Tenth Conference on Mass Spectrometry of the American Society for Testing Materials, New Orleans, La., 1962, p 51.

(20) The presence of a metastable ion for a given process is indicated in this paper by an asterisk (*) over the arrow in the fragmentation scheme.

(21) G. Eglinton, D. H. Hunneman, and K. Douraghi-Zadeh, *Tetrahedron*, **24**, 5929 (1968).

(22) G. Casparrini, M. G. Horning, and E. C. Horning, *Anal. Lett.*, **1**, 481 (1968).

(23) We wish to thank Mr. R. A. Stillman of this laboratory for writing this program.

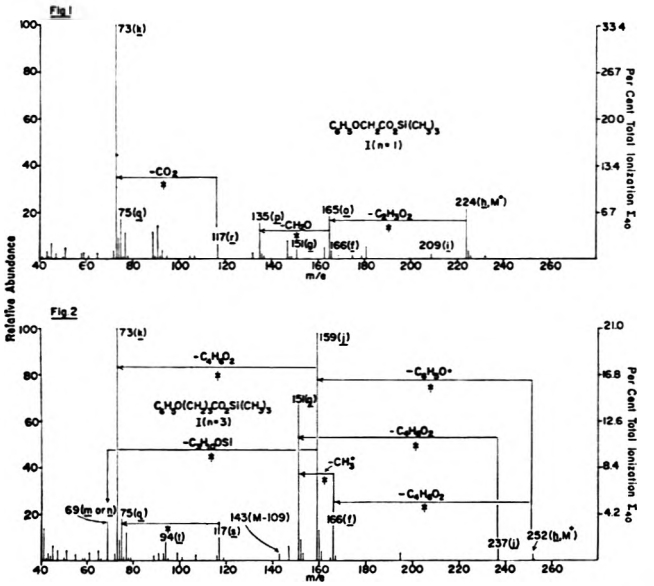


Figure 1.—Mass spectrum of trimethylsilyl phenoxyacetate (I, n = 1).
Figure 2.—Mass spectrum of trimethylsilyl 4-phenoxybutyrate (I, n = 3).

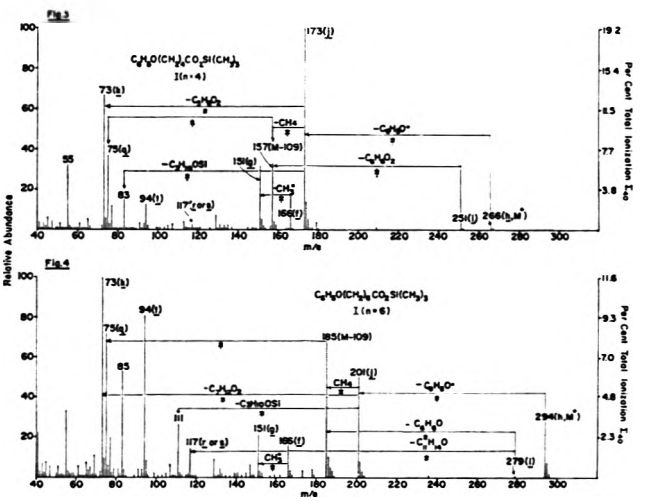


Figure 3.—Mass spectrum of trimethylsilyl 5-phenoxypentanoate (I, n = 4).
Figure 4.—Mass spectrum of trimethylsilyl 7-phenoxyheptanoate (I, n = 6).

ylsilyl esters (I, n = 1–6,10) were recorded in order to assess the influence of each functional group (the trimethylsilyl ester and the phenyl ether) upon each other in the electron impact induced fragmentation of the parent compound I. It was also pointed out that, because of the paucity of literature concerning the mass spectral behavior of trimethylsilyl esters, it is necessary to present a detailed discussion of their "characteristic" fragmentation patterns. The mass spectra of these phenoxypolymethylene trimethylsilyl esters (I) reveal some very interesting fragmentation schemes which result from interaction of the terminal functional groups, and these fragmentations are discussed prior to the "characteristic" trimethylsilyl ester fragmentations.

Fragmentation Patterns Resulting from Interaction of the Phenyl Ether and Trimethylsilyl Ester Moieties. The *m/e* 166 (f) and 151 (g) peaks.—The mass spectra (for examples, see Figures 1–4) of all of the phenoxypolymethylene trimethylsilyl esters (I) recorded in this study exhibit a peak at *m/e* 166 (see Table I), and high resolution mass measurements indicate that this peak corresponds to a fragment ion of composition $C_9H_{14}OSi$. A fragment ion having the same elemental composition was found previously[9] in the mass spectra of a series of phenoxypolymethylene trimethylsilyl ethers (IX) and was assumed to arise from the molecular ion by migration of the trimethylsilyl moiety to the phenoxy-oxygen atom with expulsion of the central portion of the molecule. An analogous fragmentation scheme (I → h → f) involving transfer of the trimethylsilyl group and expulsion of the central portion of the compound yields this same *m/e* 166 peak in the case of the trimethylsilyl esters (I). This fragmentation scheme is supported by large metastable peaks when n = 2 and n = 3. In accord with this proposed scheme is the observation that those compounds (see Table II) where deuterium atoms are incorporated into the *ortho* and *para* positions of the phenoxy ring (XI and XIV), the *m/e* 166 peak shifts to *m/e* 169. Those compounds which are labeled only in the methylene chain (see Table II) exhibit no shift of the *m/e* 166 peak in their mass spectra. It is clear, therefore, that no reciprocal hydrogen transfers are involved in this fragmentation.

At 70-eV ionizing energy, there appears to be no obvious dependence between the abundance of this *m/e* 166 peak (f) and the length of the methylene chain (see Table I). At low (12 eV) voltage, this peak increases substantially in per cent total ionization and also shows a preference for a 1,5 (n = 2) and 1,6 (n = 3) shift of the trimethylsilyl group. A similar situation had been encountered earlier[9] in the mass spectra of the phenoxytrimethylsilyl ethers (IX). Nevertheless, it is rather remarkable that the *m/e* 166 peak remains quite significant (37% relative abundance) even in the case of the trimethylsilyl ester of 11-phenoxyundecanoic acid (I, n = 10); this observation suggests that the molecular ion (h) of these molecules (I) is coiled in such a way as to permit the phenyl ether and trimethylsilyl ester moieties to remain close to one another. It is con-

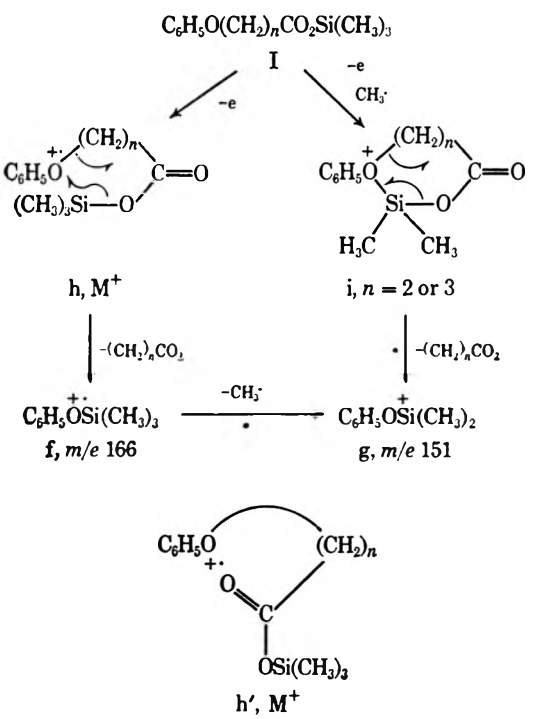


TABLE I

ABUNDANCE OF THE REARRANGEMENT PEAKS *m/e* 166 (f) AND 151 (g), M − 93 (j), AND M − 109 IN THE MASS SPECTRA OF THE PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I), $C_6H_5O(CH_2)_nCO_2Si(CH_3)_3$

	m/e 166				*m/e* 151				M − 93 (j)				M − 109			
	70 eV		12 eV		70 eV		12 eV		70 eV		12 eV		70 eV		12 eV	
	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]
n	%	%	%	%	%	%	%	%	*m/e*	%	%	%	%	*m/e*	%	%	%	%
1	0.7	2	0.3	1	1.3	4	0.0	0	131	0.0	0	0.0	0	115	0.0	0	0.0	0
2	4.1	27	11.7	39	15.1	100	4.8	16	145	5.7	38	12.6	42	129	3.8	25	4.5	15
3	3.1	15	14.4	27	14.1	67	7.0	13	159	20.6	98	53.5	100	143	0.6	3	0.0	0
4	1.2	6	6.5	10	6.1	32	0.6	1	173	19.2	100	64.9	100	157	6.3	33	2.6	4
5	1.3	10	3.2	7	3.3	25	0.0	0	187	13.3	100	45.5	100	171	9.7	73	9.6	21
6	1.9	16	4.8	22	2.4	21	0.4	2	201	5.8	50	18.8	87	185	7.9	68	10.8	50
10	4.2	37	6.2	15	2.5	22	0.0	0	257	6.3	55	11.1	27	241	8.0	70	1.2	3

[a] RI = Relative intensity of base peak.

TABLE II

SHIFTS OF THE REARRANGEMENT PEAKS IN THE MASS SPECTRA OF THE DEUTERIUM-LABELED PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I)

	Fragment[a]					
				[M − (90 + 93)],	M − C_7H_9O, *m/e*[b] (%)	
Compd	f, *m/e*[b]	g, *m/e*[b]	j, *m/e*[b]	*m/e*[b] (%)	70 eV	12 eV
2,4,6-d_3-$C_6H_2D_3OCH_2CO_2Si(CH_3)_3$ (XI)	166 → 169	151 → 154	...	...	...	...
$C_6H_5OCH_2CH_2CD_2CO_2Si(CH_3)_3$ (XII)	166 → 166	151 → 151	159 → 161	69 → 70 (*ca.* 74) 69 → 71 (*ca.* 26)	[c]	[c]
$C_6H_5OCH_2CD_2CH_2CO_2Si(CH_3)_3$ (XIII)	166 → 166	151 → 151	159 → 161	69 → 70 (*ca.* 25) 69 → 71 (*ca.* 75)	[c]	[c]
2,4,6-d_3-$C_6H_2D_3O(CH_2)_3CD_2CO_2Si(CH_3)_3$ (XIV)	166 → 169	151 → 154	173 → 175	83 → 84 (*ca.* 17) 83 → 85 (*ca.* 83)	157 → 159	157 → 159
$C_6H_5O(CH_2)_3CD_2CH_2CO_2Si(CH_3)_3$ (XV)	166 → 166	151 → 151	173 → 175	83 → 84 (*ca.* 25) 83 → 85 (*ca.* 75)	157 → 158 (36) 157 → 159 (64)	157 → 158 (41) 157 → 159 (59)
$C_6H_5OCH_2CD_2(CH_2)_2CO_2Si(CH_3)_3$ (XVI)	166 → 166	151 → 151	173 → 175	83 → 84 (*ca.* 40) 83 → 85 (*ca.* 60)	157 → 158 (24) 157 → 159 (76)	157 → 158 (20) 157 → 159 (80)

[a] In each case, the *m/e* value of the unlabeled fragment is shown being shifted to its *m/e* value for the indicated labeled analog. [b] Corrected for isotope abundance and calculated deuterium isotope composition. [c] Peak is too small to permit interpretation of the labeling data.

ceivable that a charge transfer between these functional groups could provide a means of holding these moieties in near proximity (h′).[24]

The increase in the contribution of the *m/e* 166 peak to the total ion current at 12 eV (see Table I) suggests that at higher electron voltages it fragments further to some other species; in fact, in all cases a large metastable ion is observed at *m/e* 137.4 (calcd $151^2/166$ = 137.4) corresponding to cleavage of a methyl group from f to yield the even-electron species g (*m/e* 151). The structure of this ion (g) is also supported by high resolution mass measurements ($C_8H_{11}OSi$) and deuterium-labeling experiments (see Table II).

A computer-assisted analysis[23] of all of the metastable peaks observed in the mass spectra of this series (I) points out that when $n = 2$ and $n = 3$ (but not in any of the other homologs) there exists a metastable ion corresponding to the genesis of the *m/e* 151 peak (g) from an M − CH_3 (i) precursor. An analogous fragmentation scheme was observed in the case of the trimethylsilyl ethers (IX), and it is suggested that the M − CH_3 ion (i) exists in a cyclic (6- or 7-membered ring) structure from which the *m/e* 151 ion g is generated by expulsion of the central part of the molecule.

M − 93 Rearrangement Peak.—The mass spectra of all of the ω-phenoxypolymethylene trimethylsilyl esters (I, see Figures 2–4) except the 2-phenoxyacetic acid derivative ($n = 1$, see Figure 1) exhibit an intense rearrangement peak (see Table I) resulting from the electron impact induced elimination of the terminal phenoxy group. There is abundant evidence substantiating the participation of the terminal ends of these molecules (I, n = 2–6, 10) in this important fragmentation process, which accounts for the base peak in the 70-eV spectra of trimethylsilyl 5-phenoxypentanoate ($n = 4$, see Figure 3) and 6-phenoxyhexanoate ($n = 5$). At 12 eV, this peak is outstanding in all of the spectra and accounts for more than 40% of the total ion current when n = 3, 4, and 5 (Table I). The substantiating evidence includes the following: first, the high resolution mass measurements in each case show the loss of a C_6H_5O radical; second, deuterium labeling (see Table II) verifies loss of the phenyl group in this process [the phenyl-labeled analog (XIV) exhibits cleavage of a $C_6H_2D_3O$ species (mass 96) whereas those analogs labeled in the methylene chain (XII, XIII, XV, and XVI) exhibit fission of an unlabeled C_6H_5O radical]; third, elimination of the phenoxy moiety without participation of the ester function would yield an energetically unfavorable primary radical (j″); fourth, in all instances (n = 2–6, 10) a very intense metastable peak supports the formation of this M-$C_6H_5O\cdot$ ion from the molecular ion; and finally, both high- (70 eV) and low- (12 eV) voltage spectra (see Table I) indicate some preference for a 3-, 4-, or 5-membered methylene chain in this fragmentation scheme, thus suggesting the possibility of at least a cyclic transition state and more likely a cyclic product ion. In such cases, a 5-, 6-, and 7-membered ring (n = 3, 4, and 5, respectively) might be more easily generated.

In the previously reported[9] mass spectra of some phenoxypolymethylene trimethylsilyl ethers (IX), there was reported a fragmentation involving bonding of the phenoxy radical to the charged siloxy-oxygen atom. This observation, coupled with the above experimental evidence, suggests a similar fragmentation scheme yielding an oxonium ion species j for the trimethylsilyl

(24) R. Brandt and C. Djerassi (see ref 11) have postulated a similar arrangement in their work on the mass spectra of some α-substituted tetrahydrofurans.

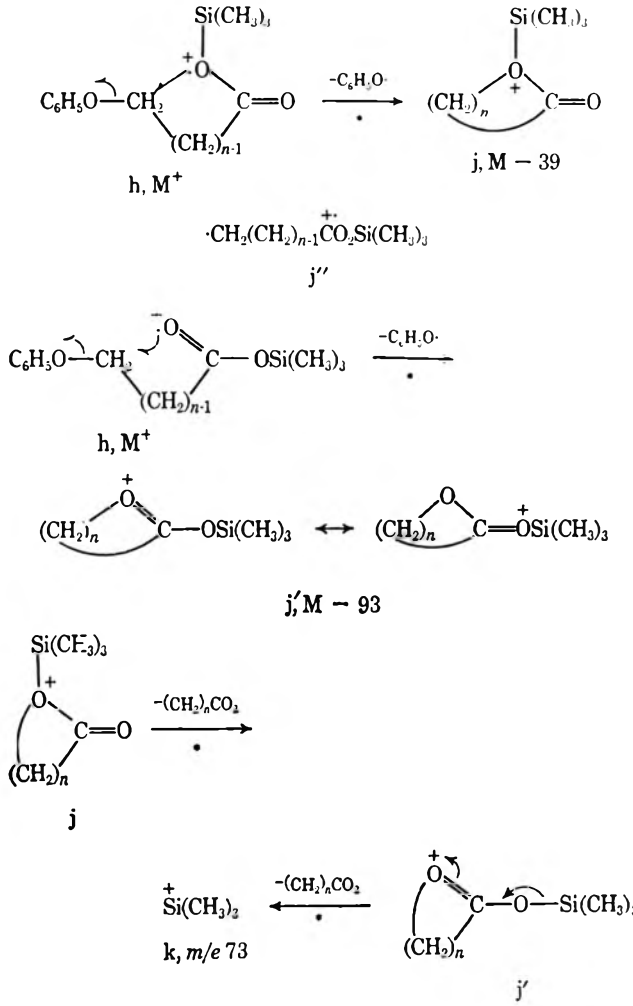
TABLE III

ABUNDANCE OF CERTAIN PEAKS "CHARACTERISTIC" OF PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I), $C_6H_5O(CH_2)_nCO_2Si(CH_3)_3$

		M⁺ (i)				M − 15 (h)				m/e 75 (q)				m/e (73 (k)				m/e 94 (t)			
		−70 eV−		−12 eV−		−70 eV−		−12 eV−		−70 eV−		−12 eV−		−70 eV−		−12 eV−		−70 eV−		−12 eV−	
		Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]	Σ40,	RI,[a]
n	m/e	%	%	%	%	m/e	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
1	224	6.7	21	37.6	100	209	0.7	6	1.9	2	5.7	17	0.4	1	33.4	100	13.9	37	3.7	11	0.8	2
2	238	6.2	41	30.0	100	223	2.3	15	3.9	13	6.8	45	0.3	1	12.1	80	0.6	2	4.7	31	9.3	31
3	252	0.6	3	3.2	6	237	1.1	5	2.1	4	3.8	18	0.0	0	21.0	00	2.1	4	1.7	8	1.1	2
4	266	0.4	2	1.9	3	251	0.8	4	0.6	1	7.1	27	0.6	1	12.9	67	1.3	2	2.5	13	0.6	1
5	280	2.3	17	14.1	31	265	0.3	2	0.5	1	8.0	60	0.5	1	12.8	96	1.8	4	5.2	39	2.7	6
6	294	3.2	28	21.6	100	279	0.1	1	0.4	2	8.4	72	0.9	4	11.6	100	2.2	10	9.4	81	6.3	29
10	350	11.4	100	41.0	100	335	0.9	8	0.0	0	3.4	30	2.9	7	3.1	27	2.5	6	3.5	31	6.6	16

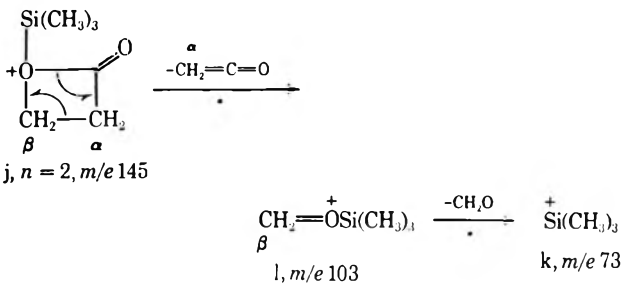
[a] RI = Relative intensity of base peak.

ester derivatives (I). Equally plausible, however, is displacement of the phenoxy radical by the carbonyl function to yield the product ion j′. In this case, j′ is seemingly energetically more favorable than j because of its resonance stabilization, and it is impossible to differentiate between these two species (j′ and j) by high-resolution mass measurements or deuterium-labeling experiments.



The significant increase in the contribution of the M − C_6H_5O ion (j or j′) to the total ion current at 12 eV (see Table I) suggests that this ion further decomposes (at 70 eV) to generate other fragment ions. In all cases, except n = 2 (the trimethylsilyl ester of 3-phenoxypropionic acid), there exists a large metastable peak corresponding to cleavage of a lactone moiety from j or j′ to yield the trimethylsilyl cation k (m/e 73). This peak (m/e 73), which is found in the mass spectra of practically all trimethylsilyl derivatives,[16,25] disappears when the spectra are recorded at low voltage.

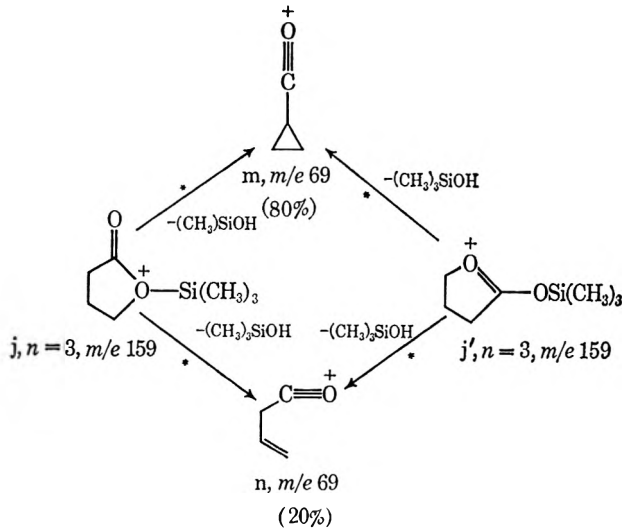
The decomposition of the M − C_6H_5O ion (j, m/e 145) in the mass spectrum of the trimethylsilyl ester of 3-phenoxypropionic acid (I, n = 2) appears to involve a fragmentation mode unique to this particular compound. A large metastable peak at m/e 73.2 (calcd $103^2/145$ = 73.2), as well as high-resolution mass measurements, suggest elimination of ketene from j to yield the ion l of mass 103 (Σ_{40} = 10.1, 67% relative abundance). This species (l) subsequently loses formaldehyde to yield the trimethylsilyl cation (k, m/e 73, Σ_{40} = 12.1) as is indicated by an intense metastable peak at m/e 51.8 (calcd $73^2/103$ = 51.7). Neither the m/e 103 peak nor any of its homologs (m/e 117, 131, etc.) are important in the mass spectra of the remaining trimethylsilyl ester derivatives (I, n = 3–6, 10). Since it is difficult to visualize a plausible path whereby this ion (l, m/e 103) could be generated from the isomeric ion j′ of mass 145, it is reasonable to assume that at least in the propionic acid case (I, n = 2), the ion of mass 145 should be represented by j rather than j′.



In every spectrum except that of the 2-phenoxyacetic acid (n = 1, Figure 1) and 3-phenoxypropionic acid (n = 2) derivatives, there is a peak of medium intensity (m/e 69 in Figure 2, m/e 83 in Figure 3, and m/e 111 in Figure 4) which, according to high-resolution mass measurements and metastable evidence, is generated by loss of trimethylsilanol [$(CH_3)_3SiOH$] from the M − C_6H_5O ion (j or j′). Labeling experiments (see Table II) indicate that the hydrogen-atom loss from the methylene chain in this process occurs in a random manner. Incorporation of deuterium atoms into the C-2 (XII) and C-3 (XIII) positions of the trimethylsilyl ester of 4-phenoxybutyric acid (I, n = 3) indicates that approximately 80% of the hydrogen lost in the expelled trimethylsilanol originates in the C-2 position and approximately 20% in the C-3 position. Although

(25) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapter 14-3; (b) see ref 14, p 35.

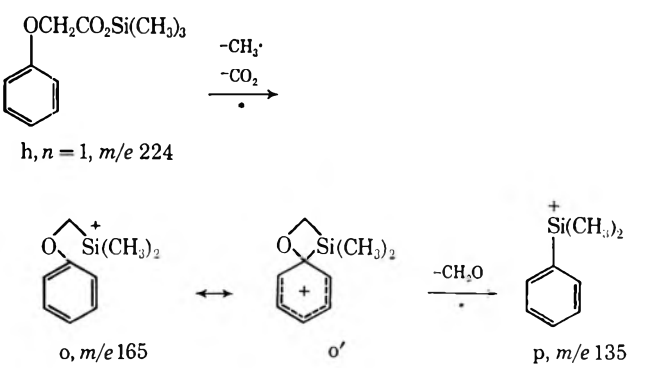
other formulations are possible, this process may be represented by elimination of trimethylsilanol from the M − C_6H_5O (j or j′, *m/e* 159) species to yield the cyclopropyl oxonium species m (*m/e* 69), and elimination of trimethylsilanol to yield the β,γ-unsaturated oxonium ion n (*m/e* 69), in a 4:1 ratio, respectively. In the case of the trimethylsilyl ester of 5-phenoxypentanoic acid (I, $n = 4$), labeling experiments (see Table II) indicate that the expelled hydrogen atom originates approximately 17% in the C-2 position, 25% in the C-3 position, and 40% in the C-4 position.[26] In the case of both labeled analogs ($n = 3$ and 4), it is impossible to determine whether these percentages differ at 12 eV, because these peaks are extremely weak under such conditions.



Other Rearrangement Species.—The mass spectra of all of the phenoxypolymethylene trimethylsilyl ester derivatives (I), except that of the 2-phenoxyacetic acid derivative ($n = 1$), exhibit a peak (see Table I) at M − C_7H_9O (M − 109), whose mode of genesis is very difficult to elucidate. Except for the case of trimethylsilyl 4-phenoxybutyrate (I, $n = 3$), where this peak is extremely small, there is metastable evidence for the production of this ion by two completely different fragmentation modes, both of which result in the same or isomeric M − C_7H_9O ions (as determined by high resolution mass measurements). One process involves elimination of methane from the M − C_6H_5O ion (j or j′), thus constituting a rearrangement process, and the other involves elimination of a C_6H_6O species, most likely phenol, from the M − CH_3 ion (i). The fact that this ion is practically nonexistent in the spectrum of the trimethylsilyl ester of 4-phenoxybutyric acid (see Table I) may be partially attributed to the preferential formation of other ions by the precursors of the M − 109 species. For instance, the M − CH_3 ion (i), which is a precursor of the M − 109 species, decomposes to g (*m/e* 151) in this case ($n = 3$) to a much greater extent than in most other cases.

The fact that two processes contribute to the same peak makes interpretation of the deuterium-labeling experiments practically impossible, especially when these experiments show (see Table II) that these two processes apparently contribute to varying extents at differing ionizing energies. About all that can be concluded is that the elimination of phenol from the M − CH_3 ion (i) most likely involves random abstraction of a hydrogen atom from the methylene chain. Similarly, loss of methane from the M − C_6H_5O ion (j or j′) probably involves ejection of a silyl-methyl group and random abstraction of a hydrogen atom as well.

All of the previously discussed electron impact induced rearrangement processes which involve participation of the terminal functional groups in the series of trimethylsilyl esters of phenoxypolymethylene acids (I) have been found to be very insignificant (see Table I) in the mass spectrum (Figure 1) of trimethylsilyl 2-phenoxyacetate (1, $n = 1$). Inspection of this spectrum (Figure 1) reveals a unique alkyl migration fragmentation scheme. The *m/e* 165 peak ($\Sigma_{40} = 6.0$), which shifts to *m/e* 168 in the spectrum of 2′,4′,6′-d_3-trimethylsilyl-2-phenoxyacetate (XI), represents a fragment ion whose elemental composition was determined by high-resolution mass measurements to be $C_9H_{13}OSi$. These results, as well as the metastable peak at *m/e* 121.6 (calcd $165^2/224 = 121.5$) suggest a fragmentation process involving concomitant loss of a silyl-methyl group and of carbon dioxide to yield the fragment ion o. This unusual scheme, which includes cleavage of two bonds bound to the same silicon atom, gives a product ion which can be stabilized by participation of the phenyl ring (o′). The increased contribution of this *m/e* 165 peak to the total ion current at 12 eV ($\Sigma_{40} = 15.4$, 41% relative abundance) and a metastable peak at *m/e* 110.5 (calcd $135^2/165 = 110.5$) provide evidence for the further decomposition of this species (o or o′), involving rearrangement of the dimethylsilyl moiety



(26) Another conceivable means of generating the M − 93 ion involves site-specific hydrogen transfer to the carbonyl-oxygen (j‴, for $n = 3$) or the silyl-oxygen atom (j⁗, for $n = 3$) with concomitant expulsion of the ω-phenoxy radical to yield the terminally unsaturated ions, j‴ or j⁗ (for $n = 3$) [see S. Meyerson, *Int. J. Mass Spectry. Ion Phys.*, **1**, 309 (1968)]. Although these schemes h → j‴ and h → j⁗ are possible, the deuterium-labeling experiments (see Table II) show that they certainly do not predominate. Loss of trimethylsilanol from j‴ ($n = 3$) would most likely involve fission of the C-3 hydrogen (j‴ or j⁗ → m″) which has been transferred to the carbonyl oxygen (j‴) or silyl oxygen (j⁗). However, only 20% of this hydrogen loss involves the C-3 hydrogen atom (see Table II). Similarly in the case of the 5-phenoxytrimethylsilyl derivative ($n = 4$), 40% of the hydrogen loss occurs from the C-4 position, thus showing that the hydrogen transfer is not site specific.

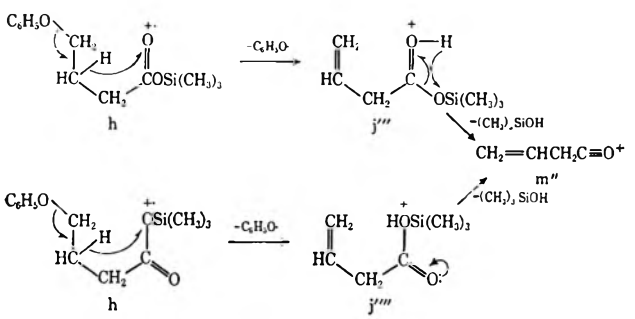


TABLE IV

SHIFTS OF THE "CHARACTERISTIC PEAKS" IN THE MASS SPECTRA OF THE DEUTERIUM-LABELED PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I)

Compd	Fragment[a] q, m/e[b] (%)	r and s, m/e[b] (%)	t, m/e[b] (%)
2,4,6-d_3-$C_6H_2D_3OCH_2Si(CH_3)_3$ (XI)	75 → 75 (74)	117 → 117	94 → 97
	75 → 76 (26)		
$C_6H_5OCH_2CH_2CD_2CO_2Si(CH_3)_3$ (XII)	75 → 75 (46)	117 → 117 (<10)	94 → 94 (80)
	75 → 76 (54)	117 → 119 (>90)	94 → 95 (20)
$C_6H_5OCH_2CD_2CH_2CO_2Si(CH_3)_3$ (XIII)	75 → 75 (90)	117 → 117	94 → 94 (50)
	75 → 76 (10)		94 → 95 (50)
2,4,6-d_3-$C_6H_2D_3OCH_2CH_2CH_2CD_2CO_2Si(CH_3)_3$ (XIV)	75 → 75 (50)	c	94 → 97 (95)
	75 → 76 (50)		94 → 98 (5)
$C_6H_5OCH_2CH_2CD_2CH_2CO_2Si(CH_3)_3$ (XV)	75 → 75 (92)	c	94 → 94 (80)
	75 → 76 (8)		94 → 95 (20)
$C_6H_5OCH_2CD_2CH_2CH_2CO_2Si(CH_3)_3$ (XVI)	75 → 75 (95)	c	94 → 94 (67)
	75 → 76 (5)		94 → 95 (33)

[a] In each case, the m/e value of the unlabeled fragment is shown being shifted to its m/e value for the indicated labeled analog. [b] Corrected for isotope abundance and calculated deuterium isotope composition. [c] Peak is too small to permit interpretation of the labeling data.

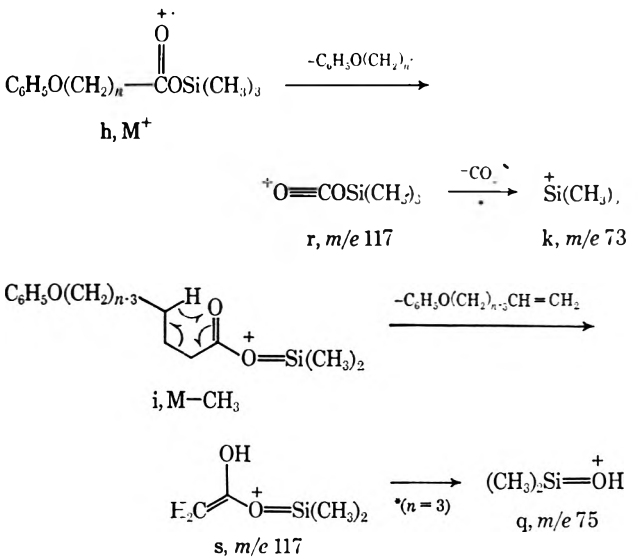
and loss of formaldehyde to yield the ion p (Σ_{40} = 3.4) of mass 135. High-resolution mass measurements ($C_8H_{11}Si$) and deuterium labeling (m/e 135 → 138 in the spectrum of XI) substantiate this fragmentation scheme. This over-all decomposition mode (i → o → p), or one analogous to it, is not found in any of the other phenoxypolymethylene trimethylsilyl ester derivatives (I, n = 2–6, 10).

Simple Fragmentations Characteristic of Trimethylsilyl ω-Phenoxypolymethylene Alkanoates (I).—In contrast to the detailed studies[16,27] concerning the characteristic electron impact induced fragmentations of trimethylsilyl ethers, there exists very little information[18,19] concerning the simple characteristic decomposition processes of trimethylsilyl esters. The present detailed analysis of the characteristic fragmentations of the series of phenoxypolymethylene trimethylsilyl esters (I), utilizing deuterium labeling, high-resolution mass measurements, and metastable analysis, sheds some light on this topic and a brief discussion of some of these observations will now be presented.

Teeter[19] stated that the M − 15 peak, resulting from loss of a silyl-methyl radical, is the most abundant peak in the mass spectra of the trimethylsilyl esters studied by him. In fact, in practically all the mass spectra of trimethylsilyl derivatives, the intensity of the molecular ion is very weak and the M − 15 peak is very intense. Table III contains the abundances of the molecular ions and the M − 15 peaks at both high and low voltages for the series of phenoxypolymethylene trimethylsilyl esters (I). It is surprising to note that this is one of the few instances where trimethylsilyl derivatives show weak M − 15 peaks and unusually intense molecular ions. At 12-eV ionizing energy, the molecular ion is the base peak when n = 1, 2, 6, and 10. The trimethylsilyl phenoxybutyric (n = 3) and pentanoic (n = 4) esters exhibit molecular ions and M − 15 peaks which are both weak. It is in these cases, however, that the M − C_6H_5O ion (j) contributes substantially more to the total ion current than in the other analogs.

Another intense characteristic ion at high voltage, which disappears at low voltage, is the dimethylsilanol ion q (m/e 75). There are metastable peaks indicating the formation of this species by multiple fragmentation pathways. When n = 4, 5, and 6, there is a large metastable peak corresponding to formation of q from the M − C_7H_9O ion (M − 109), and, when n = 3, it is generated from the McLafferty ion (s, see below, m/e 117), as is indicated by a metastable peak at m/e 48.2 (calcd $(75^2/117 = 48.2)$. Undoubtedly, other ions also fragment to form this species. These multiple pathways make quantitative interpretation of the deuterium-labeling experiments (see Table IV) impossible. It can be said, however, that the transfered hydrogen atom originates predominantly (50%) from the α position of the methylene chain.

The trimethylsilyl cation k (m/e 73) which occupies greater than 10% of the total ion current (except when n = 10, see Table III) also arises from multiple fragmentation modes. As has been previously reported,[16] there is no evidence to support its formation by simple cleavage of the molecular ion. In all cases (I), there is a large metastable peak corresponding to the genesis of the trimethylsilyl cation from the M − C_6H_5O ion (j or j′ → k), and often (n = 1, 2, 10) there exists a metastable peak at m/e 45.4 (calcd $73^2/117 = 45.5$) corresponding to ejection of carbon dioxide from the α-cleavage ion of mass 117 (r → k). The formation of k (m/e 73) from

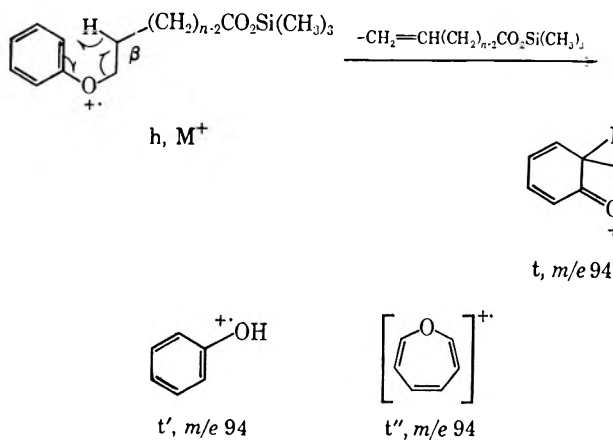


the m/e 103 precursor (l) in the spectrum of 3-phenoxypropionic trimethylsilyl ester (I, n = 2) has already been discussed.

(27) A. G. Sharkey, R. A. Friedel, and S. H. Langer, *Anal. Chem.*, **29**, 770 (1957); S. H. Langer, R. A. Friedel, I. Wender, and A. G. Sharkey, *ibid.*, **30**, 1353 (1958).

In all of the mass spectra of the phenoxypolymethylene trimethylsilyl esters (I), a relatively weak peak appears at m/e 117, which corresponds to a fragment ion of elemental composition $C_4H_9O_2Si$ (high resolution mass measurements). Cleavage of the molecular ion adjacent to the carbonyl group yields the siloxy-oxonium ion r (m/e 117) with the requisite elemental composition, and, in one instance (n = 5), a metastable peak was found to support this scheme. It appears plausible, however, that an alternative mode of fragmentation[7] can be invoked when the methylene chain contains three or more carbon atoms (n = 3–6, 10). Here, a McLafferty rearrangement of the even-electron M − CH_3 species (i) would yield an m/e 117 ion (s) having an elemental composition of $C_4H_9O_2Si$. In the spectrum of 7-phenoxyheptanoic trimethylsilyl ester (I, n = 6), there is a metastable peak at m/e 49.2 (calcd $117^2/279$ = 49.1) supporting this fragmentation. Even more important is the fact that greater than 90% of the m/e 117 peak in the mass spectrum of 2,2-d_2-4-phenoxybutyric trimethylsilyl ester (XII, see Table IV) shifts to m/e 119; thus, in this particular instance, ion s predominates over ion r by at least a 9:1 ratio.

The final "characteristic"peak to be discussed is the one at m/e 94, which is found in the mass spectra of many alkoxybenzene compounds[28] and has an elemental composition of C_6H_6O. This peak varies considerably in intensity (see Table III) in the phenoxypolymethylene trimethylsilyl ester series (I). Currently, there exists some controversy about the actual structure of this ion [ionized cyclohexadienone (t),[29,30] phenol (t'),[31] or oxepin (t'')].[32] The deuterium-labeling results (see Table IV)



support conclusions previously obtained[31] in this laboratory which negated the postulated[29] site-specific β-hydrogen atom transfer to yield the ketonic isomer (h → t). These results clearly indicate a random hydrogen transfer to the charge-retaining portion of the molecule with concomitant expulsion of an unsaturated ester moiety. The weak intensity of this peak at low voltages makes it impossible to determine if there are any variations in the labeling percentages at 12 eV.

Electron Impact Induced Interaction of Terminal Functional Groups in Some Compounds Related to the Phenoxypolymethylene Trimethylsilyl Esters (I).—The previous discussion has illustrated some important electron impact induced fragmentation schemes where the terminal phenyl ether and trimethylsilyl ester groups of some phenoxypolymethylene trimethylsilyl esters (I) have interacted with one another to produce abundant fragment ions. As was pointed out in the introduction, such behavior plays a very important role in the creation of "rules" for computer interpretation of the mass spectra of bifunctional compounds. Since the characteristic decomposition modes associated with individual phenyl ether and trimethylsilyl ester moieties do not occur entirely independently of each other when they are present in the same compound, it is necessary to develop new interpretation rules concerning the interaction of these species. The next step in "rule development" is to determine whether these interaction processes are specific for the interaction of the phenyl ether and trimethylsilyl ester groups or whether substitution of structurally similar functional groups for either or both of the phenyl ether or trimethylsilyl ester species will alter the nature of the interaction. For this reason, the mass spectra of the following substances have been recorded: some phenylpolymethylene trimethylsilyl esters (II); some benzyloxy- (III), methoxy- (IV, R = CH_3), and ethoxy- (IV, R = C_2H_5) polymethylene trimethylsilyl esters; and some phenoxypolymethylene methyl esters (V). Only brief comment will be made with regard to each mass spectrum and particular emphasis will be placed upon the interaction of the terminal functional groups.

Trimethylsilyl 3-Phenylpropionate (II, n = 2) and Trimethylsilyl 4-Phenylbutyrate (II, n = 3).—Substitution of a phenyl moiety for the phenoxy group of the previously discussed compounds I has a very significant effect upon the electron impact induced behavior of these compounds and stresses the influence of a heteroatom at each end of the molecule. Most important is the fact that neither of the two phenyl analogs investigated, trimethylsilyl 3-phenylpropionate (II, n = 2) and trimethylsilyl 4-phenylbutyrate (II, n = 3, see Figure 5), generate any significant ions due to an electron impact induced interaction of the terminal functional groups. It is particularly instructive that there is no rearrangement of the silyl function with expulsion of the central portion of the molecule either in the molecular ion (u) or in the M − CH_3 ion; an alkyl rearrangement of this type would yield species analogous to f (m/e 166) or g (m/e 151). Previous studies[16] of the mass spectral fragmentations of 3-phenylpropyl trimethylsilyl ether (VIII, n = 3, R = H) reported the existence of such a rearrangement (VIII → b), but to a rather small extent. The mass spectra of the phenyl analogs (II) also lack peaks corresponding to the M − 93 (j) and M − 109 ions found in the mass spectra of the phenoxy analogs.

Unlike the spectra of the phenoxy derivatives (I), the primary peaks in the mass spectra of the phenyl analogs (II, n = 2, 3, see Figure 5) result from the independent decomposition of the two functional groups, the trimethylsilyl ester and the alkyl phenyl moiety. The molecular ion is still unusually strong and the M − CH_3 peak is also quite intense. The trimethylsilyl cation k (m/e 73) and the dimethylsilanol ion q (m/e 75) are intense at 70 eV and practically disappear at 12 eV; metastable peaks indicate the formation of the latter

(28) See ref 25a, p 240–242.
(29) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).
(30) R. G. Gillis, G. J. Long, A. G. Moritz, and J. L. Occolowitz, *Org. Mass Spectrom.*, **1**, 527 (1968).
(31) J. K. MacLeod and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 1840 (1966).
(32) F. W. McLafferty, M. M. Bursey, and S. M. Kimball, *ibid.*, **88**, 5022 (1966).

species (q) from the M − CH_3 precursor. Both spectra exhibit abundant C_7H_7 tropylium ions at *m/e* 91.[33] It is interesting to note the absence of an *m/e* 92 peak. The mass spectra of alkyl benzene derivatives[33] with a propyl (or longer) side chain usually exhibit this *m/e* 92 peak (C_7H_8) which results from a McLafferty rearrangement[33] involving hydrogen transfer to the phenyl ring.

Both compounds (II, *n* = 2 and 3) exhibit an *m/e* 104 peak which is often found in the mass spectra of alkylbenzene derivatives.[33] In the case of trimethylsilyl 4-phenylbutyrate (*n* = 3, see Figure 5), a McLafferty rearrangement with charge retention on the phenyl group yields this species (u → v, Σ_{40} = 4.4); charge retention on the ester moiety affords the *m/e* 132 ion w (Σ_{40} = 2.9), which subsequently eliminates a methyl group, giving the *m/e* 117 ion (s, Σ_{40} = 19.3). The α-cleavage ion r (*m/e* 117) also undoubtedly contributes to this peak. Formation of the C_8H_8 ion of mass 104 (Σ_{40} = 21.9) in the mass spectrum of trimethylsilyl 3-phenylpropionate (II, *n* = 2) possibly involves transfer of a C-3 hydrogen atom to yield the conjugated product ion v. There is no *m/e* 132 peak (w) in this spectrum, presumably because the alkyl chain is not long enough to permit a McLafferty rearrangement. The base peak in the spectrum of trimethylsilyl 4-phenylbutyrate (II, *n* = 3) at 12 eV is at *m/e* 146, and a metastable peak at *m/e* 90.3 (calcd $146^2/236$ = 90.3) corresponds to elimination of trimethylsilanol from the molecular ion. The propionate derivative (II, *n* = 2) does not lose trimethylsilanol upon electron impact. Meyerson and Leitch[34] postulated that the elimination

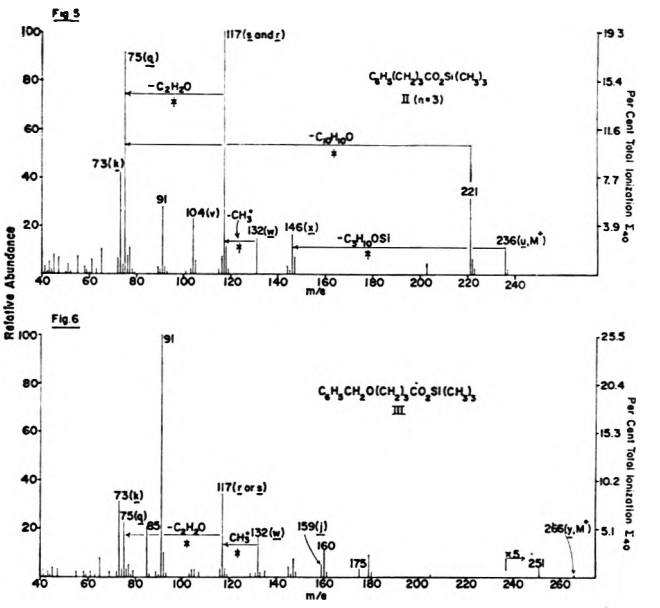
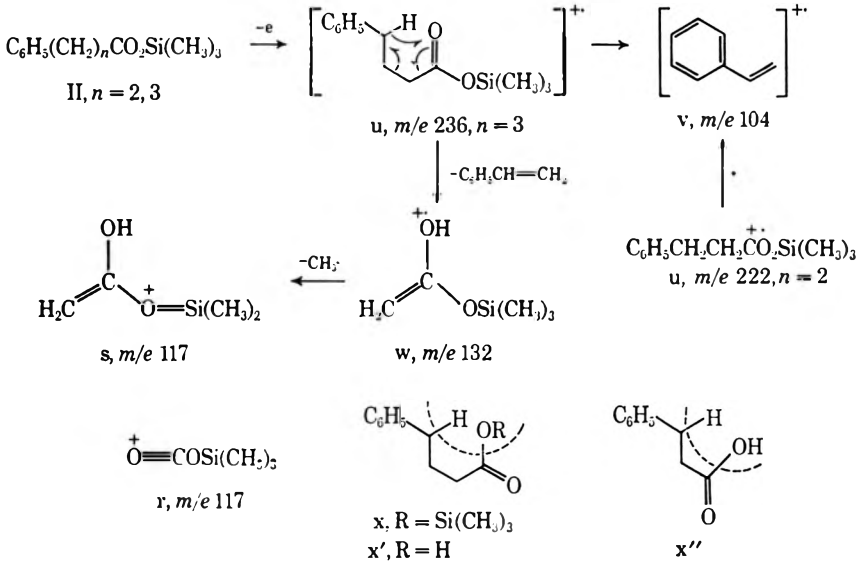


Figure 5.—Mass spectrum of trimethylsilyl 4-phenylbutyrate (II, *n* = 3).

Figure 6.—Mass spectrum of trimethylsilyl 4-benzyloxybutyrate (III, *n* = 3).

of Meyerson and Leitch.[34] As a supplementary piece of information which corroborates the above conclusion about the importance of ring size in the transition state, we now find that the loss of methanol from methyl 4-phenylbutyrate produces the base peak in the mass spectrum of this species at 12 eV (Σ_{40} = 32.5), whereas



of water from 4-phenylbutyric acid proceeds by a 1,4 elimination (x′) involving the hydroxyl group and the benzylically activated C-4 hydrogen atom. In the case of 3-phenylpropionic acid (x″) they found practically no elimination of water, which suggests that the size of the transition state rather than benzylic activation plays the key role in this reaction. The loss of trimethylsilanol (x) from trimethylsilyl 4-phenylbutyrate (II, *n* = 3) and not from its propionate analog (II, *n* = 2) can be explained by reasoning identical with that similar elimination of methanol from methyl 3-phenylpropionate is insignificant (Σ_{40} = 1.4).

Trimethylsilyl 4-Benzyloxybutyrate (III).—The mass spectra of 4-benzyloxybutyric acid and its methyl ester have been studied in other investigations[12] of the electron impact induced interactions of functional groups. The mass spectrum (Figure 6) of its trimethylsilyl ester (III) shows considerable interaction between the terminal benzyl ether and trimethylsilyl ester functions, as was found in the trimethylsilyl phenoxypolymethylene ester series (I).

(33) See ref 25a, Chapter 1–4, for leading references to the work of Meyerson and others.

(34) S. Meyerson and L. C. Leitch, *J. Amer. Chem. Soc.*, **88**, 56 (1966).

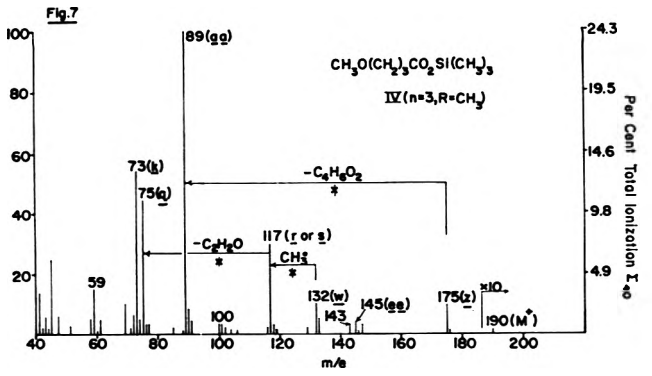
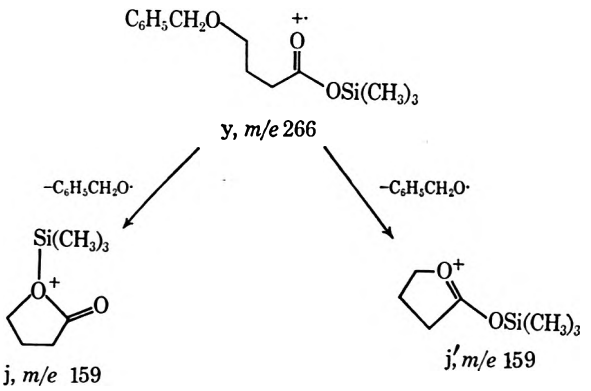


Figure 7.—Mass spectrum of trimethylsilyl 4-methoxybutyrate (IV, n = 3, R = CH_3).

Expulsion of a benzyloxy radical in a manner similar to the expulsion of a phenoxy radical in the parent series (I) probably accounts for the relatively small (Σ_{40} = 1.3) m/e 159 peak (y → j or j′) which becomes more intense at 12 eV (Σ_{40} = 3.2, 22% relative abundance). The fact that this process (y → j or j′) is much less prevalent here (Figure 6) than in the trimethylsilyl phenoxy case (Figure 2) can be partially explained by the observation that the benzyloxy group directs a greater number of fragmentation modes than does the phenoxy group, and thus less ion current is available for the y → j process (Figure 6) than for the h → j process (Figure 2). Unlike the mass spectrum of trimethylsilyl 4-phenoxybutyrate (I, n = 3, Figure 2), this spectrum (Figure 6) exhibits no metastable evidence for the decomposition of this ion (j) to yield the trimethylsilyl cation k (m/e 73), and also there is no loss of trimethylsilanol from this ion to yield the m/e 69 oxonium ion (m or n). Three other peaks, m/e 175 (Σ_{40} = 0.8), 160 (Σ_{40} = 2.8), and 85 (Σ_{40} = 5.4), which are particularly intense at 12 eV (Σ_{40} = 2.8, 14.7, and 4.3, respectively), are generated in fragmentation patterns involving the interaction of the benzyloxy and ester functions. They are exactly analogous to the M − $C_6H_5CH_2$·, M − C_6H_5CH=O, and M − ($C_6H_5CH_2$· + CH_3OH) ions observed[12] in the spectrum of methyl 4-benzyloxybutyrate.

The remaining important peaks in Figure 6 are independently characteristic of the benzyl ether and trimethylsilyl ester functions, and include the McLafferty ion w at m/e 132 (Σ_{40} = 4.1 increasing to Σ_{40} = 14.1 at 12 eV), the McLafferty − CH_3· ion s or α-cleavage ion r at m/e 117 (Σ_{40} = 8.7), the tropylium ion at m/e 91 (Σ_{40} = 25.5), the dimethylsilanol ion q at m/e 75 (Σ_{40} = 5.1), and the trimethylsilyl cation k at m/e 73 (Σ_{40} = 8.2).



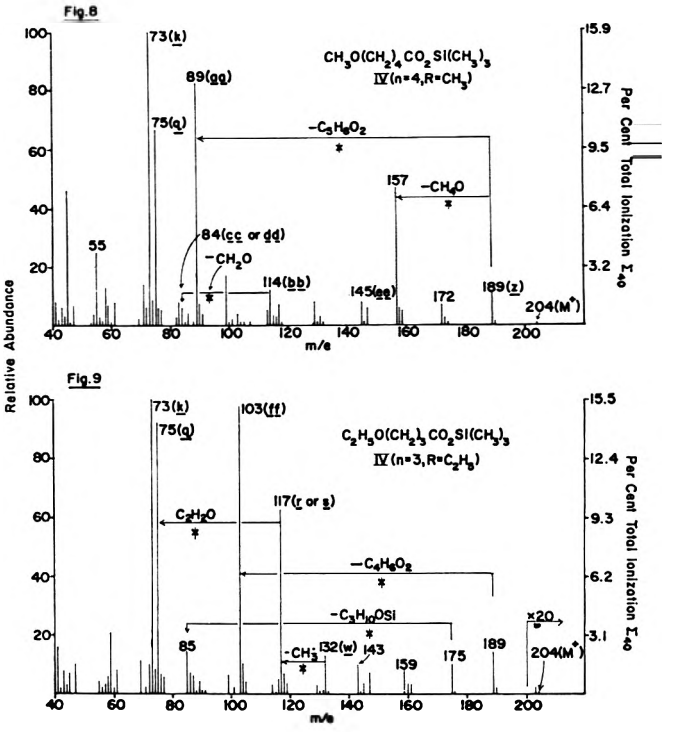


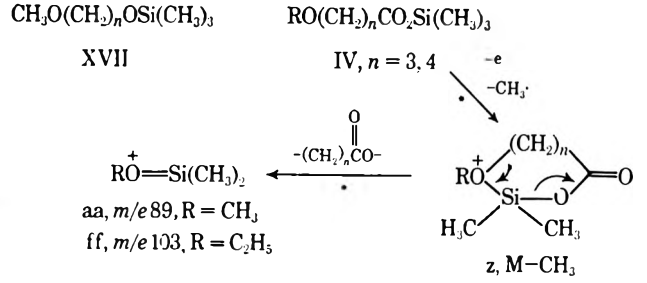
Figure 8.—Mass spectrum of trimethylsilyl 5-methoxypentanoate (IV, n = 4, R = CH_3).

Figure 9.—Mass spectrum of trimethylsilyl 4-ethoxybutyrate (IV, n = 3, R = C_2H_5).

Trimethylsilyl 4-Methoxybutyrate (IV, n = 3, R = CH_3) and Trimethylsilyl 5-Methoxypentanoate (IV, n = 4, R = CH_3).—It is apparent that, in the comparison of the mass spectra of some phenoxy- (Figures 1–4), phenyl- (Figure 5), and benzyloxy- (Figure 6) polymethylene trimethylsilyl esters, the presence of a heteroatom-containing functional group at each of the ends of the polymethylene chain appears to be a requisite for observing electron impact induced functional group interactions. The mass spectra of two trimethylsilyl methoxypolymethylene esters (IV, R = CH_3, n = 3, 4) were recorded (see Figures 7 and 8, respectively) in order to assess what the effect of replacing the aromatic ether with an aliphatic ether would have upon these functional group interactions.

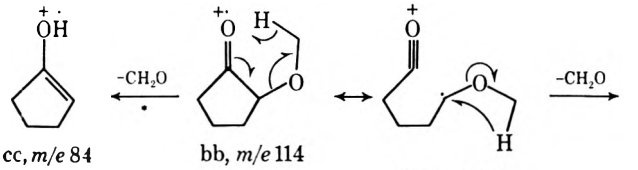
Observation of an intense peak at m/e 89 in both spectra (Figure 7 and 8) makes it immediately evident that the methoxy derivatives (IV, n = 3, 4), like the phenoxy and benzyloxy derivatives, exhibit fragmentation paths involving interaction of the methyl ether and trimethylsilyl ester functions. Consideration of the mode of genesis of the m/e 151 peak in the mass spectra of the phenoxypolymethylene trimethylsilyl esters (i → g, Figures 2–4), the previously reported[16] mass spectra of some methoxypolymethylene trimethylsilyl ethers (XVII), the high resolution mass measurements, the metastable evidence, and the intensity changes upon lowering the ionizing voltage make it obvious that the m/e 89 species (aa, C_3H_9OSi) results from rearrangement of the M − CH_3 peak (z) with expulsion of the central portion of the molecule. This species occupies 24.3 and 13.0% of the total ionization in Figures 7 and

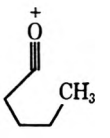
, respectively. The loss of a methoxyl radical from the molecular ion of these compounds (IV) in a manner

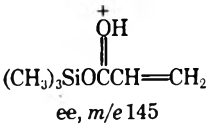


analogous to the formation of the M − C_6H_5O peak (j or j′) in Figures 2–4 is not significant. If there were a peak corresponding to the M − 109 (M − C_7H_9O) peak observed in the phenoxy series (I), it would have an elemental composition of M − C_2H_7O and fall at *m/e* 143 and 157 in Figures 7 and 8, respectively. Analogous to the previous series (I), a very small peak (Σ_{40} = 0.7) exists in the spectrum of the trimethylsilyl butyrate (*m/e* 143), and an intense peak, which is the base peak at 12 eV, is found at *m/e* 157 (Σ_{40} = 7.5) in Figure 8. As in the phenoxy series, a metastable peak corresponding to the loss of methanol from the M − CH_3 species (*m/e* 189) is observed at *m/e* 130.4 (calcd $157^2/189$ = 130.4) in this spectrum.

Although it is not an important fragmentation mode in the mass spectra of the trimethylsilyl phenoxypolymethylene esters (I), loss of trimethylsilanol from the molecular ion to give the *m/e* 100 (Σ_{40} = 0.7, Figure 7) and *m/e* 114 (Σ_{40} = 1.9, Figure 8) peaks could possibly involve interaction of the terminal ends of the methylene chain, especially in light of the metastable evidence found for the subsequent decomposition of the *m/e* 114 species (bb). Although no deuterium labeling has been performed, the *m/e* 114 species can be visualized to exist in the form of ionized 2-methoxycyclopentanone (bb); subsequent elimination of formaldehyde is suggested by the appropriate metastable peak and the fact that the *m/e* 114 peak increases substantially in intensity at 12 eV (Σ_{40} = 7.5 and 3.7, respectively). Loss of formaldehyde from the species







bb (*m/e* 114) could possibly involve a McLafferty rearrangement to yield the enolic species cc (*m/e* 84) in a manner analogous to the loss of ethylene from 2-ethylcyclopentanone.[35] It could also be visualized as occurring from the open-chain form of the *m/e* 114 ion bb′ to yield the oxonium ion species dd (*m/e* 84). Other formulations for this fragmentation are also conceivable, but are not reproduced for the sake of brevity.

The remaining important peaks are characteristic of the independent trimethylsilyl ester and methyl ether functions. The trimethylsilyl (k, *m/e* 73) and dimethylsilanol (q, *m/e* 75) ions are abundant in both cases. The *m/e* 145 ion, which is significant in the 12-eV spectrum (Σ_{40} = 4.5) of the methoxy butyrate derivative (IV, *n* = 3) has been shown by McCloskey[7] to have structure ee. Also significant in this spectrum (Figure 7) is the McLafferty peak w (*m/e* 132, Σ_{40} = 2.4) and its decomposition peak s (*m/e* 117, Σ_{40} = 7.3). Two peaks which are characteristic of the methyl ether and are very intense at low voltage (12 eV) are the *m/e* 172 (M − CH_3OH) peak in Figure 8 and the *m/e* 59 (C_3H_7O) peak[12] in Figure 7.

Trimethylsilyl 4-Ethoxybutyrate (IV, R = C_2H_5, *n* = 3).—The mass spectrum (Figure 9) of trimethylsilyl 4-ethoxybutyrate is very similar to that (Figure 7) of the methoxy analog (IV, *n* = 3, R = CH_3) in that it contains peaks corresponding to fragmentations involving terminal group participation as well as fragmentations independently characteristic of the ethyl ether and trimethylsilyl ester functions.

Peaks resulting from functional group interaction are the ones at *m/e* 103 (Σ_{40} = 15.2), 159 (Σ_{40} = 1.2), 143 (Σ_{40} = 1.5), 135 (Σ_{40} = 1.5), and 85 (Σ_{40} = 2.2). The abundant *m/e* 103 ion ff is generated from the M − CH_3 species (*m/e* 189) with expulsion of the central portion of the molecule in a manner analogous to the fragmentation paths z → aa and i → g in the trimethylsilyl methoxy- (IV, R = CH_3) and phenoxy- (I) polymethylene ester series, respectively. The weak *m/e* 159 (M − C_2H_5O) and 143 (M − C_3H_9O) peaks are probably generated in a manner similar to the electron impact induced formation of the M − C_6H_5O ion (j) and M − C_7H_9O ion in the phenoxy analogs (I). Elimination of an ethyl radical *via* participation of the silyl function[12] yields the *m/e* 175 ion, which occupies 8.1% of the total ion current at 12 eV, and a metastable peak at *m/e* 41.1 (calcd $85^2/175$ = 41.3) suggests elimination of trimethylsilanol from this species[12] to yield the *m/e* 85 ion. Those ions in Figure 9 characteristic of the trimethylsilyl moiety are the trimethylsilyl cation k (*m/e* 73), the dimethylsilanol ion q (*m/e* 75), the McLafferty ion w (*m/e* 132), and the McLafferty decomposition ion s or α-cleavage ion r (*m/e* 117). The *m/e* 73 peak remains the base peak at 12 eV implying that much of it may be due to the C_4H_9O ion found in 4-ethoxybutyric acid and its methyl ester;[12] the trimethylsilyl cation k, C_3H_9Si (*m/e* 73), normally disappears at 12 eV because it is never generated directly from the molecular ion as is the C_4H_9O ion.

Methyl 3-Phenoxypropionate (V, *n* = 2) and Methyl 4-Phenoxybutyrate (V, *n* = 3).—Substitution of a methyl ester function for the trimethylsilyl ester function of trimethylsilyl 3-phenoxypropionate (I, *n* = 2) and trimethylsilyl 4-phenoxybutyrate (I, *n* = 3) does not reduce the amount of the ion current attributed to fragmentation processes which result from interaction of the terminal functional groups. Although the mass

(35) J. Seibl and T. Gäumann, *Z. Anal. Chem.*, **197**, 33 (1963).

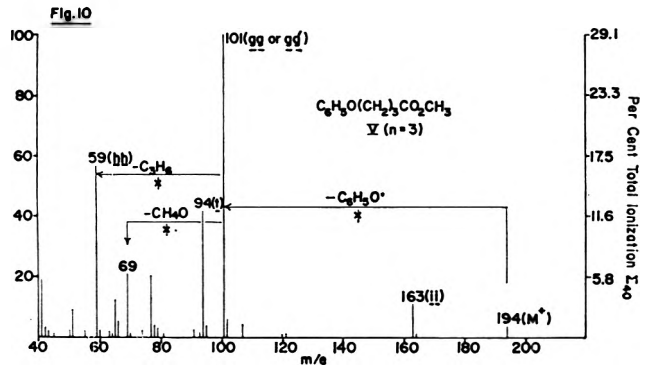
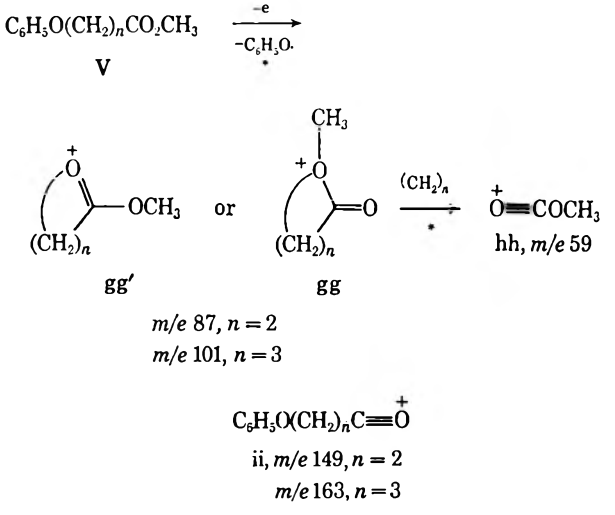


Figure 10.—Mass spectrum of methyl 4-phenoxybutyrate (V, $n = 3$).

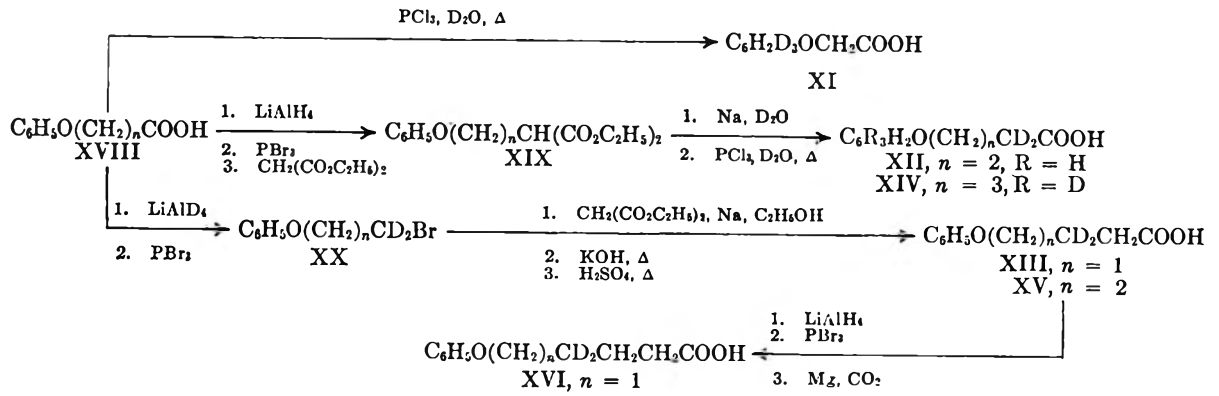
spectra of methyl 3-phenoxypropionate (V, $n = 2$) and methyl 4-phenoxybutyrate (V, $n = 3$, see Figure 10) show no evidence of fragmentations similar to the trimethylsilyl migration processes h → f and i → g, the M − 93 ion (gg or gg′) is considerably more intense ($\Sigma_{40} = 17.9$ and 29.1 for $n = 2$ and 3, respectively) than is the M − 93 ion in the mass spectra of the corresponding trimethylsilyl esters (see Table I). At 12 eV, this species (gg or gg′) amounts to 25.7 and 79.4% of the total ion current when $n = 2$ and $n = 3$, respectively. Analogous to the species j or j′ in the mass spectra of the trimethylsilyl analogs, this species gg or gg′ subsequently eliminates methanol (to produce the *m/e* 69 peak in Figure 10), as is evidenced by the appropriate metastable peaks. This species also decomposes to yield approximately 33% of the abundant *m/e* 59 ion (hh); the remaining portion of this *m/e* 59 species has the elemental composition C_3H_7O. The *m/e* 94 peak (t) has been previously discussed and is characteristic of alkoxy benzene derivatives. The only remaining important peak is the α-cleavage peak corresponding to ion ii (*m/e* 163 in Figure 10).



Summary.—It was the purpose of this work to investigate the interactions of the functional groups in the electron impact induced fragmentations of some trimethylsilyl ω-phenoxyalkanoates (I) and related compounds (II–V). In general, the mass spectra of the parent trimethylsilyl esters (I) exhibit four fragmentation schemes which yield peaks (*m/e* 166, *m/e* 151, M − 93, and M − 109) resulting from functional group participation (see Table I). Having determined the extent of analogous fragmentations in the related species II–V, it is evident that, because of one important exception, no *general* rules can be formulated which will account for the existence of these interaction processes in *all* of the cases studied (I–V). This exception relates to the observation that *none* of these processes is evident in the mass spectra of the ω-phenylalkanoates (II). Thus, for functional group interaction of the type discussed in this work, it is necessary to have a heteroatom-containing species (alkyl ether and alkyl ester) at *both* ends of the molecule. This observation firmly supports the conclusion of Brandt and Djerassi[11] that many rearrangement processes involving participation of functional groups at the ends of long polymethylene chains may depend upon the molecular ion existing in a coiled manner (see structure h′), which permits these groups to be in sufficiently close proximity so as to allow charge exchange between the heteroatoms. Each analog containing *both* an ether and an ester group at the ends of the polymethylene chain (III–V) did not produce *all* of the four interaction peaks found in the mass spectra of the trimethylsilyl ω-phenoxyalkanoates (I, see Table I). Instead, the extent of participation of their functionalities in these processes is affected by the nature of the ether or ester moiety itself. For instance, benzyl ethers exhibit a much greater degree of independent fragmentation (see Discussion) than do phenyl ethers, thus limiting the amount of ion current available for interaction processes (compared to the phenoxy analogs). Another example is the stability of the eliminated radical in the fragmentation analogous to the M − 93 (C_6H_5O) elimination in I, which certainly plays a role in determining the extent of this decomposition mode in the analogs (III–V). There are other peculiarities of each particular functional group which govern the amount of ion current occupied by the discussed interaction processes, but what is most important is that these processes do not occur at all unless the functional groups contain an oxygen heteroatom.

Synthesis of Labeled Compounds.—It is only necessary to describe the syntheses of the parent carboxylic acids, as all trimethylsilyl derivatives are prepared with the commonly employed hexamethyldisilazane reagent.[9,16,36] 2′,4′,6′-d_3-Phenoxyacetic acid (XI) is prepared by an unusually facile exchange procedure which involves heating a mixture of deuterium oxide, phenoxyacetic acid (XVIII, $n = 1$), and phosphorus trichloride under reflux for 20 hr. Utilizing a similar procedure, 2-(2′-phenoxyethyl) diethyl malonate (XIX, $n = 2$), prepared from diethyl malonate and 2-phenoxyethyl bromide, is hydrolyzed with sodium deuterioxide and subsequently decarboxylated and exchanged with phosphorus trichloride and deuterium oxide to yield 2,2-d_2-4-phenoxybutyric acid (XII). The nuclear magnetic resonance and mass spectra reveal approximately 39% d_3 species and 15% d_4 species. From the *m/e* 166 peak (f) and the *m/e* 159 peak (j) of the mass spectrum (see Discussion), it is determined that the phenyl ring is about 53% d_0, 32% d_1, 9% d_2, and 5% d_3, and that the α position is approximately 90% d_2. Reduction of phenoxyacetic acid (XVIII, $n = 1$) with lithium aluminum deuteride yields 1,1-d_2-2-phenoxyethanol, which is converted into its bromide

(36) S. H. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958); see ref 14, Chapters 1–7.



(XX, $n = 1$) with phosphorus tribromide. A diethyl malonate condensation followed by hydrolysis and decarboxylation affords 3,3-d_2-4-phenoxybutyric acid (XIII). Hydrolysis and exchange of 2-(3′-phenoxypropyl) diethyl malonate (XIX, $n = 3$), prepared from 3-phenoxypropionic acid (XVIII, $n = 2$), with deuterium oxide and phosphorus trichloride yields 2′,4′,6′,-2,2-d_5-5-phenoxypentanoic acid (XIV) in high isotopic purity. A lithium aluminum deuteride reduction of 3-phenoxypropionic acid (XVIII, $n = 2$) followed by a phosphorus tribromide bromination gives 1,1-d_2-4-phenoxybutyl bromide (XX, $n = 3$). A diethyl malonate alkylation followed by hydrolysis and decarboxylation produces 3,3-d_2-5-phenoxypentanoic acid (XV). Reduction of 3,3-d_2-4-phenoxybutyric acid (XIII) with lithium aluminum hydride, bromination of the product with phosphorus tribromide, and carbonation of the corresponding Grignard reagent yields 4,4-d_2-5-phenoxypentanoic acid (XVI).

Experimental Section[37]

Trimethylsilyl Esters.[9,16,36]—A mixture of 1.0 mmol of the disilazone[38] was heated under reflux with 1 drop of trimethylchlorosilane[38] until evolution of ammonia ceased (1–4 hr). The trimethylsilyl esters were isolated by preparative gas-liquid partition chromatography of the reaction mixture; Table V indicates the column and conditions utilized for each derivative. Retention times varied from 5 to 10 min. In all cases the yields of the colorless liquids were quantitative.

5-Phenoxypentanoic Acid.—To a well-stirred suspension of 1.7 g of lithium aluminum hydride in 30 ml of anhydrous ether at 0° was added dropwise 5.4 g of 4-phenoxybutyric acid[40] in 20 ml of anhydrous ether. After complete addition, the mixture was heated under reflux for 6 hr, cooled to 10°, and the excess lithium aluminum hydride decomposed by the dropwise addition of a saturated sodium sulfate solution. The mixture was filtered, dried over anhydrous magnesium sulfate, and refiltered, and the ether stripped on a rotary evaporator, yielding 4.9 g of 4-phenoxybutanol. The infrared spectrum exhibited characteristic absorptions at λ_{max} 3.1, 8.1, 9.5, 13.2, and 14.4 μ.[42] Utilizing the conditions of Wood,[43] 4-phenoxybutanol was treated with 1.0 ml of phosphorus tribromide to yield, after distillation at 134–135° (10 mm),[44] 4.4 g of 4-phenoxy-1-bromobutane (λ_{max} 8.1, 9.6, 13.2, and 14.4 μ). Utilizing the procedure and apparatus described in previous work,[16] 1.0 g of 4-phenoxy-1-bromobutane was converted into its Grignard regent with 200 mg of magnesium. Subsequent carbonation with anhydrous carbon dioxide[16] gave, after recrystallization from ether–hexane (1:1), 630 mg of 5-phenoxypentanoic acid: mp 62–63° (lit.[45] mp 65–66°); λ_{max}^{Nujol} 3.4 (broad), 5.8, 8.0, 9.6, 13.2, and 14.4 μ.

7-Phenoxyheptanoic Acid.—To a stirred solution of 268 mg of 7-phenoxyheptanol[9] in 10 ml of pure acetone at room temperature was added dropwise 0.80 ml of Jones reagent.[46] The mixture was stirred for 20 min and enough isopropanol was added to consume the excess Jones reagent. The solution was added to water, acidified, and extracted twice with 50-ml portions of ether. The combined ethereal layers were washed with water, dried over anhydrous magnesium sulfate, and filtered; solvent was stripped on a rotatory evaporator. The crude product, mp 52–53° (lit.[47] mp 55°) exhibited characteristic infrared absorptions at λ_{max}^{Nujol} 3.0 (broad), 5.8, 8.0, 9.6, 13.3, and 14.4 μ. It was converted directly into its trimethylsilyl ester without recrystallization.

11-Phenoxyundecanoic Acid.—In 40 ml of water was placed 13.8 g of 11-bromoundecanoic acid,[39] 10.0 g of phenol, and 7.0 g of sodium hydroxide, and the solution was heated under reflux for 3 hr. After cooling, the solution was acidified with dilute hydrochloric acid and extracted twice with ether; the combined ethereal layers were extracted with a sodium bicarbonate solution. The sodium bicarbonate layer was acidified with dilute hydrochloric acid and extracted twice with ether; the combined ether-

TABLE V

CHROMATOGRAPHY CONDITIONS FOR TRIMETHYLSILYL ESTERS[a]

Compd	Column (ft)	Column temp, °C
$C_6H_5OCH_2CO_2Si(CH_3)_3$ (I, $n = 1$)	5% SE-30	150
$C_6H_5O(CH_2)_2CO_2Si(CH_3)_3$ (I, $n = 2$)	10% SE-30	190
$C_6H_5O(CH_2)_3CO_2Si(CH_3)_3$ (I, $n = 3$)	1% SE-30	200
$C_6H_5O(CH_2)_4CO_2Si(CH_3)_3$ (I, $n = 4$)	1% SE-30	200
$C_6H_5O(CH_2)_5CO_2Si(CH_3)_3$ (I, $n = 5$)	5% SE-30	205
$C_6H_5O(CH_2)_6CO_2Si(CH_3)_3$ (I, $n = 6$)	1% SE-30	185
$C_6H_5O(CH_2)_{10}CO_2Si(CH_3)_3$ (I, $n = 10$)	1% SE-30	225
$C_6H_5(CH_2)_2CO_2Si(CH_3)_3$ (II, $n = 2$)	3% SE-30 (5)	180
$C_6H_5(CH_2)_3CO_2Si(CH_3)_3$ (II, $n = 3$)	3% SE-30 (5)	200
$C_6H_5CH_2O(CH_2)_2CO_2Si(CH_3)_3$ (III)	3% SE-30 (5)	210
$CH_3O(CH_2)_2CO_2Si(CH_3)_3$ (IV, $n = 3$, R = CH_3)	3% SE-30 (5)	130
$CH_3O(CH_2)_4CO_2Si(CH_3)_3$ (IV, $n = 4$, R = CH_3)	3% SE-30 (5)	150
$C_2H_5O(CH_2)_3CO_2Si(CH_3)_3$ (IV, $n = 3$, R = C_2H_5)	3% SE-30 (5)	140

[a] The dimensions of all columns were 10 ft × 0.25 in., and they were packed with indicated liquid phase on Chromosorb W. A He flow rate of 90 ml/min was employed.

(37) Melting points (uncorrected) were determined on the Kofler block and infrared absorption spectra were measured with a Perkin-Elmer Model 700 infrared spectrophotometer. Most low-resolution mass spectra and all high-resolution mass measurements were carried out by Mr. R. G. Ross using an A. E. I. MS-9 instrument equipped with a 200° heated inlet system. Mass spectra of a few synthetic intermediates were obtained on a Finnigan 1015 Quadrupole mass spectrometer. Nmr spectra werer ecorded by Dr. R. T. Gray with a Varian A-60 spectrometer, employing deuteriochloroform as solvent and tetramethylsilane as internal reference.

(38) Hexamethyldisilazane and chlorotrimethylsilane were purchased from Pierce Chemical Co., Rockford, Ill.

(39) Phenoxyacetic acid, 3-phenylpropionic acid, 4-phenylbutyric acid, and 11-bromoundecanoic acid were purchased from Eastman Organic Chemicals, Rochester, N. Y.

(40) 2-Phenoxyethyl bromide and 3-phenoxypropionic acid were purchased from Aldrich Chemicals, Milwaukee, Wis.

(41) 4-Phenoxybutyric acid, 3-phenoxypropyl bromide, and 6-phenoxyhexanoic acid were purchased from K and K Laboratories, Plainview, N. Y.

(42) E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

(43) H. B. Wood and E. C. Horning, *J. Amer. Chem. Soc.*, **75**, 5511 (1953).

(44) R. F. Brown and G. H. Schmid, *J. Org. Chem.*, **27**, 1288 (1962).

(45) A. N. Nesmeyanov and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 224 (1955).

(46) C. Djerassi, E. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(47) E. Dobrowolska and Z. Eckstein, *Przemysl Chem.*, **42**, 556 (1963).

eal layers were dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent, the yellow oil obtained was recrystallized twice from ether–hexane (1:1), yielding 2.0 g of yellow crystals; analytic thin layer chromatography (tlc) on silica gel GF_{254} (Merck A. G. Darmstadt) indicated a mixture of two compounds. Preparative tlc of 100 mg of the crude product on silica gel HF_{254} (Merck A. G. Darmstadt) having a thickness of 1.0 mm and utilizing a 1:1 benzene–ethyl acetate development yielded 67 mg of 11-phenoxyundecanoic acid (λ_{max} 3.3, 5.8, 8.0, 9.8, 13.3, and 14.5 μ) which still appeared to be slightly impure. This crude product was isolated in pure form as its trimethylsilyl ester.

Methyl 3-Phenoxypropionate (V, n = 2).—Diazomethane, prepared from N-nitrosomethylurea,[48] was added dropwise to 1.7 g of 3-phenoxypropionic acid[39] in 20 ml of ether until nitrogen evolution ceased and a yellow color persisted. The solution was dried over anhydrous magnesium sulfate, filtered, and the ether removed on a rotary evaporator. Analytic tlc (benzene–ethyl acetate, 85:15) indicated only one product. Preparative glpc on a 10 ft × 0.25 in. 3% SE-30 column at 190° yielded 1.5 g of the desired product, whose infrared spectrum exhibited characteristic absorptions at λ_{max} 5.7, 8.0, 8.4, 9.6, 13.2, and 14.4 μ.

Methyl 4-Phenoxybutyrate (V, n = 3).—Addition of diazomethane to 1.8 g of 4-phenoxybutyric acid[40] in a manner identical with the preparation of methyl 3-phenoxypropionate (V, n = 2) yielded 1.7 g of methyl 4-phenoxybutyrate (λ_{max} 5.7, 8.0, 8.5, 9.5, 13.2, and 14.4 μ).

2′,4′,6′-d_3-Phenoxyacetic Acid (XI).—In a nitrogen atmosphere was placed 1.98 g of phenoxyacetic acid[38] in 9 ml of deuterium oxide (99.8% d_2). The mixture was cooled to 10° and 3.8 ml of phosphorus trichloride was added dropwise with stirring. The solution was gradually warmed to room temperature and then heated under reflux for 20 hr. After cooling, the mixture was added to mildly acidic deuterium oxide and extracted twice with ether; the combined ethereal extracts were dried over anhydrous magnesium sulfate. After filtering and evaporating the solvent, the solid product was recrystallized from ether–hexane (1:1), yielding 1.8 g of white needles, mp 98–99°. The mass spectrum indicated the following isotopic composition: 4.2% d_2, 68.4% d_3, and 27.4% d_4. The nmr spectrum exhibited singlets at δ 10.52, 7.32, and 4.70, which integrated for 0.3, 2.0, and 1.4 protons, respectively; the infrared absorption at $\lambda_{max}^{CHCl_3}$ 3.4 μ was considerably weaker than in the spectrum of unlabeled phenoxyacetic acid. The mass spectrum of the trimethylsilyl ester derivative indicated the following isotopic composition: 7.2% d_2, 79.2% d_3, and 13.7% d_4.

2,2-d_2-4-Phenoxybutyric Acid (XII).—In a nitrogen atmosphere, 230 mg of finely divided sodium was dissolved in 5 ml of absolute ethanol, and to the stirred solution was added 1.76 ml of diethyl malonate followed by 2.0 g of 2-phenoxyethyl bromide.[39] The mixture was heated under reflux for 4 hr, cooled, and the ethanol removed by distillation, leaving a blue solid, which was added to water. The aqueous solution was extracted three times with ether and the combined ethereal layers were dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether gave 2.7 g of a colorless oil (λ_{max} 5.7, 8.0, 9.6, 13.2, and 14.4 μ).

Deuterium labeling was accomplished *via* a procedure similar to one previously employed by Duffield, *et al.*[49] In a nitrogen atmosphere and at 0°, 1.4 g of finely divided sodium was cautiously dissolved in 7.2 ml of deuterium oxide (99.8% d_2). To the stirred solution was added dropwise the alkylated diethylmalonate, and the mixture was heated under reflux for 3 hr. Ethanol was removed by distillation until the temperature of the solution reached 100°. After cooling to 0°, 3.04 ml of phosphorus trichloride was slowly added, and the mixture was warmed to room temperature and then heated under reflux for 20 hr. The solution was cooled, poured into acidic deuterium oxide, and extracted twice with ether; the combined ethereal extracts were dried over anhydrous magnesium sulfate. After filtration and removal of the ether by evaporation, 1.3 g of labeled 4-phenoxybutyric acid was obtained: mp 59–61° (lit.[50] mp 64–65°). The mass spectrum indicated the following isotopic composition: 40.7% d_2, 39.0% d_3, 14.7% d_4, and 5.6% d_5. The nmr spectrum exhibited a singlet at δ 11.9, a multiplet at δ 7.1, a triplet at δ 4.0, and a triplet at δ 2.1, which integrated for 0.6, 4.1, 2.0, and 2.0 protons respectively. The mass spectrum of the trimethylsilyl ester derivative indicated the following isotopic composition: 55.0% d_2, 29.0% d_3, 10.1% d_4, and 5.0% d_5. From the mass spectrum of this derivative it was determined [from m/e 159 (j), see Discussion] that the C-2 position contained 89.0% d_2 and 11.0% d_1 and from the m/e 166 peak (f) (see Discussion) that the phenyl ring had the following isotopic composition: 53.2% d_0, 32.1% d_1 8.7% d_2, and 6.0% d_3.

3,3-d_2-4-Phenoxybutyric Acid (XIII).—In a procedure identical with that utilized in the preparation of 5-phenoxypentanoic acid, 4.6 g of phenoxyacetic acid[38] was reduced with 1.3 g of lithium aluminum deuteride[51] (whereas lithium aluminum hydride was used in the previous case) to yield 4.1 g of 1,1-d_2-2-phenoxyethanol (λ_{max} 3.0, 8.0, 9.5, 13.2, and 14.4 μ). Bromination of this compound with 1.0 ml of phosphorus tribromide, again according to the previously described procedure, yielded 3.7 g of 1,1-d_2-2-phenoxyethyl bromide: λ_{max} 8.1, 9.5, 13.2, and 14.4 μ.

In a nitrogen atmosphere, 415 mg of finely divided sodium metal was dissolved in 9.0 ml of absolute ethanol, and to this solution was added dropwise 3.2 ml of diethyl malonate followed by 3.7 g of 1,1-d_2-2-phenoxyethyl bromide. The mixture was then heated under reflux for 4 hr. The ethanol was distilled from the reaction mixture and 4.5 g of potassium hydroxide in 5.4 ml of water was slowly added; the solution was again heated under reflux for 4 hr. After the addition of 3 ml of water, the remaining ethanol was distilled from the reaction mixture until the temperature reached 100°. The solution was cooled to 5°, 8.1 ml of concentrated sulfuric acid in 13.1 ml of water was added, and the mixture was again heated under reflux for 15 hr. After cooling, threefold extraction with dichloromethane, and drying with anhydrous magnesium sulfate, the dichloromethane was evaporated, yielding a yellow solid. Recrystallization, first from ether–hexane (1:1) and then from hexane, gave 2.0 g of 3,3-d_2-4-phenoxybutyric acid, mp 63–64° (lit.[50] mp 64–65°), whose mass spectrum indicated the following isotopic composition: 99.0% d_2 and 1.0% d_1.

2′,4′,6′,2,2-d_5-5-Phenoxypentanoic Acid (XIV).—In a manner identical with the preparation of 2,2-d_2-4-phenoxybutyric acid (XII), 2.15 g of 3-phenoxypropyl bromide[40] yielded impure diethyl 2-(3-phenoxypropyl)malonate (XXIV, n = 2), which was distilled at 160–162° (0.7 mm) to give 1.8 g of pure material (λ_{max} 5.8, 8.0, 9.7, 13.2, and 14.4 μ). Deuteration with 4.5 ml of deuterium oxide, 900 mg of finely divided sodium, and 1.9 ml of phosphorus trichloride yielded 890 mg of labeled 5-phenoxypentanoic acid after one recrystallization from ether–hexane (1:1), mp 62–64° (lit.[45] mp 65–66°). The mass spectrum indicated the following isotopic composition: 76.3% d_5, 20.6% d_4, and 3.1% d_3. The nmr spectrum exhibited a singlet at δ 11.75 (1 H), a singlet at δ 7.17 (2 H), a triplet at δ 3.92 (2 H), and a multiplet at δ 1.81 (4 H). The mass spectrum of the trimethylsilyl ester derivative indicated that the isotopic composition at C-2 (from m/e 173, see Discussion) was 87.0% d_2 and 13.0% d_1, and at the phenyl ring, 86.1% d_3 and 13.9% d_2 (from m/e 151, see Discussion).

3,3-d_2-5-Phenoxypentanoic Acid (XV).—Utilizing a procedure identical with that employed in the synthesis of 3,3-d_2-4-phenoxybutyric acid (XII), 4.15 g of 3-phenoxypropionic acid[39] was reduced with 1.26 g of lithium aluminum deuteride,[51] yielding 3.8 g of 1,1-d_2-3-phenoxypropanol (λ_{max} 3.0, 8.1, 9.6, 13.3, and 14.4 μ). Bromination with 0.8 ml of phosphorus tribromide gave 4.02 g of 1,1-d_2-3-phenoxypropyl bromide (λ_{max} 8.0, 9.5, 13.1, and 14.2 μ). Alkylation with 3.17 ml of diethylmalonate, followed by hydrolysis and decarboxylation as previously described, yielded, after recrystallization from ether–hexane (1:1) followed by recrystallization from hexane, 2.40 g of 3,3-d_2-5-phenoxypentanoic acid, mp 64.3–64.8° (lit.[45] mp 65–66°), whose mass spectrum indicated the following isotopic composition: 96.2% d_2 and 3.8% d_1.

Registry No.—I, n = 1, 21273-08-5; I, n = 2, 21273-09-6; I, n = 3, 21273-10-9; I, n = 4, 21273-11-0; I, n = 5, 21273-12-1; I, n = 6, 21273-13-2; I, n = 10, 21273-14-3; II, n = 2, 21273-15-4; II, n = 3, 21273-16-5; III, n = 3, 21273-17-6; IV, n = 3, R = Me,

(48) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 165.

(49) A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 805 (1965).

(50) W. J. Huff and R. D. Leitch, *ibid.*, **44**, 2643 (1922).

(51) Lithium aluminum deuteride was purchased from Karl Roth OHG, Karlsruhe, Germany.

21273-18-7; IV, n = 4, R = Me, 21273-24-5; IV, n = 3, R = Et, 21273-25-6; V, n = 2, 7497-89-4; V, n = 3, 21273-27-8; XI, 21273-28-9; XI (trimethylsilyl ester), 21273-40-5; XII, 21273-29-0; XII (trimethylsilyl ester), 21273-41-6; XIII, 21273-30-3; XIII (trimethylsilyl ester), 21273-42-7; XIV, 21273-31-4; XIV (trimethylsilyl ester), 21273-43-8; XV, 21273-32-5; XV (trimethylsilyl ester), 21273-44-9; XVI, 21273-33-6; XVI (trimethylsilyl ester), 21273-45-0; 5-phenoxypentanoic acid, 7170-40-3; 4-phenoxy-1-bromobutane, 1200-03-9; 7-phenoxyheptanoic acid, 7170-42-5; 11-phenoxyundecanoic acid, 7170-44-7; 1,1-d_2-2-phenoxyethanol, 21273-38-1; 1,1-d_2-2-phenoxyethyl bromide, 21273-39-2.

Pyrimido[5,4-e]-as-triazines. IV. The Preparation and Some Reactions of Pyrimido[5,4-e]-as-triazine-5(6H)-thiones[1]

CARROLL TEMPLE, JR., CONRAD L. KUSSNER, AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

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Reaction of 5-(benzylthio)- and 5-chloro-1,2-dihydropyrimido[5,4-e]-as-triazine (**8** and **4**), respectively, with NaSH gave 1,2-dihydropyrimido[5,4-e]-as-triazine-5(6H)-thione (**3**). Treatment of **4** with thiourea also gave **3** and a 2-thiospeudourea addition product that was rearranged in HCl to give 9-amino-9H-purine-8(7H)-one-6(1H)-thione (**11**). Oxidation of **3** and some 5-alkylthio derivatives with diethyl azodicarboxylate gave the corresponding heteroaromatic compounds. Replacement of the 5-alkylthio group with various nucleophiles occurred readily to give 5-substituted pyrimido[5,4-e]-as-triazines. Also, the rearrangement of 7-hydrazinothiazolo[5,4-d]pyrimidine to **3** is demonstrated.

In the previous papers of this series, the preparation and some reactions of 5-substituted pyrimido[5,4-e]-as-triazines were reported.[2] The present paper is concerned with the preparation of pyrimido[5,4-e]-as-triazine-5(6H)-thione and some of its 5-alkylthio derivatives. The latter were desired as potential substrates for nucleophilic displacement reactions to give various 5-substituted compounds. In addition, rearrangements involving the 7-hydrazinothiazolo[5,4-d]pyrimidine–pyrimido[5,4-e]-as-triazine-5(6H)-thione ring systems are discussed.

The preparation of **3** by the reaction of **1** with hydrazine to give **2**,[3] and cyclization of the latter with the $(EtO)_3CH$–concentrated HCl reagent[2c] was unsuccessful (see Scheme I). This reaction gave only the HCl salt of **2**. To increase the solubility and reactivity of **2**, the thione group was blocked by alkylation. Although **2** has been reported to undergo rapid oxidation in an alkaline medium,[3] treatment of a NaOH solution of **2** with $C_6H_5CH_2Cl$ gave a good yield of 4-(benzylthio)-pyrimidine **5**. Cyclization of **5** with the $(EtO)_3CH$–concentrated HCl reagent gave the HCl of 5-(benzylthio)-1,2-dihydropyrimido[5,4-e]-as-triazine (**8**), and a smaller amount of the 9-[(ethoxymethylene)amino]-purine **6**. Acid hydrolysis of the latter gave the known 9-aminopurine **7**.[4] The free base of **8** was obtained by neutralization of a solution of the HCl with $NaHCO_3$.

The interaction of **8** with hydrated NaSH in EtOH replaced the benzylthio group to give a 59% yield of **3**.[5] Similarly, the reaction of **4**[2c] with NaSH gave an 85% yield of **3**. The preparation of **3** was also attempted by reaction of **4** with thiourea. This reaction gave a 13% yield of **3**, apparently formed from the 2-thiopseudourea **9**. Also, a second product was obtained in 52% yield that analyzed correctly for the hydrochloride of **9**, but treatment of this material with aqueous NaOH gave none of **3**. This result suggested that **9** had undergone an intramolecular addition reaction to give the hydrochloride of the isomeric tricyclic compound **10** (see Scheme II). Support for structure **10** was provided by its rearrangement in HCl to give **11**, identified by elemental anaylses and comparison of its ultraviolet spectrum with that of purine-8(7H)-one-6(1H)-thione.[6] A similar tricyclic compound, obtained from the reaction of 6-chloropurine with thiourea, also undergoes this type of rearrangement,[7] which, in the present case, involves cleavage of both the thiazole and as-triazine rings, and hydrolysis of the guanidino moiety of **10** to give, presumably, the intermediate pyrimidine **12** which then undergoes cyclization and deformylation to give **11**.

Reaction of **3** with 4 N HCl at room temperature cleaved the as-triazine ring to give the pyrimidine **2**. In contrast, the product resulting from treatment of **3** with CF_3CO_2H was identified by elemental analyses and spectral data as the thiazolo[5,4-d] pyrimidine **13** (see Scheme III). The nmr spectrum of **3** in CF_3CO_2D showed the appearance of two new CH peaks in about 20 min and the disappearance of the two CH peaks of **3** in about 1 hr. Presumably, this rearrangement involves the trifluoroacetylation and ring opening of **3** to give **15**, which then undergoes recyclization to give **13**. The nmr data suggested that the recyclization step might have occurred during the reaction work-up. The assignment of the position of the CF_3CO group in **13** is based on analogy with the products obtained from the acylation and ring opening of the triazine ring of other 1,2-dihydropyrimido[5,4-e-]-as-triazines with carboxylic acids.[2a,c] To study the reverse rearrangement (**14** → **16** → **3**), the preparation of the known 7-hydra-

(1) This investigation was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract PH43-64-51.

(2) (a) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **34**, 2102 (1969); (b) C. Temple, Jr., and J. A. Montgomery, *ibid.*, **28**, 3038 (1963); (c) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *ibid.*, **28**, 923 (1963).

(3) E. C. Taylor, J. W. Barton, and W. W. Paudler, *ibid.*, **26**, 4961 (1961).

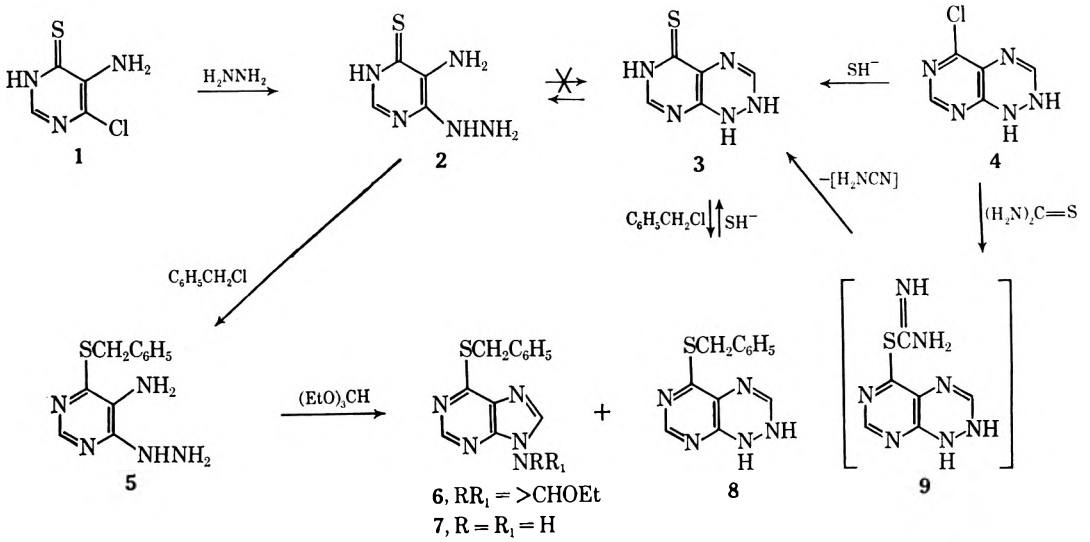
(4) C. Temple, Jr., A. G. Laseter, and J. A. Montgomery, *J. Heterocycl. Chem.*, **5**, 711 (1968).

(5) A similar reaction with a 4-(benzylthio)pteridine has been described by J. J. McCormach and H. G. Mautner, *J. Org. Chem.*, **29**, 3370 (1964).

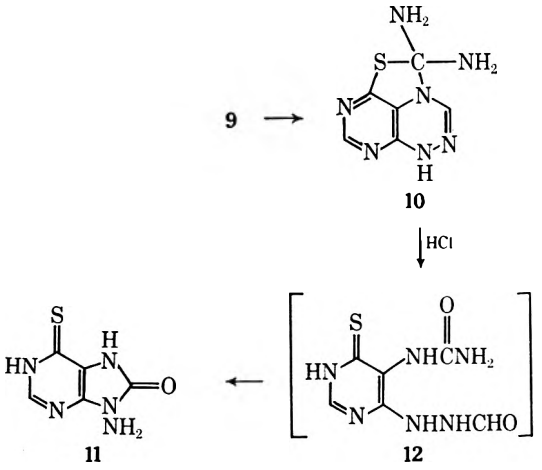
(6) R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 6671 (1958).

(7) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1417 (1966).

SCHEME I



SCHEME II



zinothiazolo[5,4-*d*]pyrimidine (**14**) was undertaken.[8] Treatment of **19**[8] in ethanolic N_2H_4 by the reported procedure gave a mixture from which only the hydrazinopyrimidine **2** was obtained. In reactions carried out in MeOH, the products were identified as **1**, **2**, and 5-hydrazinopyrimido[5,4-*e*]-*as*-triazine.[2a] Compound **1** results from cleavage of the thiazolo ring of **19** and presumably **2** results from cleavage of the thiazolo ring of **14**. The sequence of reactions leading to the formation of the pyrimido[5,4-*e*]-*as*-triazine is unknown, but must involve the replacement of both the chloro and sulfur atoms of **19** with hydrazine moieties and air oxidation of an intermediate dihydro compound. Treatment of **19** with $N_2H_5^+OAc^-$ in aqueous dioxane, however, gave a product that was shown by its nmr spectrum to be a 1:2 mixture of **14**–**3**. A sample of **14** was finally obtained by treatment of an Et_2O solution of **19** with N_2H_4. Although the nitrogen analysis on this material for anhydrous **14** was 1% low, the CH analysis was correct and its ultraviolet spectrum was consistent with that previously reported for the hemihydrate of **14**.[8] The nmr spectrum of this material in deuterated DMSO initally showed only two CH peaks, but after 24 hr the two CH peaks of **3** were also detected. Additional studies on this type of rearrangement are being investigated and will be reported at a later date.

The benzylation of **3** gave the 5-benzylthio compound **8** described above. The alkylation of **3** with chloroacetonitrile gave a product that analyzed correctly for **17**, but the absence of a CN band in its ir spectrum indicated that intramolecular cyclization of the latter to a tricyclic compound might have occurred as in the conversion of **9** to **10**. Comparison of the ultraviolet spectrum of this material with that of **10** and **18**, however, provided support for structure **17**. In the methylation of **3** a 50% yield of the dihydro compound **18** and a 6% yield of the heteroaromatic compound **21** were obtained. Presumably, **21** is formed during the reaction by the air oxidation of **18**. Oxidation of **3** with diethyl azodicarboxylate in $CHCl_3$ gave the heteroaromatic compound **20**, identified by elemental analysis and by methylation to give the 5-methylthio compound **21** described above. Apparently this is the first instance in which diethyl azodicarboxylate has been used for the oxidation of a heterocyclic system.[9] Similarly, oxidation of **18** and **8** with this reagent gave **21** and **22**, respectively. As with **8**, reaction of **18** with ethanolic NaSH gave **3**. Treatment of **21** with NaSH, however, gave a mixture of **3** and **24**[2a] rather than **20**, the product expected from simple displacement of the methylthio group. The formation of **3** results from replacement of methylthio group and reduction of the *as*-triazine ring, both by NaSH. Apparently, **24** results from hydrolysis of the methylthio group of **21**. Also, the replacement of the benzylthio group of **22** with nitrogen nucleophiles occurred readily. Reaction of **22** with ethanolic NH_3 at room temperature gave a mixture of **23** (60%), **24** (37%), and benzyl disulfide (77%).[2a] Similarly, reaction of **22** with hydroxylamine, guanidine, and (diphenylmethyl)amine, respectively, gave **25**, **26**, and **27**.

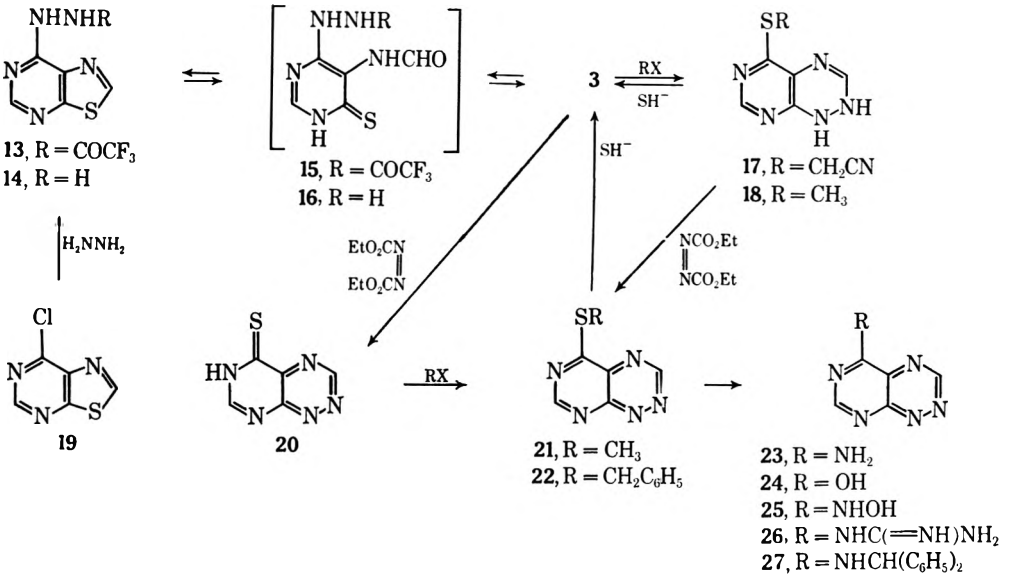
Experimental Section

Melting points were determined on a Kofler–Heizbank apparatus and are corrected. The uv absorption spectra of solutions were determined with a Cary Model 14 spectrophotometer, whereas the ir absorption spectra were determined in pressed

(8) L. Marchad, R. Promel, R. H. Martin, and A. Cardon, *Bull. Soc. Chim. Belges.*, **69**, 177 (1960).

(9) For other types of oxidation with this reagent, see (a) O. Diels, *Ber.*, **56**, 1933 (1923); (b) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Amer. Chem. Soc.*, **88**, 2328 (1966).

SCHEME III



potassium bromide disks with Perkin-Elmer Models 221-G and 521 spectrophotometers. The nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal reference. Thin layer chromatograms (tlc) were prepared from silica gel H (Brinkmann) and were usually developed with mixtures of $CHCl_3$ and MeOH.

5-Amino-4-hydrazinopyrimidine-6(1H)-thione (2)[3] was prepared from **1** by the reported procedure in 82% yield. This compound also results from **3** by the action of 4 *N* HCl. Nmr (<5% DMSO d_6 w/v) τ 5.20, 3.17 (broad, NH) and 2.18 (CH); nmr (<5% CF_3CO_2D w/v) τ 1.52 and 1.39[10] (CH).

1,2 Dihydropyrimido[5,4-*e*]*as*-triazine-5(6H)-thione (3).—A mixture of **4** (24 g) and hydrated NaSH (96 g) in EtOH (2400 ml) was refluxed for 1 hr, evaporated to dryness *in vacuo*, and the resulting residue suspended in H_2O (1100 ml). After filtration, the filtrate was neutralized with HOAc; the solid that precipitated was collected by filtration and washed with H_2O (1200 ml). The dried solid was stirred in C_6H_6 (1200 ml) to remove sulfur, then suspended in H_2O (530 ml) and dissolved by the addition of 1 *N* NaOH (128 ml). The solution was filtered and the filtrate was acidified with 1 *N* HCl (150 ml) to deposit **3**, which was dried *in vacuo* over P_2O_5 at 78°: yield 20 g (85%); mp >264°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 238 (6.83), 256 (7.95) 328 (2.63), and 412 mμ (5.60); ir 3280, 3190, 1650 (NH); 1600, 1580, and 1510 cm^{-1} (C=C, C=N); nmr (<10% DMSO-d_6 w/v) τ 3.75 (d, 1, J = 3 Hz, 3-CH), 3.18 (d, 1,2-NH), 2.45 (1, 7-CH), 1.27 (1, 1-NH), and −2.65 (1, 6-NH); nmr (<5% CF_3CO_2D w/v)[12] τ 2.70 and 1.98 (1, 1, CH).

Anal. Calcd for $C_5H_5N_5S$: C, 35.92; H, 3.02; N, 41.89. Found: C, 35.72; H, 3.20; N, 41.82.

B.—Similarly a mixture of **8** (1.0 g) and hydrated NaSH (2.5 g) was treated as described above to give **3**; yield 0.38 g (59%). Likewise, **18** (0.50 g) gave **3**; yield 0.27 g (58%). Reaction of **21** (0.34 g) with NaSH (2 g) also gave crude **3**; yield 0.12 g (38%). The solid obtained from this reaction filtrate was identified as **24** by tlc.

5-Amino-4-(benzylthio)-6-hydrazinopyrimidine (5).—To a suspension of **2** (35 g) in H_2O (350 ml) was added with stirring $C_6H_5CH_2Cl$ (26 ml) and 1 *N* NaOH (228 ml). After the mixture stirred at room temperature for 95 hr, the solid (55 g) was collected by filtration and recrystallized from C_6H_6 to give **5** in two crops: yield 43 g (78%); mp 131° with presoftening from 127°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11b] 277 (5.5) and 328 mμ (8.9); ir 3420, 3340, 3280, 3230, 1640 (NH); 1575, 1535, and 1490 cm^{-1} (C=C, C=N).

Anal. Calcd for $C_{11}H_{12}N_6S$: C, 53.42; H, 5 30; N, 28 29; S, 12.96. Found: C, 53.47; H, 5.38; N, 28.38; S, 12.90.

5-(Benzylthio)-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (8). A.—Concentrated HCl (6.8 ml) was added slowly to a suspension of **5** (20 g) in $(EtO)_3CH$ (400 ml). The resulting orange mixture was stirred with a strong and efficient stirrer for 4 hr at room temperature. The crude HCl (19 g) was collected by filtration, washed with ether, and suspended in H_2O (900 ml). After the addition of $NaHCO_3$ (5.8 g), the solid was collected by filtration and crystallized from C_6H_6: yield 14 g (67%); mp 160°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 356 mμ (5.76); ir 3280 (NH), 1660, 1585, and 1530 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 5.70 (2, CH_2), 3.84 (d, 1, J = 3 Hz, 3-CH), 2.68 (6, C_6H_5, 2-NH), 2.33 (1, 7-CH), and 1.37 (1, 1-NH).

Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.25; S, 12.46. Found: C, 56.22; H, 4.46; N, 27.11; S, 12.2.

The combined $(EtO)_3CH$ filtrate and Et_2O wash from above was evaporated to dryness to give **6**: yield 3.9 g (15%); mp 125° with presoftening.

Anal. Calcd for $C_{15}H_{16}N_5OS$: C, 57.30; H, 5.13. Found: C, 57.28; H, 4.91.

A suspension of **6** in 1% HCl (100 ml) was stirred at room temperature for 20 hr. The solid was collected by filtration and recrystallized from THF–petroleum ether (bp 85–105°) to give **7**: yield 2.1 g (10%); mp 166–167° (lit.[4] mp 167–168°).

Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; S, 12.46. Found: C, 56.27; H, 4.52; S, 12.2.

B.—A mixture of **3** (1.0 g), $C_6H_5CH_2Cl$ (0.7 ml), and K_2CO_3 (0.85 g) in DMF (10 ml) was stirred at room temperature for 20 hr, evaporated to dryness *in vacuo*, and the residue washed with H_2O to give crude **8**; yield 1.2 g (78%). The alkylation of **3** (1.0 g) with $C_6H_5CH_2Cl$ (0.7 ml) was also effected in aqueous NaOH to give crude **8**; yield 0.89 g (58%).

Reaction of 4 with Thiourea.—A suspension of **4** (2.0 g) in PrOH (40 ml) containing thiourea (1.0 g) was refluxed for 1.5 hr. The solid was collected by filtration and extracted with hot MeOH (250 ml). The residue was identified as **3** (75% pure) by its uv, ir, and nmr spectra; yield 0.25 g (13%). The extract was evaporated to dryness, and the resulting residue was dried *in vacuo* over P_2O_5 at 100° to give **10**; yield 1.5 g (52%). This sample melted with decomposition from 190°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$) 230 (12.0) and 308 mμ (9.68); ir 1670 (NH), 1590, 1550, and 1530 cm^{-1} (C=C, C=N).

Anal. Calcd for $C_6H_7N_7S \cdot HCl$: C, 29.33; H, 3.28; N, 39.91; Found: C, 29.08 H, 3.49; N, 39.66.

9-Amino-9H-purine-8(7H)-one-6(1H)-thione Hydrochloride (11).—A solution of **10** (0.2 g) in 1 *N* HCl (10 ml) was refluxed for 2 hr. The solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5 at 78°; yield 0.05 g (28%); mp >264°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 239 (11.7) and 332 mμ (14.2); ir 3300–2600 (NH), 1720 (CO), 1615 (NH_2), and

(10) This peak increased with time and was assigned to the product resulting from the interaction of **2** with the solvent.

(11) Each solution contains 10% dissolving solvent and 90% appropriate aqueous solvent (a) 8% methanolic DMSO; (b) H_2O; (c) MeOH; (d) dissolved in 0.1 *N* NaOH and neutralized with 0.1 *N* HCl.

(12) After 1 hr, this spectrum exhibited peaks only at τ 0.96 and 0.46 (CH), which, on comparison with the peaks exhibited by **13**, suggested the ring opening of **3** to give **15**.

1570 and 1525 cm^{-1} (C=C, C=N); nmr (<2.5 DMSO-d_6-D_2O w/v) τ 1.81 (CH).

Anal. Calcd for $C_5H_5N_5OS \cdot HCl$: C, 27.34; H, 2.75; N, 31.88. Found: C, 27.11; H, 2.87; N, 32.05.

7-[2-(Trifluoroacetyl)hydrazino]thiazolo[5,4-*d*]pyrimidine (13).—A solution of **3** (0.64 g) in CF_3CO_2H (25 ml) was stirred at room temperature for 18 hr and evaporated to dryness. The residue was washed with Et_2O and dried *in vacuo* over P_2O_5 at 78°; yield 0.85 g (84%); mp 209° with decomposition and sublimation; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 266 (10.3), uv (MeOH), 262 mμ (10.2); ir 1715 (CO), 1620 (NH), 1560, 1550, and 1530 cm^{-1} (C=C, C=N); nmr (< 5% DMSO-d_6 w/v) τ 1.42, 0.60 (1, 1, CH); nmr (5% CF_3CO_2D w/v) τ 0.95 and 0.55 (1, 1, CH).

Anal. Calcd for $C_7H_4F_3N_5OS$: C, 31.94; H, 1.53; N, 26.61. Found: C, 31.72; H, 1.74; N, 26.78.

Reaction of 19 with Hydrazine. A.—Hydrazine (95+%) (0.17 ml) was added with stirring to a solution of **19**[8] (0.88 g) in Et_2O (200 ml). After 2 hr, the solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 at 78° to give **14**:[3] yield 0.16 g (19%); mp, rapid decomposition above 200° with sublimation; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 222 (15.3) and 263 mμ (9.75); nmr (<2.5% DMSO-d_6 w/v) τ 1.55 and 0.77 (1, 1, CH) and broad NH;[13] nmr (2.5% CF_3CO_2D w/v) τ 1.07 and 0.57 (1, 1, CH).[14]

B.—A solution of **19** (1.0 g) in dioxane was added with stirring to a mixture of hydrazine (95+%, 1.0 ml), glacial HOAc (1.8 ml), and H_2O (25 ml). After 2 hr, the solid (0.36 g) that deposited was collected by filtration and identified as about a 1:2 mixture of **14**–**3**; nmr (<5% DMSO-d_6 w/v) τ 1.57 and 0.78 (1, 1, CH) (**14**); 3.77 and 2.50 (2, 2, CH) (**3**).

C.—Compound **19** (1.0 g) was added with stirring to a mixture of hydrazine (95+%, 1.0 ml) and MeOH (10 ml). After 18 hr, the solid (0.37 g) that deposited was collected by filtration and identified as **2**[3] by its uv spectrum and tlc [BuOH (5)/HOAc (2)/H_2O (3)]. Acidification of the filtrate with HOAc deposited a solid (0.39 g) that was identified as **1**[3] by its uv spectrum and tlc.

When the same reactants as described above were maintained near 0° for 18 hr, the solid (0.52 g) that deposited was identified as 5-hydrazinopyrimido[5,4-*e*]-*as*-triazine[2a] by its uv and nmr spectra.

[(1,2-Dihydropyrimido[5,4-*e*]-*as*-triazin-5-yl)thio]acetonitrile (17).—To a suspension of **3** (1.0 g) in H_2O (20 ml) was added 1 *N* NaOH (6 ml) and $ClCH_2CN$ (0.4 ml). After 2 hr, the solid was collected by filtration and extracted with hot C_6H_6 (700 ml). This extract deposited the product in two crops: yield 0.38 g (31%); mp about 228° with decomposition; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 258 (13.2), 356 (3.54); ir 1650 (NH), 1625, 1590, 1555, and 1495 cm^{-1} (C=C, C=N); nmr (<10% DMSO-d_6 w/v) τ 6.27 (2, CH_2), 2.64, 2.16 (1, 1, CH), 1.43 (broad), and 0.43 (1, 1, NH).

Anal. Calcd for $C_7H_6N_6S$: C, 40.76; H, 2.93; N, 40.75. Found: C, 41.11; H, 3.13; N, 40.63.

1,2-Dihydro-5-(methylthio)pyrimido[5,4-*e*]-*as*-triazine (18).—To a mixture of **3** (10 g) and MeI (3.8 ml) in H_2O (100 ml) was added with stirring 1 *N* NaOH (60 ml). After 1 hr, the solid was collected by filtration and dried *in vacuo* over P_2O_5. This residue was boiled in C_6H_6 (2800 ml), and the unreacted **3** (1.5 g) was removed by filtration. The filtrate was allowed to cool to deposit **18**, which was dried *in vacuo* over P_2O_5: yield 4.6 g (50% based on reacted **7**); mp 208–209° with presoftening from 202°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 239 (10.4) and 381 (5.21); ir 1650, 1590, 1560, and 1510 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 7.63 (CH_3), 3.83 (d, 1, J = 3 Hz, 3-CH), 2.39 (1, 7-CH), 2.72 (d, 1, 2-NH), and 1.50 (1, 1-NH).

Anal. Calcd for $C_6H_7N_5S$: C, 39.73; H, 3.89; N, 38.67; S, 17.68. Found: C, 39.92; H, 3.90; N, 38.79; S, 17.47.

The C_6H_6 filtrate was evaporated to dryness, and the residue was recrystallized from petroleum ether (bp 85–105°) to give **21**: yield 0.53 g (6%); mp 137°.

Pyrimido[5,4-*e*]-*as*-triazine-5(6H)-thione (20).—A mixture of **3** (1.0 g), diethyl azodicarboxylate (1.1 ml), and $CHCl_3$ (100 ml) in a flask completely covered with aluminum foil was stirred at room temperature for 18 hr. The solid was collected by filtration and washed with EtOAc; yield 0.70 g. The nmr spectrum in DMSO-d_6 indicated that this material was a 3:1 mixture of **20** and **3**. The mixture (0.65 g) was treated again with diethyl azodicarboxylate (0.55 ml) in $CHCl_3$ (50 ml) to give pure **20**: yield 0.52 g (53%); mp <260°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11d] 259 (11.7) and 450 mμ (4.96); ir 1585, 1540, 1505, and 1495 cm^{-1} (C=C, C=N); nmr (<5% DMSO-d_6 w/v) τ 1.56, −0.02 (1, 1, CH), and −3 (broad, NH).

Anal. Calcd for $C_5H_3N_5S$: C, 36.35; H, 1.83; N, 42.39; S, 19.41. Found: C, 36.60; H, 2.04; N, 42.68; S, 19.10.

5-(Methylthio)pyrimido[5,4-*e*]-*as*-triazine (21).—**A.** A mixture of **18** (3.7 g), diethyl azodicarboxylate (3.7 ml), and $CHCl_3$ (185 ml) was stirred at room temperature for 4 hr in a flask completely covered with aluminum foil. The resulting solution was evaporated to dryness *in vacuo*, and the residue was recrystallized from MeOH: yield 2.6 g (71%); mp 137–139°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 238 (11.3), 262 (5.33), and 888 mμ (7.27); ir 3060, 3010 2920, 2845 (CH), 1545, 1525, and 1500 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 7.30 (3, CH_3), 0.73, and −0.20 (1, 1, CH).

Anal. Calcd for $C_6H_5N_5S$: C, 40.20; H, 2.79; N, 39.10; S, 17.87. Found: C, 40.38; H, 3.00; N, 38.99; S, 17.92.

B.—To a suspension of **20** (0.30 g) in H_2O (10 ml) was added MeI (0.12 ml) and 1 *N* NaOH (1.9 ml). After 2 hr, the product was collected by filtration and washed with H_2O: yield 0.18 g (55%); mp 137°.

5-(Benzylthio)pyrimido[5,4-*e*]-*as*-triazine (22) was prepared in 63% yield from **8** and diethyl azodicarboxylate: mp 113°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 240 (13.5) and 391 mμ (8.30, unstable); ir 1550, 1530, 1500 and 1490 cm^{-1} (C=C, C=N); nmr (10% DMSO-d_6 w/v) τ 5.32 (2, CH_2); 2.57 (5, C_6H_5); 0.62, and −0.30 (1, 1, CH).

Anal. Calcd for $C_{12}H_9N_5S$: C, 56.45; H, 3.55; N, 27.44. Found: C, 56.63; H, 3.73; N, 27.25.

Amination of 22.—A solution of **22** (200 mg) in 10% ethanolic NH_3 (10 ml) was stirred at room temperature for 18 hr to deposit **23**,[2a] identified by its tlc; yield 70 mg (60%). The residue obtained from evaporation of the filtrate to dryness was washed with Et_2O to give **24**,[2a] identified by its uv and ir spectra; yield 43 mg (37%). Evaporation of the Et_2O wash gave benzyldisulfide; yield 75 mg (77%); mp 70° (lit. mp 71–72°).

5-(Hydroxyamino)pyrimido[5,4-*e*]-*as*-triazine (25).—A suspension of 22 (1.0 g) in methanolic hydroxylamine (25 ml), prepared from the HCl salt (1.5 g) and NaOMe (1.1 g), was stirred for 4 hr at room temperature. The solid was collected by filtration, washed with MeOH, and dried *in vacuo* over P_2O_5 at 78°: yield 0.62 g (96%); mp >264°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11a] 381 mμ (6.67); ir 3240, 3050, (NH, OH), 1630 (NH), 1595, and 1510 (C=C, C=N); nmr (<5% DMSO-d_6 w/v) τ 2.26, 0.55 (1, 1, CH), and −1.68 (1, NH).

Anal. Calcd for $C_5H_4N_6O$: C, 36.59; H, 2.46; N, 51.21. Found: C, 36.69; H, 2.60; N, 51.49.

Pyrimido[5,4-*e*]-*as*-triazin-5-ylguanidine (26).—A solution of **22** (0.50 g) in methanolic guanidine (25 ml), prepared from the HCl salt (1.0 g) and NaOMe (0.45 g), was stirred for 1 hr at room temperature to deposit **26**; yield 0.34 g (91%). Recrystallization from H_2O gave the analytical sample: mp >264°; uv (pH 7) λ_{max} ($\epsilon \times 10^{-3}$)[11b] 246 (14.4), 400 (7.53); ir 3445, 3300–3050 (NH), 1640 (NH), 1550, 1535, and 1495 cm^{-1} (C=C, C=N); nmr (<6% DMSO-d_6 w/v) τ 2.03 (NH), 1.35, and 0.03 (1, 1, CH).

Anal. Calcd for $C_6H_6N_8$: C, 37.90; H, 3.18; N, 58.92. Found: C, 37.73; H, 3.10; N, 58.96.

5-[(Diphenylmethyl)amino]pyrimido[5,4-*e*]-*as*-triazine (27).—A solution of **22** (5.0 g) and (diphenylmethyl)amine (17 ml) in MeOH (125 ml) was refluxed for 6 hr and evaporated to a small volume *in vacuo*. This residue was stirred in petroleum ether (700 ml) (bp 80–105°) for 2 hr, and the crude product that formed was collected by filtration: yield 6.0 g (98%); mp 141° dec with presoftening. Recrystallization from petroleum ether (bp 85–105°) and drying the resulting solid *in vacuo* over P_2O_5 at 78° gave the analytical sample: mp 155° with presoftening from 150°; uv (0.1 *N* HCl) λ_{max} ($\epsilon \times 10^{-3}$)[11c] 253 (sh) and 369 mμ (10.5); ir 3360 (NH), 3055, 3025 (CH), 1575, 1565, and 1520 cm^{-1} (C=C, C=N); nmr (8% DMSO-d_6–D_2O w/v) τ 3.10 [1, $CH(C_6H_5)_2$], 2.63 (10, C_6H_5), 1.20, and −0.13 (1, 1, CH).

Anal. Calcd for $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.64; H, 4.68; N, 26.53.

Registry No.—**3**, 21308-86-1; **5**, 21308-87-2; **6**,

(13) After 24 hr, this spectrum also showed CH peaks at τ 3.75 and 2.49 (**3**).

(14) After 1 hr, this spectrum also showed CH peaks at τ 0.96 and 0.58 (**13**).

21308-88-3; **8**, 21308-89-4; **10**, 21308-90-7; **11**, 21308-91-8; **13**, 21308-92-9; **14**, 21308-93-0; **17**, 21308-94-1; **18**, 21308-95-2; **20**, 21308-96-3; **21**, 21308-97-4; **22**, 21308-98-5; **25**, 21308-99-6; **26**, 21309-00-2; **27**, 21309-01-3.

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Alternate Precursors in Biogenetic-type Syntheses. V.[1] 3-(Indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline as a Precursor. The Synthesis and Stereochemistry of 2-Methylcyclohex[*d*]indolo[2,3-*f*]morphan-15-one

Harold Zinnes, Francis R. Zuleski, and John Shavel, Jr.

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey

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A biogenetic-type synthesis employing 3-(indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**2**) as an alternate precursor in place of the corresponding 1-(indol-3-ylmethyl) analog is described. Birch reduction of **2** followed by acid-catalyzed hydrolysis and cyclization leads to the formation of a mixture of epimeric 2-methylcyclohex[*d*]indolo[2,3-*f*]morphan-15-ones (**7a** and **7b**), which differ only in the configuration at C-4. Chemical and spectroscopic evidence indicates the higher melting ketone (major product) to have the geometry of a *trans*-decahydroisoquinoline (**7a**), the other being a *cis*-decahydroisoquinoline (**7b**).

Earlier publications in this series have described the use of 1-(indol-3-ylmethyl)isoquinoline derivatives as alternative precursors[2] for the biogenetic-type synthesis[3] of missing alkaloid systems[1] related to naturally occurring alkaloids. Thus, the indole isosteres of dihydrothebainone[4] and argemonine (N-methylpavine)[1] as well as an indoline analog in the aporphine series[5] have been prepared.

Our observation[1] of the relatively mild conditions required for the rearrangement of 2-alkyl-1-(indol-3-ylmethyl)-1,2-dihydroisoquinolines to 2-alkyl-3-(indol-3-ylmethyl)-3,4-dihydroisoquinolinium salts suggests that compounds derived from the latter may be considered as examples of another type of biologically feasible alternate precursor. Insertion of a 3-(indol-3-ylmethyl)isoquinoline derivative such as **2** at some stage of a biogenetic-type synthesis would be expected to give rise to new types of alkaloidal systems. The present investigation concerns the use of **2** as a precursor in a synthetic scheme, analogous to that employed[4] in the preparation of the indole isostere of dihydrothebainone. The resulting products, the epimeric ketones **7a** and **7b**, are representative of the previously unreported cyclohex[*d*]indolo[2,3-*f*]morphan ring system.[6,7]

Precursor **2** was prepared by reduction of **1** as described previously.[1] While **2** itself could be used as a starting material for the synthetic sequence (Chart I), it was found most convenient to subject **1** directly to the conditions of Birch reduction. The resulting hexahydroisoquinoline **3** was refluxed with aqueous methanolic hydrochloric acid to give the epimeric unsaturated ketones **5**. These were not isolated, since they cyclized, under the reaction conditions, to give a mixture of the epimeric cyclic ketones **7a** and **7b**.[8] The major product, isolated in 48% yield, had a higher melting point (260–262°), a lower solubility in chloroform and methanol, and a slower migration rate on thin layer chromatography than the minor product (mp 227.5–228.5°), which was isolated in 12% yield.[9] Both compounds gave a negative Ehrlich test and ultraviolet spectra which were typical of 2,3-dialkylindoles.

The configuration of the higher melting ketone was established as that of **7a** by examination of the NH frequencies of the alcohols **9a** and **10a** produced, respectively, by lithium aluminum hydride reduction and reaction with phenyllithium. Dreiding models indicate that, in the chair conformation of **9a** and **10a** with the axial hydroxyl, there should be strong intramolecular bonding between the oxygen and the indole

(1) Paper IV in this series: H. Zinnes, F. R. Zuleski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 3605 (1968).

(2) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavel, Jr., *ibid.*, **32**, 2551 (1967).

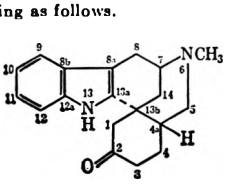
(3) E. E. van Tamelen, "Progress in the Chemistry of Organic Natural Products," Vol. 19, L. Zeckmeister, Ed., Springer-Verlag, Vienna, Austria, 1961, p 242.

(4) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2555 (1967).

(5) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *ibid.*, **33**, 1663 (1968).

(6) The numbering system (see Chart I) was chosen to conform as closely as possible with that used for the cyclohex[*f*]indolo[2,3-*f*]morphan series.[2] Compounds **7a** and **7b** differ only in the ring junction at C-4. In **7a**, the hydrogen at C-4 is *trans* with respect to the indole group at C-5, so that the geometry of the ring system resembles that of a *trans*-decahydroisoquinoline (see structure **9a**). The geometry of **7b** resembles that of a *cis*-decahydroisoquinoline (see structure **9b**), the hydrogen at C-4 being *cis* to the indole at C-5. Thus, **7a** is referred to as the *trans* epimer and **7b** as the *cis* epimer. In naming compounds of the **a** series, the prefix "*trans*-[5(indolo),4H]" is used, whereas "*cis*-[5(indolo),4H]" is used for the **b** series. The geometry of the *trans* epimer (**a** series) most closely resembles that of the compounds known as *cis*-morphinans (including morphine) since the latter also contain a *trans*-decahydrosioquinoline moiety. This apparent discrepancy arises from the fact that in the morphinans, ring E is fused with both ring C and ring D; the conventional stereochemical designation of the series was apparently chosen with reference to the CE ring fusion. In **7**, the only fusion of ring E is with ring D.

(7) The systematic name for **7a** is *trans*-[13b(indolo),4aH]1,2,3,4,4a,5,6,-7,8,13-decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-one, with the numbering as follows.

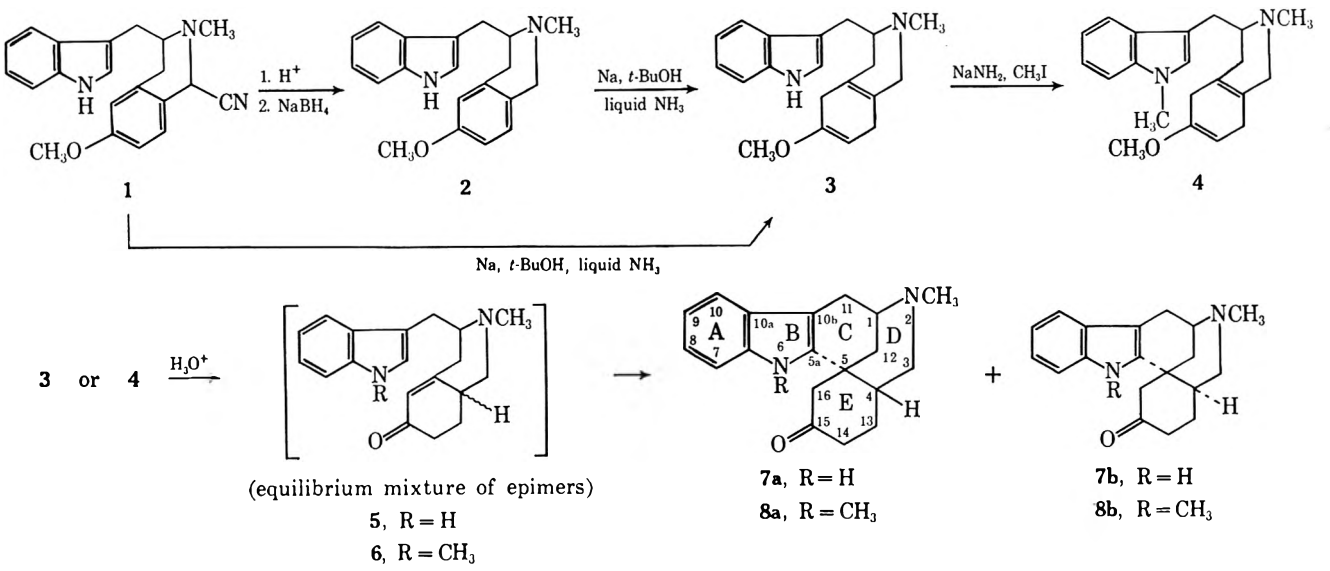


It differs from its *cis* epimer in the configuration at C-4a.

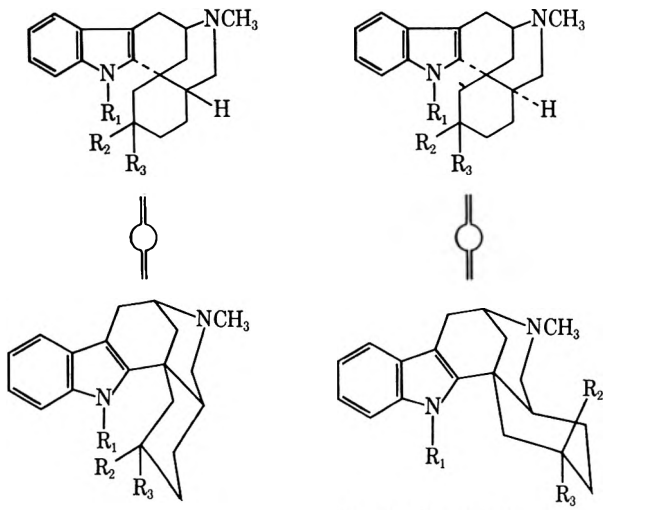
(8) Thin layer chromatograms suggested approximately a 70:30 mixture.

(9) Another 18% was isolated as a crystalline mixture of the two ketones.

CHART I



hydrogen; no such interaction exists in **9b** or **10b**. Dichloromethane solutions of **9a** and **10a** showed hydrogen-bonded NH absorption at 3260 and 3300 cm^{-1}, respectively, whereas the corresponding alcohols **9b** and **10b**, derived from the lower melting ketone, showed normal absorption at 3480 cm^{-1}.



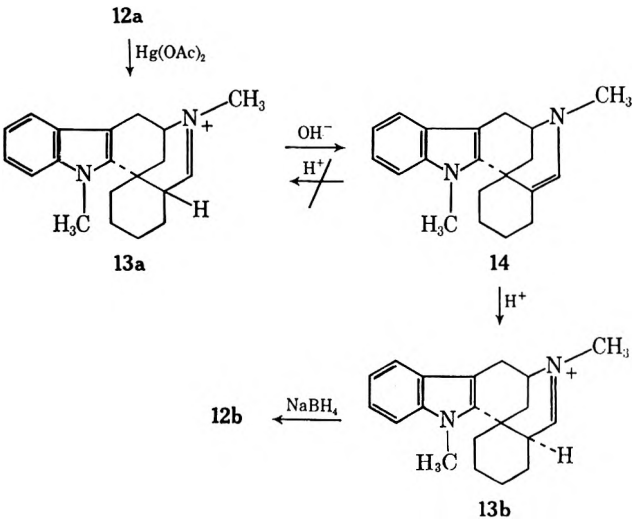
9a, $R_1 = R_3 = H$, $R_2 = OH$ **9b**, $R_1 = R_3 = H$, $R_2 = OH$
10a, $R_1 = H$, $R_2 = OH$, $R_3 = C_6H_5$ **10b**, $R_1 = H$, $R_2 = OH$, $R_3 = C_6H_5$
11a, $R_1 = R_2 = R_3 = H$ **11b**, $R_1 = R_2 = R_3 = H$
12a, $R_1 = CH_3$, $R_2 = R_3 = H$ **12b**, $R_1 = CH_3$, $R_2 = R_3 = H$

Wolff–Kishner reduction of **7a** and **7b** took place readily to give **11a** and **11b**, respectively. Examination of a model of the chair form of **11a** shows a considerable interaction between a hydrogen at C-15 and the indole NH. In the case of the derivative **12a**, the N_{Ind}-methyl group and a C-15 hydrogen practically overlap, so that it is unlikely that this compound could exist in an all-chair conformation. These interactions are absent in **11b** and its N_{Ind}-methyl derivative **12b**.

As expected, the reaction of **11b** (derived from the lower melting ketone) with sodium amide and methyl iodide in liquid ammonia proceeded smoothly and completely to give **12b**. When **11a** (derived from the higher melting ketone) was subjected to the same conditions, less than 25% conversion took place and **12a** could not be isolated. This slower rate of alkylation of **11a** relative to that of **11b** is further evidence that the higher melting ketone is the *trans* epimer **7a** and the lower melting ketone the *cis* epimer **7b**. Compound **12a** was ultimately prepared in 43% yield by prolonged refluxing of **11a** with an excess of sodium hydride and dimethyl carbonate in tetrahydrofuran.[10]

That the two series were indeed epimeric at C-4 was established experimentally by conversion of **12a** to **12b**, as depicted in Chart II. Compound **12a** was

CHART II



oxidized by heating with mercuric acetate in acetic acid.[11] The resulting immonium salt **13a** was treated with alkali to cause shifting of the double bond to give **14**, thus destroying the asymmetric center at C-4. Conversion of **14** to the salt **13b** followed by sodium borohydride reduction yielded a product whose major component was identified as **12b**. Thin layer chromatograms indicated the presence of an unidentified, faster moving impurity, but the slower spot characteristic of **12a** was completely absent. The essentially

(10) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Med. Chem.*, **8**, 200 (1965).

(11) N. J. Leonard and F. P. Hauch, Jr., *J. Amer. Chem. Soc.*, **79**, 5279 (1957).

complete epimerization of **12a** to **12b** is understandable in view of the severe interaction between the N-methyl and a C-15 hydrogen, which would tend to inhibit formation of **13a** on acidification of **14**.

The results of the latter experiment suggested that we might achieve stereoselective cyclization to the *cis* epimer **8b** (Chart I) if we started with the N_{Ind}-methyl derivative **6**. Though not so severe as in **12a**, the steric interaction between the N_{Ind}-methyl and the C-15 substituent (carbonyl) of **8a** appears considerable. In order to explore the possibility that this interaction might be sufficient to retard the formation of **8a**, we prepared the N_{Ind}-methylhexahydroisoquinoline **4** by treating **3** with sodium amide and methyl iodide in liquid ammonia. However, the product obtained on refluxing **6** with acid was the same type of epimeric mixture (**8a** and **8b**) as was obtained from **5**, with the major component being the *trans* epimer **8a**. Thus, it appears that the aforementioned steric interaction is insufficient, when C-15 is trigonal, to alter the normal course of the cyclization.[12]

The identity of **8b** was established by refluxing it with potassium hydroxide and hydrazine in ethylene glycol to give **12b** in 73% yield. Under the same conditions, **8a** gave a mixture from which **12a** could be isolated in only 13% yield. The difficulty encountered in carrying out the Wolff–Kishner reduction of **8a** is evidently another reflection of the unfavorable steric interaction existing in **12a**. Still further evidence for our configurational assignment is given by the nmr spectra, which indicate greater shielding of the N_{Ind}-methyl hydrogens of **8a** relative to those of **8b**, **12a**, and **12b**.[13]

Experimental Section[14,15]

3-(Indol-3-ylmethyl)-6-methoxy-2-methyl-1,2,3,4,5,8-hexahydroisoquinoline (3). A. Preparation from 1.—A solution of 20 g of **1**[1] in 340 ml of tetrahydrofuran was added to 680 ml of liquid ammonia, and 30 g of sodium and 127 ml of *t*-butyl alcohol were alternately added in portions over a period of 1 hr. The solution was stirred at reflux for 1 hr and the blue color was discharged by the addition of 120 ml of *t*-butyl alcohol. The ammonia was evaporated off and the tetrahydrofuran solution was poured into 3500 ml of ice–water. The resulting precipitate was collected and triturated with ethanol to give 16 g of crystalline product, mp 167–169° dec. Recrystallization of a portion from benzene gave pure **3**: mp 168–169° dec; ir ν_{max}^{Nujol} 3100 (m), 1710 (w), and 1668 cm^{-1} (m), absence of the strong band at 1615 cm^{-1} which is present in **2**.

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.79; H, 7.97; N, 9.27.

B. Preparation from 2.—To a mixture of 66 ml of liquid ammonia and 2.5 ml of water was added a solution of 1.0 g of **2**[1] in 33 ml of tetrahydrofuran. This was followed by treatment with 4.5 g of sodium and 7 ml of *t*-butyl alcohol, added alternately in portions over a 1-hr period. The solution was stirred at reflux for 1 hr and the blue color was discharged by the addition of 5 ml of *t*-butyl alcohol. The ammonia was evaporated off, the tetrahydrofuran solution was poured into 1000 ml of water, and the resulting mixture was extracted with dichloromethane. Evaporation of the solvent and trituration of the residue with ethanol gave 0.8 g of crystalline material, mp 260–262° dec; the ir spectrum was identical with that of the product described in A, above. Recrystallization from benzene gave 0.5 g of product, mp 165–167° dec. Recrystallization from acetonitrile raised the melting point to 167–168° dec.

***trans*- and *cis*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ones (7a and 7b).**—A mixture of 43 g of **3**, 310 ml of concentrated hydrochloric acid, and 750 ml of methanol was refluxed under nitrogen for 1 hr, the methanol was distilled off, and 2000 ml of water was added. The mixture was made alkaline with ammonium hydroxide and extracted with dichloromethane. Concentration of the dried dichloromethane solution to a volume of *ca.* 100 ml gave 20.1 g of chromatographically pure (R_f 0.11) **7a**, mp 259–261° dec, which gave a negative Ehrlich test. Recrystallization from methanol gave analytical material: mp 260–262°; ir ν_{max} 3480 (s, NH) and 1706 cm^{-1} (s, C=O); uv λ_{max} 225 (ϵ 36,500), 282 (ϵ 8000), and 290 mμ (ϵ 7000).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.28; H, 7.72; N, 9.63.

The phosphate salt, which precipitated when a methanol–dichloromethane solution of the base was treated with a slight excess of phosphoric acid, had mp 294–296° dec.

Anal. Calcd for $C_{19}H_{22}N_2O \cdot H_3PO_4 \cdot {}^1/_2CH_3OH$: C, 57.35; H, 6.66; N, 6.86; P, 7.58. Found: C, 57.36; H, 6.47; N, 6.85; P, 7.36.

The hemimethanolate was stable to drying *in vacuo* at 140°.

Recrystallization from water gave the hemihydrate, mp 290–296° dec.

Anal. Calcd for $C_{19}H_{22}N_2O \cdot H_3PO_4 \cdot {}^1/_2H_2O$: C, 56.86; H, 6.53; N, 6.98; P, 7.72; H_2O, 2.2. Found: C, 56.85; H, 6.74; N, 7.08; P, 7.44; H_2O (by Karl Fischer), 2.9.

The dichloromethane mother liquor was concentrated to a small volume and chromatographed over 430 g of alumina (column height 48 cm), using dichloromethane as the eluent. The first 2000 ml of eluate was found to contain a mixture of **7a** and the faster-moving (R_f 0.31) **7b**, the former being the major component. Evaporation of the next 10 l. of eluent gave 8.5 g of a solid consisting predominately of **7b**. Recrystallization from acetonitrile–dichloromethane gave 4.8 g of chromatographically pure **7b**, mp 225–226.5° dec, which gave a negative Ehrlich test. Recrystallization from acetonitrile gave analytical material: mp 227.5–228.5° dec; ir ν_{max} 3480 (s, NH) and 1714 cm^{-1} (s, C=O); uv λ_{max} 225 (ϵ 36,400), 283 (ϵ 8250), and 290 mμ (ϵ 7600).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.74; H, 7.67; N, 9.80.

***trans*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ol (9a).**—A mixture of 1.0 g (0.003 mol) of **7a**, 1.0 g (0.026 mol) of lithium aluminum hydride, and 150 ml of tetrahydrofuran was stirred at room temperature for 20 hr, hydrolyzed, and filtered. Evaporation of the filtrate gave a solid residue which was triturated with ethyl acetate and then recrystallized from the same solvent to give 0.5 g of crystalline product: mp 218–220° dec; ir ν_{max} (2.5, 0.625, and 0.31% in CH_2Cl_2) 3600 (m, OH) and 3260 cm^{-1} (s, NH).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.71; H, 8.18; N, 9.19.

***cis*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2] benzazocin-2-ol (9b).**—The same conditions were employed with 1.0 g (0.003 mol) of **7b**. Evaporation of the tetrahydrofuran filtrate gave a solid residue which was triturated with acetonitrile to give 0.86 g of crystalline product, mp 275–277° dec (darkens at 260°). Recrystallization from acetonitrile–dichloromethane gave 0.45 g of material: mp 275–277° dec (darkens at 260°); ir ν_{max} (0.31% in CH_2Cl_2) 3600 (m, OH) and 3480 cm^{-1} (s, NH).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.19; H, 8.14; N, 9.65.

(12) In the case of *cis* epimer formation, attack of the indole perpendicular to the plane of the carbonyl requires that ring D have the boat conformation in the transition state. Formation of the *trans* epimer is favored because the required perpendicular attack can occur in a transition state having ring D in the chair form. See L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965).

(13) See Experimental Section. A Dreiding model of **8a** shows the N_{Ind}-methyl to lie above the plane of the carbonyl group.

(14) Systematic names of compounds are used in the titles of the experiments. See ref 7.

(15) Melting points were determined using the Thomas–Hoover capillary melting point apparatus, which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DKI spectrophotometer and a Baird Model 455 double-beam instrument. The former were determined as solutions in 95% ethanol and the latter, unless otherwise stated, as chloroform solutions. The nmr spectra were determined in $CDCl_3$ with the Varian A-60 spectrometer using Me_4Si as an internal standard. Thin layer chromatography was carried out on Brinkmann aluminum oxide (type 1) precoated glass plates using a mixture of *n*-heptane and 2-butanone (1:3) as the eluent. Chromatograms were developed with iodine. The drying agent used throughout was sodium sulfate.

trans-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-2-phenyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ol (10a).—To a mixture of 5 ml of 3 *M* ethereal phenylmagnesium bromide and 125 ml of tetrahydrofuran was added 0.59 g (0.002 mol) of **7a** in 25 ml of tetrahydrofuran. The mixture was refluxed for 6 hr, poured into excess aqueous ammonium chloride solution, and extracted with dichloromethane. The gummy extract was triturated with methanol to give 0.39 g of product, mp 265–270° dec (darkens at 245°). Recrystallization from methanol–dichloromethane gave 0.20 g of an analytical sample: mp 270–273° dec (darkens at 260°); ir ν_{max} (0.3 and 0.15% in CH_2Cl_2) 3550 (m, OH) and 3300 cm^{-1} (s, NH).

Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.41; H, 7.72; N, 7.70.

cis-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-2-phenyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ol (10b).—The same conditions were employed with 0.59 g (0.002 mol) of **7b**. Trituration of the gummy extract with methanol gave 0.39 g of product, mp 235–240° dec. Recrystallization from methanol–dichloromethane gave 0.25 g of an analytical sample: mp 241–242° dec; ir ν_{max} (0.3 and 0.15% in CH_2Cl_2) 3570 (m, OH) and 3480 cm^{-1} (s, NH).

Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.35; H, 7.40; N, 7.38.

trans-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (11a).—A mixture of 13.6 g (0.046 mol) of **7a**, 136 g of hydrazine hydrate, 13.6 g of sodium hydroxide, and 820 ml of ethylene glycol was refluxed under nitrogen for 1 hr and distilled at atmospheric pressure until the reflux temperature was a constant 194°. Additional ethylene glycol was added to replace that lost in the distillation, and refluxing was continued for 3 hr. The reaction mixture was concentrated to half of its volume and poured into 2800 ml of ice–water. The precipitated solid was collected, washed well with water, and dissolved in dichloromethane. The dried solution was evaporated to a residue which was triturated with methanol to give 10.3 g of product, mp 142–145°. Recrystallization from methanol gave analytical material: mp 144–145°; ir ν_{max} 3480 cm^{-1} (s, NH); uv λ_{max} 227 (ϵ 36,000), 282 (ϵ 7400), and 289 mμ (ϵ 6500).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.57; H, 8.77; N, 9.91.

cis-[13b(Indolo)4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6-methyl-17,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (11b).—The above conditions were employed with 2.0 g (0.066 mol) of **7b**, 20 g of hydrazine hydrate, 2 g of sodium hydroxide, and 125 ml of ethylene glycol. The dried dichloromethane solution was evaporated to a residue which was triturated with 5 ml of methanol to give 1.5 g of crystalline product, mp 130.5–132°. Recrystallization from methanol–dichloromethane gave 1.3 g of analytical material: mp 132.5–133.5°; ir ν_{max} 3480 cm^{-1} (s, NH); λ_{max} 227 (ϵ 37,000), 282 (ϵ 7600), and 290 (ϵ 6800).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.40; H, 8.60; N, 10.28.

cis-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6,13-dimethyl-17,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (12b).—To a solution of 0.36 g (0.0092 mol) of sodium amide in 50 ml of liquid ammonia was added 0.65 g (0.0023 mol) of **11b**. The mixture was stirred for 1 hr, 0.84 ml (0.0138 mol) or methyl iodide was added, and stirring was continued for 3 hr. Evaporation of the ammonia followed by the addition of ice–water gave a precipitate which was collected and dissolved in dichloromethane. Evaporation of the dried solution gave 0.56 g of solid residue which was devoid of NH absorption. Trituration with methanol gave 0.465 g of crystalline product: mp 125–126.5°; uv λ_{max} 231 (ϵ 36,000), 286 (ϵ 7600), and 293 mμ (ϵ 7300); nmr δ 3.85 (3 H, N_{Ind}-methyl) and 2.32 (3 H, N_B-methyl).

Anal. Calcd for $C_{70}H_{26}N_2$: C, 81.60; H, 8.90; N, 9.51. Found: C, 81.50; H, 8.77; N, 9.69.

Attempted Alkylation of 11a by $NaNH_2$ and CH_3I in Liquid Ammonia.—The quantities, reaction conditions, and work-up procedure were *exactly* the same as those described above for the corresponding reaction with **11b**. Evaporation of the dried dichloromethane solution gave a semisolid which was triturated with methanol to give 0.57 g of a solid, mp 119–124°. The infrared spectrum showed a strong NH band at 3480 cm^{-1}. The nmr spectrum showed a N_{Ind}-methyl signal at 3.90 ppm which integrated for only 25% of the theoretical value for **12a**.

trans-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6,13-dimethyl-17,13b-methano-13bH-indolo[3,2-*e*][2]benzazocine (12a).—A mixture of 4.0 g (0.014 mol) of **11a**, 1.8 g (0.042 mol) of a 55% mineral oil dispersion of sodium hydride, 6.3 g (0.07 mol) of dimethyl carbonate, and 150 ml of tetrahydrofuran was refluxed with stirring for 96 hr. The tetrahydrofuran was evaporated off, the residue was stirred with ice–water, and the mixture was made acidic by the addition of dilute hydrochloric acid. It was then made basic with sodium bicarbonate solution and extracted with ether. The ether solution was washed well with water, dried, and evaporated. The residue (4 g) was chromatographed over 120 g of alumina using ether as the eluent. Evaporation of the eluate gave a residue which was devoid of NH absorption. Recrystallization from Skellysolve B gave 1.8 g of product, mp 122–124°. Another recrystallization gave an analytical sample: mp 123–124°; uv λ_{max} 231 (ϵ 35,000), 285 (ϵ 7500), and 293 mμ (ϵ7100); nmr δ 3.90 (3 H, N_{Ind}-methyl) and 2.40 (3 H, N_B-methyl).

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.60; H, 8.90; N, 9.51. Found: C, 81.84; H, 8.88; N, 9.48.

Epimerization of 12a to 12b.—A mixture of 1.7 g of **12a**, 10 g of mercuric acetate, and 100 ml of 10% acetic acid was heated on a steam bath for 4 hr and the precipitated mercurous acetate was filtered off. The filtrate was heated to boiling and treated with 1 ml of 10% hydrochloric acid, and then hydrogen sulfide was bubbled through. The mixture was filtered through supercel, the dark filter cake being washed well with 10% acetic acid. The clear yellow filtrate (containing **13a**) was made alkaline with sodium hydroxide and the resulting precipitate was collected and dissolved in dichloromethane. The dichloromethane solution was washed well with water, dried, and evaporated. Most of the residue dissolved in petroleum ether (bp 30–40°), leaving a small amount of dark insoluble material which was removed by filtration. Dilution of the filtrate (containing **14**) with ether, followed by the addition of ethereal hydrogen chloride, gave a precipitate (**13b**) which was collected and washed well with ether. It was dissolved in 25 ml of ethanol, 1 g of sodium borohydride was added, and the mixture was stirred at room temperature for 4 hr. Addition of 600 ml of water followed by extraction with dichloromethane and evaporation of the latter solvent gave 1.2 g of a solid residue; thin layer chromatograms indicated a major component (R_f 0.44) which corresponded to **12b** and a minor, faster-moving (R_f 0.60) component; the spot (R_f 0.28) corresponding to **12a** was completely absent. Recrystallization from acetonitrile gave 700 mg of crystalline material, mp 123–126°, which still showed a trace of the faster moving component. Another recrystallization gave 450 mg of **12b**, mp 127–128°, identified by mixture melting point and comparison of its infrared spectrum with that of a sample prepared by alkylation of **11b**.

trans- and *cis*-[13b(Indolo),4aH]1,2,3,4,4a,5,6,7,8,13-Decahydro-6,13-dimethyl-7,13b-methano-13bH-indolo[3,2-*e*][2]benzazocin-2-ones (8a and 8b).—To a solution of 6.4 g (0.165 mol) of sodium amide in 800 ml of liquid ammonia was added 17.0 g (0.55 mol) of **3**. The mixture was stirred for 1.5 hr, 31.2 g (0.22 mol) of methyl iodide was added, and stirring was continued for 2.5 hr. Evaporation of the ammonia followed by addition of ice–water gave a crystalline precipitate (**4**) which was collected, washed well with water, and sucked dry. This was not purified further but was refluxed with a mixture of 300 ml of methanol and 120 ml of concentrated aqueous hydrochloric acid, under a nitrogen atmosphere, for 2 hr. The methanol was distilled off, and the residue was partitioned between dilute aqueous ammonium hydroxide and dichloromethane. Concentration of the dried dichloromethane solution to a small volume gave 5.6 g of crystalline material. The remainder of the dichloromethane was evaporated and the residue was triturated with 10 ml of methanol to give 2.8 g of additional crystals. These products were combined and recrystallized from methanol–dichloromethane to give 6.7 g of chromatographically pure (R_f 0.15) **8a**: mp 210–212° dec; ir ν_{max} 1704 cm^{-1} (s, C=O); uv λ_{max} 228 (ϵ 36,000), 285 (ϵ 7850), and 294 mμ (ϵ 7700); nmr δ 3.55 (3 H, N_{Ind}-methyl) and 2.47 (3 H, N_B-methyl).

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.77; H, 7.86; N, 9.33.

The methanol filtrate was evaporated to dryness and the residue was dissolved in dichloromethane and chromatographed over 210 g (34-cm column) of alumina using dichloromethane as the eluent. The first 150 ml of eluate was discarded, and the next 1500 ml was evaporated to dryness. The residue (4.7 g) was recrystallized from Skellysolve B to give 1.75 g of chromatographically pure (R_f 0.38) **8b**: mp 161–162°; ir ν_{max} 1708 cm^{-1} (s, C=O);

uv λ_{max} 229 (ε 37,000), 286 (ε 8300), and 294 mμ (ε 7700); nmr δ 3.85 (3 H, N_{Ind}-methyl) and 2.32 (3 H, N_B-methyl).

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.91; H, 7.94; N, 9.18.

Wolff–Kishner Reduction of 8b.—A mixture of 1.0 g (0.00325 mol) of **8b**, 9.2 g of hydrazine hydrate, 1.0 g of sodium hydroxide, and 55 ml of ethylene glycol was refluxed under nitrogen for 1 hr and distilled at atmospheric pressure until the reflux temperature was a constant 194°. Additional ethylene glycol was added to replace that lost in the distillation and refluxing was continued for 2.5 hr. The reaction mixture was concentrated by distillation until crystals started to separate and was poured into 500 ml of ice–water. The precipitated solid was collected, washed well with water, and dissolved in dichloromethane. Evaporation of the dried solution gave 900 mg of a solid residue which showed a single spot (R_f 0.44) on thin layer chromatography. Recrystallization from acetonitrile gave 700 mg of **12b**, mp 127–128°, identified by mixture melting point, thin layer chromatography, and infrared spectrum.

Wolff–Kishner Reduction of 8a.—A Wolff–Kishner reduction was carried out with 3.2 g (0.01 mol) of **8a**, using *exactly* the same conditions described above. The precipitate which separated on pouring the reaction mixture into water was dissolved in dichloromethane. The solution was washed well with water, dried, and evaporated to an oily residue. This was chromatographed over 60 g of alumina, using dichloromethane as the eluent. Evaporation of the first 1000 ml of eluate gave 900 mg of a crystalline residue which could be shown by chromatography to consist of a mixture of the expected product together with some faster moving material. Recrystallization from Skellysolve B gave 400 mg of **12a**, mp 121–123°, which showed a single spot (R_f 0.28) on thin layer chromatography. Recrystallization gave material, mp 123–124°, which was identified as **12a** by mixture melting point, thin layer chromatography, and comparison of infrared spectra.

Registry No.—**2**, 16957-67-8; **3**, 21369-44-8; **7a**, 21369-45-9; **7a** (phosphate salt), 21369-46-0; **7b**, 21369-47-1; **7b** (phosphate salt), 21369-48-2; **8a**, 21372-16-7; **8b**, 21372-17-8; **9a**, 21372-18-9; **9b**, 21372-19-0; **10a**, 21372-20-3; **10b**, 21372-21-4; **11a**, 21372-22-5; **11b**, 21372-23-6; **12a**, 21372-24-7; **12b**, 21372-25-8.

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Substituted γ-Pyrans[1]

JOSEPH WOLINSKY AND HELEN SCHOEN HAUER

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

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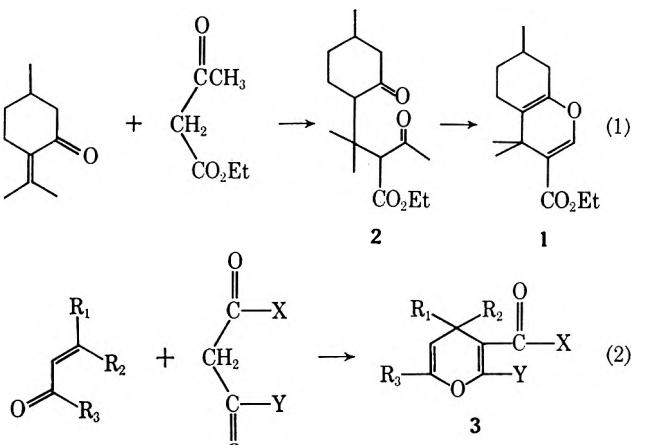
A general route to substituted γ-pyran derivatives involving the zinc chloride catalyzed condensation of β-dicarbonyl compounds with aldehydes or α,β-unsaturated ketones and aldehydes is described. For example, ethyl acetoacetate reacts with formaldehyde to give 3,5-dicarboethoxy-2,6-dimethyl-4H-pyran, and with mesityl oxide to give 3-carboethoxy-2,4,4,6-tetramethyl-4H-pyran. Chemical and spectral properties of these γ-pyran derivatives are described.

γ-Diketones are readily converted by acid into resonance stabilized furan derivatives,[2] while δ-diketones, when subjected to similar conditions, are generally assumed to undergo intramolecular aldol cyclization to cyclohexenone derivatives.[3] γ-Pyran derivatives have only been obtained in cases where structural features, such as the lack of an enolizable hydrogen[4] or improper geometric relationships,[5] prohibit the formation of cyclohexenone derivatives. The formation of γ-pyran (1)[6] in the zinc chloride catalyzed reaction of pulegone with ethyl acetoacetate (eq 1) under conditions which minimize the reconversion of pyran **1** to the intermediate δ-diketone **2** suggests that the cyclization of δ-diketones to γ-pyrans might be a general reaction which has been long overlooked. We have in fact found that the condensation of α,β-unsaturated aldehydes and ketones with β-dicarbonyl compounds provides a general route to substituted γ-pyran derivatives (eq 2).



$R_1 = R_2 = R_3 = CH_3$

a, X = OEt, Y = CH_3

b, X = OCH_3, Y = CH_3

c, X = Y = CH_3

d, Y = C_6H_5, X = OEt

Mesityl oxide condenses with ethyl or methyl acetoacetate, 2,4-pentandione, and ethyl benzoyl acetate to give γ-pyrans **3a**, **b**, **c**, and **d**, respectively. Although the yields are relatively low, 10–25%, the ready availability of the starting material and the lack of an alternate route to these compounds makes this an attractive synthetic procedure.

(1) Based on the thesis submitted by H. S. H. in partial fulfillment of the requirements for the Ph.D. degree from Purdue University, Jan 1969.

(2) R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1950, p 127.

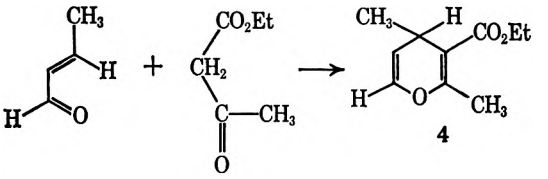
(3) (a) E. Knoevenagel, *Ann.*, **281**, 25 (1894); (b) R. E. Fargher and W. H. Perkin, *J. Chem. Soc.*, **105**, 1353 (1914).

(4) E. Blaise and H. Gault, *Bull. Soc. Chim. Fr.*, **1**, 129 (1907); C. F. Huebner, W. R. Sullivan, M. A. Stahmann, and K. P. Link, *J. Amer. Chem. Soc.*, **65**, 2292 (1943); P. deCarvalho, *Ann. Chim.* (Paris), **4**, 449 (1935).

(5) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

(6) J. Wolinsky and H. Hauer, *J. Org. Chem.*, **34**, 380 (1969).

Crotonaldehyde reacts with ethyl acetoacetate to give 3-carbethoxy-2,4-dimethyl-4H-pyran (**4**). This pyran, unlike **3a–d**, is quite unstable and difficult to obtain in a state of high purity.

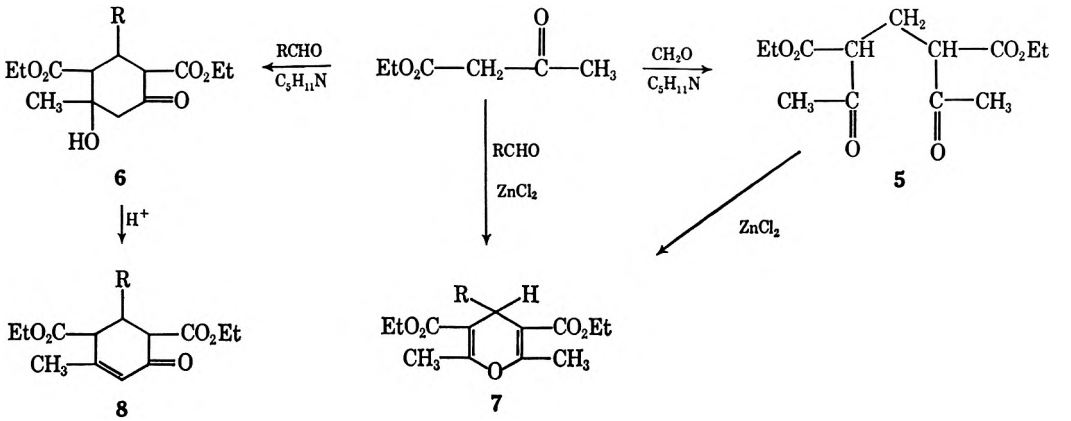


4

An attempt to react dypnone[7] with ethyl acetoacetate resulted in the recovery of starting materials.

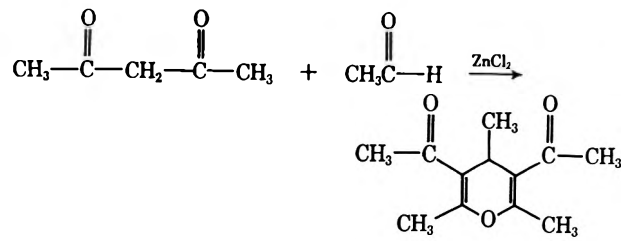
δ-Diketones are also available by the condensation of aldehydes with β-dicarbonyl compounds.[3a] Formaldehyde reacts with ethyl acetoacetate in the presence of piperidine to afford diketone **5**. Benzaldehyde and acetaldehyde under the same conditions yield the aldol **6** and not the diketone claimed by Knoevenagel[3a] and other investigators.[8]

When aldehydes are condensed with ethyl acetoacetate in the presence of zinc chloride in acetic acid–acetic anhydride, γ-pyran derivatives **7** are produced in 35–50% yield. Furthermore, diketone **5** is converted to γ-pyran **7** (R = H) when subjected to these conditions.



6 **8** **7** **5**

2,4-Pentanedione combined with acetaldehyde in the presence of zinc chloride to give 3,5-diacetyl-2,4,6-trimethyl-4H-pyran (**9**). However, ethyl benzoyl acetate condensed with formaldehyde to give the δ-diketone **10** and all attempts to cyclize **10** to a γ-pyran have been unsuccessful.



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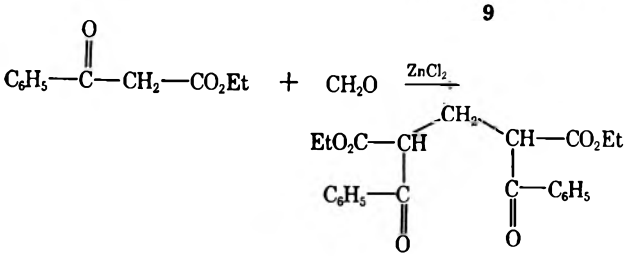

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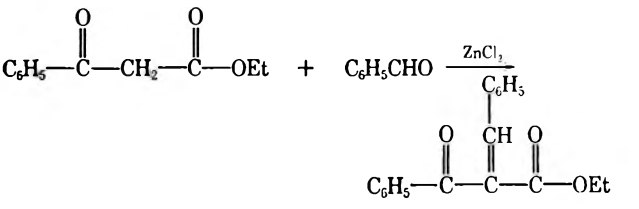
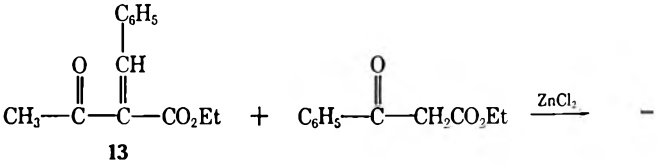


11



13 **12**

The condensation of benzaldehyde with ethyl benzoyl acetate also failed to give a pyran derivative; only the unsaturated keto ester **11** was isolated. However, a "mixed" pyran **12** could be obtained in 37% yield by condensing unsaturated ester **13**[9] with ethyl benzoylacetate.

Chemical Properties of γ-Pyrans.—4,4-Disubstituted 4H-pyrans with an electron-withdrawing substituent at position 3 are relatively stable and can be easily handled, providing contact with strong acid is avoided. 4-Monosubstituted 3-carbethoxy-4H-pyrans, by contrast, are quite unstable and decompose on standing at room temperature. Introduction of a second electron-withdrawing substituent at position 5 markedly increases the stability of the ring system, and even **7** (R = H), with two hydrogens at C-4, can be stored for some time at 4°.

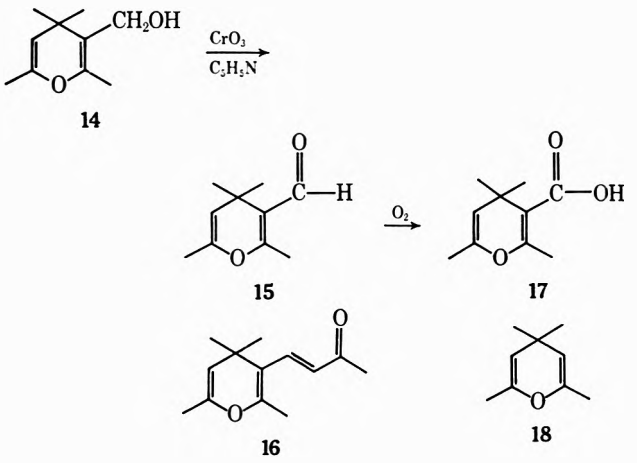
Lithium aluminum hydride reduction of 3-carbethoxy-2,4,4,6-tetramethyl-4H-pyran (**3a**) affords 3-hydroxymethyl-2,4,4,6-tetramethyl-4H-pyran (**14**). The pyran ring in **14** is far more reactive than that of its precursor **3a** and treatment of the alcohol with acid under mild conditions affords products which are currently under investigation.

(7) W. Wayne and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1953, p 367.

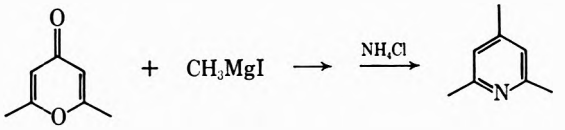
(8) L. Kuss and P. Karrer, *Helv. Chim. Acta*, **40**, 740 (1957); R. I. Reed and V. V. Takhistov, "Some Newer Physical Methods in Structural Chemistry," R. Bonnet and J. G. Davis, Ed., United Trade Press Ltd., London, 1967, p 39.

(9) L. Claisen and F. E. Matthews, *Ann.*, **218**, 170 (1883).

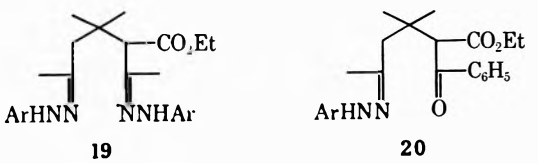
Oxidation of alcohol **14** with chromium trioxide in pyridine gives aldehyde **15**. Base-catalyzed aldol condensation of the aldehyde **15** with acetone affords the unsaturated ketone **16**. Further oxidation of **15** to the acid **17** is best performed by exposing it to air. When heated with a small amount of copper powder, the acid **17** undergoes decarboxylation and yields 2,4,4,6-tetramethyl-4H-pyran (**18**).



The synthesis of pyran **18** by the condensation of excess methylmagnesium iodide with 2,6-dimethyl-4-pyrone has been claimed by Gompper.[10] We have repeated this reaction and have found no trace of pyran **18** among the products. This observation is similar to those recorded by other investigators.[11] The only point worth noting is the production of a 40% yield of collidine when the reaction mixture is worked up with ammonium chloride instead of saturated salt solution,[12] suggesting that 2,4,6-trimethyl-4-hydroxy-4H-pyran is the major produt of the Grignard reaction.



γ-Pyrans react with 2,4-dinitrophenylhydrazine (2,4-DNP) reagent, but there seems to be no general trend in the type of derivative which will form. Pyran **3a** affords the bis-2,4-DNP **19**, whereas pyran **3d** gives a mono-2,4-DNP formulated as **20**. By contrast, pyran **1** yields a dihydropyridine derivative.[6]



Spectral Properties.—Owing to the small number of γ-pyrans described in the literature, there is a paucity of spectral data available. With a large number of pyrans now on hand, certain spectral correlations are worth mentioning as guidelines for future work involving the identification of the γ-pyran ring system.

The infrared spectra of pyrans are summarized in Table I. These compounds are all characterized by absorption at 5.80 and 6.0 μ. In 2,4,4,6-tetramethyl-4H-pyran (**18**), the 5.80-μ peak is of medium intensity and could be mistaken for a carbonyl group, while the 6.0-μ peak is weak and could be overlooked if the sample is too dilute. The absorption of carbonyl groups generally coincides with the 5.80-μ peak; an additional peak at 5.85–6.0 μ may also be noted; and the double-bond stretching band is shifted to 6.10–6.15 μ or as high as 6.40 μ in acid **17**. The pyrans with two carbonyl substituents at positions 3 and 5 show a trio of strong peaks at 5.8, 6.0, and 6.15 μ.

The ultraviolet spectra of γ-pyrans (see Table I) are characterized by a weak shoulder at *ca.* 225 mμ; they do not show absorption at *ca.* 240–250 mμ, as claimed by Gompper.[10] Introduction of a carbethoxy or acetyl group at position 3 causes a shift to 270 and 284 mμ, respectively. These maxima are considerably displaced from those of ordinary β-alkoxy-α,β-unsaturated esters and ketones,[13] suggesting additional conjugation with the second double bond in the molecule. The presence of a second carbethoxy or acetyl group at position 5 provides a further bathochromic shift to 285 and 296 mμ, respectively.

The nmr spectra of γ-pyrans are unexceptional. It is worth noting that the vinyl hydrogen at position 5 gives rise to a signal at 4.27–4.43 ppm. In most instances, homoallylic coupling with a methyl group at position 6 is clearly resolved (see Table I), whereas in other cases, *i.e.*, acid **17**, the vinyl hydrogen signal appears as a broad singlet.

The mass spectra of various γ-pyran derivatives are collected in Tables II and III. The major mode of fragmentation in 4,4-dimethyl-3-carboethoxypyrans involves loss of a methyl group and formation of a stable pyrylium ion (A) (see Scheme I). 4-Monosubstituted pyrans lose methyl or phenyl from position 4 in preference to hydrogen and also give rise to stable pyrylium ions A. Further fragmentation appears to be limited to the carboethoxy group, which loses ethylene in a McLafferty rearrangement to give acid B. Acid B loses a water molecule to yield ion C, which also arises from pyrylium ion A by a McLafferty rearrangement involving loss of an alcohol molecule. If a second carbethoxy group is present, the fragmentation of another ethylene molecule is observed. The original parent ion also ejects an alkoxy radical to give ion D, which eliminates carbon monoxide to form ion E.

The fragmentation of derivatives with other substituents at position 3 or 5 follows the same pattern mentioned above. The hydroxymethyl and carboxylic acid derivatives lose a methyl group and a water molecule, while the acetyl derivatives eject methyl and then a fragment of *m/e* 42, which is probably ketene.

These fragmentation patterns are documented by high-resolution studies and by the appearance of metastable ions. For example, in the mass spectrum of **3a**, metastable ions at *m/e* 143 (195 − 167), 133 (167 − 149), and 114 (195 − 149) establish paths A → B, B → C, and A → C.

(10) R. Gompper and O. Christmann, *Chem. Ber.*, **94**, 1784 (1961).

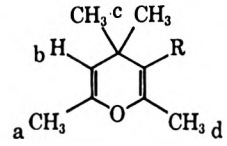
(11) *Cf.* A. Hinnen and J. Dreux, *Compt. Rend.*, **255**, 1747 (1962); A. Hinnen and J. Dreux, *Bull. Soc. Chim. Fr.*, 1492 (1964); J. Royer, and J. Dreux, *Compt. Rend.*, **258**, 2895 (1964); J. Royer and J. Dreux, *Tetrahedron Lett.*, 5589 (1968).

(12) *Cf.* K. Dimroth, *Angew. Chem.*, **72**, 331 (1960), for a review of reactions of pyrones with nucleophiles.

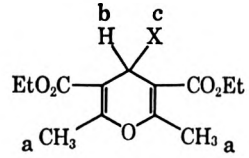
(13) A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957); F. E. Bader, *Helv. Chim. Acta*, **36**, 215 (1953).

TABLE I

INFRARED, ULTRAVIOLET, AND NUCLEAR MAGNETIC RESONANCE SPECTRA OF SUBSTITUTED γ-PYRAN DERIVATIVES



Registry no.	R	Ir, μ	Uv, λ_{max}^{MeOH} (log ε)	Nmr, ppm (J, Hz) H_a	H_b	H_c	H_d	H_R
21298-98-6	H	5.8 (m), 6.0 (w)	225 (3.08)	s, 1.78	s, 4.41	s, 1.01		
21298-99-7	CH_2OH	2.95 (m–w), 5.8 (m), 6.0 (w)						
21299-00-3	$C(=O)-CH_3$	5.80 (s), 5.89 (s), 6.03 (m)	215 (3.21) 284 (2.93)	d, 1.73 (1)	q, 4.35 (1)	s, 1.13	s, 1.83	s, 2.23
21298-97-5	$C(=O)-OH$	5.8 (m), 6.0 (m), 6.4 (m)		s, 1.78	s, 4.43	s, 1.32	s, 2.20	s, 12.53
21299-01-4	$C(=O)-OCH_3$	5.73 (s), 5.85 (s), 6.15 (m)		d, 1.77 (1.5)	m, 4.40 (1.5)	s, 1.18	s, 2.02	s, 3.70
21299-02-5	$C(=O)-OCH_2CH_3$	5.80 (s), 6.15 (m)	208 (3.45) 270 (3.34)	d, 1.73 (1.0)	m, 4.32	s, 1.18	s, 1.98	q, 4.12 (τ) t, 1.28 (τ)
21299-03-6	$CH=CH-C(=O)-CH_3$	5.8 (m), 5.9 (w), 6.1 (s)	216 (4.52) 336 (4.70)	d, 1.75 (1.0)	q, 4.33 (1)	s, 1.23	s, 2.02	d, 6.17 (16) d, 7.18 (16) s, 2.15



21299-10-5	H	5.80 (s), 5.95 (s), 6.1 (s)		t, 2.28 (1.5)	m, 3.15 (1.5)			q, 4.32 (7) t, 1.33 (7)
21299-04-7	CH_3	5.80 (s), 5.95 (s), 6.1 (s)	214 (4.04) 221 (4.04) 285 (3.46)	s, 2.27	q, 3.57	d, 1.07		q, 4.23 (7) t, 1.15 (7)
21299-05-8	C_6H_5	5.85 (s), 6.00 (s), 6.15 (s)		s, 2.33	s, 4.78	m, 7.18		q, 4.67 (7) t, 1.15 (7)

SCHEME I

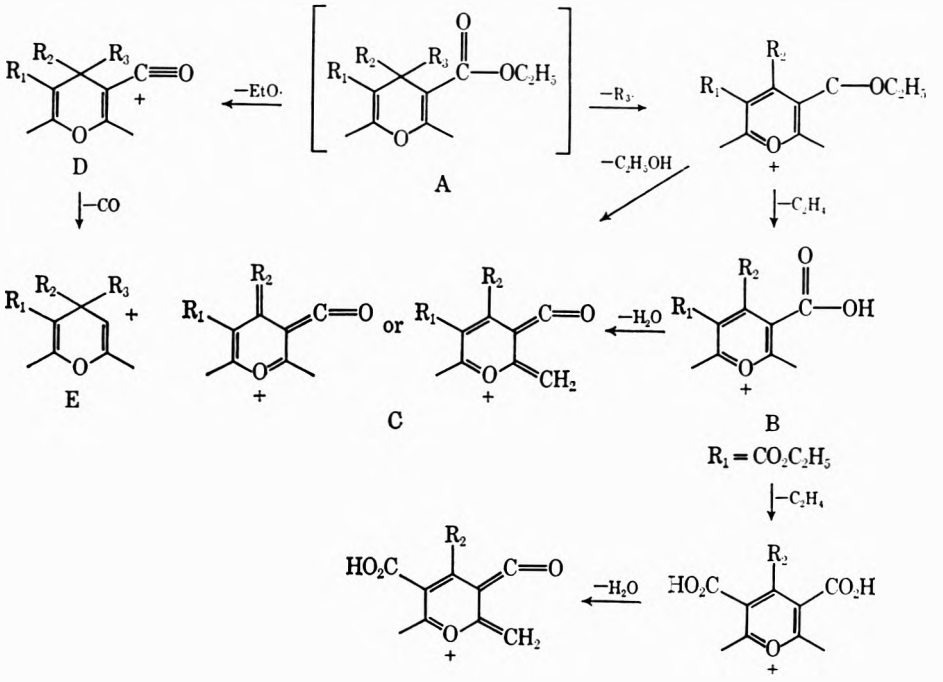
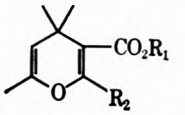


TABLE II

IMPORTANT IONS IN THE MASS SPECTRA OF 3-CARBOALKOXY-4,4-DIMETHYL-4H-PYRANS

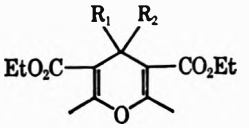


Registry no.	R_1	R_2	m/e (% relative abundance) P	P − CH_3	P − CH_3 − C_2H_4	P − CH_3 − C_2H_5 − H_2O	P − OR	P − OR − CO	
	CH_2CH_3	CH_3	210 (2)	195 (100)	167 (46)	149 (25)	165 (19)	137 (3)	43 (11)
	CH_3	CH_3	196 (3)	181 (100)		149 (44)[a]	165 (11)	137 (2)	43 (57)
	H	CH_3	182 (2)	167 (100)		149 (20)[b]			43 (50)
2129-09-2	CH_2CH_3	C_6H_5	272 (3)	257 (100)	229 (23)	211 (5)	227 (8)	199 (3)	43 (33)

[a] Established by high-resolution studies. [b] P − CH_3 − H_2O.

TABLE III

IMPORTANT IONS IN THE MASS SPECTRA OF 3,5-DICARBETHOXYPYRANS



R_1	R_2	m/e (% relative abundance) P	P − R_1	P − R_2	P − R_2 − C_2H_4	P − R_2 − $2C_2H_4$	P − R_2 − $2C_2H_4$ − H_2O	P − OC_2H_5	P − OC_2H_5 − CO	
H	H	254 (8)	253 (3)		225 (100)	197 (41)	179 (9)	209 (20)	181 (18)	43 (91)
H	CH_3	268 (2)	267 (0.2)	253 (100)	225 (18)	197 (15)	179 (6)	223 (17)	195 (1)	43 (31)
H	C_6H_5	330 (24)	329 (1)	253 (100)	225 (2)	197 (18)	179 (7)	285 (15)	257 (19)	43 (41)

Experimental Section[14]

A. General Procedure for Pyran Synthesis.—A mixture of α,β-unsaturated aldehyde or ketone and the appropriate β-dicarbonyl compound was added dropwise to a vigorously stirred solution of fused $ZnCl_2$ in *ca.* 80 ml of acetic acid and *ca.* 100 ml of acetic anhydride. The solution was kept at room temperature for 1–3 weeks and was then poured into 400 ml of water and extracted with ether. The ether extracts were washed with water, 5% $NaHCO_3$ solution, and saturated salt solution. The ether solution was dried over anhydrous $MgSO_4$ and the ether was removed. The pyran was isolated by distillation *in vacuo*. Analytical samples were generally obtained by vpc using a DEGS column at 180°.

B.—A mixture of aldehyde and β-dicarbonyl compound was added dropwise to a vigorously stirred solution of fused $ZnCl_2$ in *ca.* 40 ml of acetic acid and *ca.* 50 ml of acetic anhydride. The solution was kept at room temperature for 1–2 weeks and was worked up as described in general procedure A. The products were purified by recrystallization.

3-Hydroxymethyl-2,4,4,6-tetramethyl-4H-pyran (14).—A solution of 9.39 g of 3-carboethoxy-2,4,4,6-tetramethyl-4H-pyran (**3a**) in 20 ml of ether was added slowly under a nitrogen atmosphere to a stirred suspension of 1.52 g of lithium aluminum

(14) All boiling and melting points are uncorrected. Infrared spectra were measured with Perkin-Elmer Infracord or 221 spectrophotometers. Nuclear magnetic resonance spectra were determined with a Varian Associates A-60 spectrometer. Mass spectra were measured with a Hitachi RMU-6A and a CDC-110 high-resolution mass spectrometer by the Purdue University Spectral Service Department. Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 505. Microanalysis were performed by Dr. C. S. Yeh and associates.

TABLE IV

γ-PYRANS PREPARED BY THE CONDENSATION OF ALDEHYDES AND α,β-UNSATURATED KETONES AND ALDEHYDES WITH β-DICARBONYL COMPOUNDS

Pyran	Yield, %	Bp, °C (mm)	n_D	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
3a	15	52 (0.3)	1.4703		68.54	8.63	68.47	8.81
3b	15	48–54 (0.5)	1.4714		67.32	8.22	67.58	8.31
3c	10	49–54 (0.2)	1.4758		73.30	8.95	73.21	9.20
3d	20			49–50	74.97	7.40	75.12	7.53
4		90–100 (~10)			65.91	7.74	65.44	7.88
7a	38			76.5–78	69.07	6.71	69.30	6.79
7b	50			42–43	62.67	7.51	62.81	7.47
7c				40–45	61.41	7.14	60.91	6.91
9	21	86–100 (0.15)	1.5071		69.21	7.74	68.92	7.57
12	35			60–62	73.45	6.16	73.41	6.08

hydride and 50 ml of ether containing 0.52 ml of absolute ethanol.[15] The mixture was heated for 30 min, and saturated ammonium chloride solution was added to the cooled mixture. The salts were removed by filtration, and the ether solution was dried over anhydrous magnesium sulfate and distilled to yield 7 g of alcohol **14**, bp 62° (0.2 mm); mass spectrum *m/e* (rel intensity) 168 (0.5), 153 (1), 150 (7), 135 (43), and 43 (100).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.63; H, 9.75.

2,4,4,6-Tetramethyl-4H-pyran-3-carboxylic acid (17).—A solution of 7.0 g of alcohol **14** in 20 ml of pyridine at 0° was added to a solution of 12.2 g of chromium trioxide in 140 ml of pyridine.[16] The mixture was stirred for 30 min and then kept at room temperature for 20 hr. The mixture was poured into 600 ml of water and extracted with ether. The ether extracts were washed with dilute hydrochloric acid, water, and saturated salt solution. The ether solution was dried and the ether was removed to leave 4.4 g (64%) of crude aldehyde **15** which was used directly in the next step.

The crude aldehyde was stirred at room temperature in an open flask for *ca.* 20 hr and was then taken up in ether. The ether solution was extracted with 5% sodium carbonate solution. The basic extract was acidified with 5% hydrochloric acid and extracted with ether. The ether extracts were dried and the ether was removed to leave 1.8 g of crude acid. Recrystallization of the acid from pentane gave 1.04 g of a white solid, mp 132–134°. The aldehyde recovered from the original ether solution could be recycled to provide additional acid **17**; mass spectrum *m/e* (rel intensity) 182 (2), 167 (100), 149 (20), and 43 (50).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.21; H, 7.79.

3-(3-oxo-2-butenyl)-2,4,4,6-tetramethyl-4H-pyran (16).—A solution of 9.72 g of crude aldehyde **15** in 50 ml of ether was treated in a nitrogen atmosphere with 0.63 g of sodium hydride and 10 ml of dry acetone. The mixture was heated to reflux for 30 min, let stand at room temperature for 90 min, and then washed with water. Distillation gave **16**, bp 70–85° (0.26 mm), which was crystallized from pentane to afford a white solid, mp 42.5–44.5°. An analytical sample was prepared by sublimation *in vacuo;* mass spectrum *m/e* (rel intensity 206 (8), 191 (100), 149 (12), and 43 (59).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.70; H, 8.92.

2,4,4,6-Tetramethyl-4H-pyran (18).—A mixture of 0.4 g of acid **17** and 0.4 g of copper powder was heated at 230–280° until distillation of 0.15 g of colorless liquid, bp *ca.* 193°, was complete; mass spectrum *m/e* (rel intensity) 138 (4), 123 (100), and 43 (40).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.78; H, 10.43.

(15) R. S. Davidson, W. H. H. Gunther, S. M. Waddington-Feather, and B. Lythgoe, *J. Chem. Soc.*, 4907 (1964).

(16) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

Reaction of 3a with 2,4-Dinitrophenylhydrazine.—A solution of 1 ml of pyran **3a** in 10 ml of ethanol was added to a solution of 0.85 g of 2,4-dinitrophenylhydrazine in 30 ml of 65% aqueous ethanol containing 5 ml of concentrated sulfuric acid. A solid precipitated within 1 min. After standing overnight, the solid was collected and recrystallized from 3:1 ethyl acetate–ethanol to give orange-yellow crystals of **19**, mp 154–155.5°; uv λ_{max}^{MeOH} 228 and 357 mμ (log ε 4.0 and 4.2); nmr ($CDCl_3$) 1.30 (t, 3, CH_3CH_2O), 2.20 and 2.30 (s, 6, 2 CH_3CO), and 4.27 ppm (q, 2, CH_3CH_2O).

Anal. Calcd for $C_{24}H_{28}N_8O_{10}$: C, 48.98; H, 4.80; N, 19.04. Found: C, 48.90; H, 4.77; N, 19.18.

Reaction of Pyan 3d with 2,4-Dinitrophenylhydrazine.—A solution of 0.5 g of **3d** in 10 ml of ethanol was added to a solution of 0.43 g of 2,4-dinitrophenylhydrazine and 2.5 ml of concentrated sulfuric acid in 15 ml of 65% aqueous ethanol. After standing overnight, the orange-yellow solid which separated was collected and recrystallized from ethyl acetate–ethanol to give crystals of **20**, mp 94–96°; ir 5.8 and 5.9 μ.

Anal. Calcd for $C_{23}H_{26}N_4O_7$: C, 58.72; H, 5.57; N, 11.91. Found: C, 58.64; H, 5.93; N, 11.98.

2,4-Dicarbethoxy-1,5-diphenyl-1,5-pentanedione (10).—A mixture of 9.3 g (0.31 mol) of paraformaldehyde, 97.1 g (0.50 mol) of ethyl benzoylacetate, and 19.5 g of fused zinc chloride in acetic acid–acetic anhydride was stirred at room temperature for 4 days. The mixture was worked up as described under general procedure A to give an oil which slowly solidified. Recrystallization from 1:1 hexane–ethyl acetate gave 32.5 g (33%) of diketone **10**, mp 91.5–92.5° (lit. mp 86°); ir (Nujol) 5.7, 5.8, and 5.95 μ; nmr ($CDCl_3$) 1.27 (t, 6, J = 7.5 Hz, CH_3CH_2O), 2.64 (t, 2, J = 8 Hz, $CHCH_2CH$), 4.28 (q, 4, J = 7.5 Hz, CH_3CH_2O), 4.72 (t, 2, J = 8 Hz, $CHCH_2CH$), 7.67 (m, 6 *meta* and *para* H), and 8.17 ppm (m, 4, *ortho* H).

Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.51; H, 6.18.

Attempts to cyclize this diketone with zinc chloride in acetic acid–acetic anhydride, *p*-toluenesulfonic acid in benzene, or diphenylphosphoryl chloride failed.

Ethyl β-Benzoylcinnamate (11),—The reaction of 13.6 g (0.13 mol) of benzaldehyde, 48.6 (0.25 mol) of ethyl benzoylacetate, and 9.3 g of fused zinc chloride, following general procedure B, gave an oil which solidified on scratching. Recrystallization from 1:1 hexane–ethyl acetate gave 23.4 g (33%) of a white solid, mp 95.5–97.5° (lit.[17] mp 98–99°); ir (Nujol) 5.9 and 6.0 μ; nmr 1.13 (t, 3, J = 7 Hz, CH_3CH_2O), 4.20 (q, 2, J = 7 Hz, CH_3CH_2O), 7.3 and 7.9 ppm (m, 11).

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.91; H, 5.50.

Registry No.—**4**, 21299-13-8; **9**, 21299-14-9; **10**, 21299-15-0; **11**, 17451-18-2; **12**, 21299-17-2; **19**, 21299-18-3; **20**, 21299-19-4.

(17) G. S. Cruikshanks, *J. Prakt. Chem.*, **89**, 194 (1914).

The Synthesis, Structure Proof, and Spectral Properties of the Six Pyridylthiophenes[1]

HANS WYNBERG, T. J. VAN BERGEN, AND RICHARD M. KELLOGG

Department of Organic Chemistry, The University Bloemsingel 10, Groningen, The Netherlands

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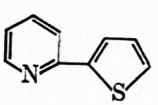
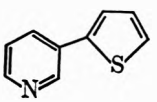
The synthesis and spectra of the six isomeric pyridylthiophenes are described. The 3-thienyl isomers (IV, V, and VI) could be prepared uniquely by reaction of the appropriate lithiopyridines with 3-ketotetrahydrothiophene and subsequent aromatization of the carbinols in over-all yields ranging from 2 to 10%. A specific synthesis for III (yield 2%) was accomplished starting from the 2-thienyl Grignard reagent and 1-benzoyl-4-chloro-1,4-dihydropyridine. II was obtained pure in 40% yield after chromatographic separation of the reaction mixture resulting from the interaction of the 3-pyridyl radical with thiophene, while I could be isolated in 1% yield from a mixture of two isomers obtained from the reaction of 2-thienylmagnesium iodide with pyridine. Their structures are proved by desulfurization to butylpyridines and by comparison of their proton magnetic resonance spectra with those of the phenylpyridines.

Since a reasonably large number of phenyl-, thienyl-, and alkyl-substituted thiophenes have been shown to undergo photochemical rearrangements,[2] we decided to prepare and study the pyridylthiophenes. The photochemical behavior of nitrogen-containing aromatic systems is of obvious intrinsic interest, and competition between photochemical reactions of the thiophene ring and those of the pyridine ring could be examined. To this end the six isomeric pyridylthiophenes were prepared and subjected to a variety of photochemical reaction conditions. Preliminary investigations with I, II, and III indicate that the normal[2] photochemical rearrangement in the thiophene ring does not obtain.

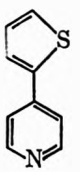
The present paper describes the synthesis of the isomers I–VI. Future communications will deal with some photochemical reactions.



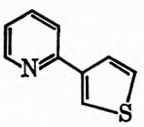
I
2-(2′-pyridyl)thiophene



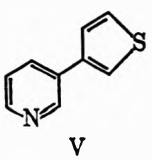
II
2-(3′-pyridyl)thiophene



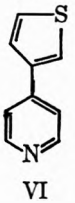
III
2-(4′-pyridyl)thiophene



IV
3-(2′-pyridyl)thiophene



V
3-(3′-pyridyl)thiophene



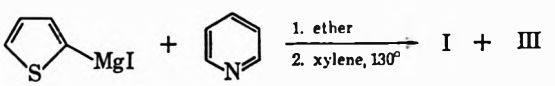
VI
3-(4′-pyridyl)thiophene

Although in principle a number of synthetic schemes are feasible we limited ourselves to a route involving coupling reactions between appropriately substituted intact thiophenes and pyridines.

(1) According to the usual nomenclature rules these ring systems should be called thienylpyridines. However, in order to stress the similarities and/or differences in the reaction of the thiophene ring, we prefer the nomenclature used in this paper.

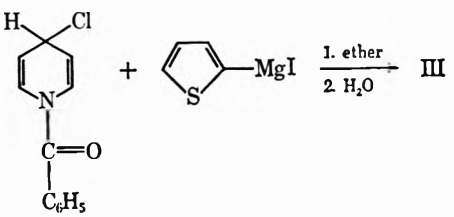
(2) R. M. Kellogg and H. Wynberg, *Tetrahedron Lett.*, 5895 (1968).

A. 2-(2′-Pyridyl)thiophene (I)[3] and 2-(4′-Pyridyl)-thiophene (III).—In 1964 Kahmann, Sigel, and Erlenmeyer[4] described the synthesis of a pyridylthiophene by addition of 2-thienylmagnesium bromide to pyridine and subsequent aromatization of the dihydro product at 160°. Repetition of their work with the Grignard reagent of 2-thienyl iodide and some other minor modifications (see Experimental Section) led to the isolation of a mixture of two pyridylthiophenes with melting points of 60.5–62 and 92–92.5° in a combined yield of 4%, separated by column chromatography.



Kahmann, Sigel, and Erlenmeyer ascribed to their pyridylthiophene, mp 90–91°, structure I. We have assigned structure I, 2-(2′-pyridyl)thiophene, to the low melting isomer and structure III, 2-(4′-pyridyl)thiophene, to the high melting isomer. This assignment appears unambiguous on the basis of desulfurization experiments to 2- and 4-*n*-butylpyridine, respectively (see Experimental Section), as well as on the basis of the proton magnetic resonance spectra, which clearly differentiate between a 2-substituted (I) and 4-substituted (III) pyridyl isomer (see Structure Proofs and Spectra).[5]

An independent synthesis of 2-(4′-pyridyl)thiophene (III) using 2-thienylmagnesium iodide and 1-benzoyl-4-



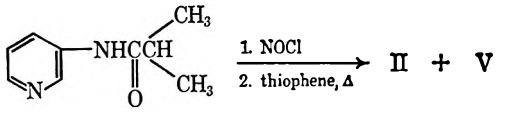
(3) Attempts to prepare I from pyridine and 2-thienyllithium, a route similar to the one used for the synthesis of 2-phenylpyridine and 2-*n*-butylpyridine [see K. Ziegler and H. Zieser, *Liebigs Ann. Chem.*, **485**, 174 (1931)], were all unsuccesfull.

(4) K. Kahmann, H. Sigel, and H. Erlenmeyer, *Helv. Chim. Acta*, **47**, 1754 (1964).

(5) Kahmann, *et al.*, assumed preferential 1,2 addition of the Grignard reagent to pyridine.[4] However, 1,4 addition, *e.g.*, of benzylmagnesium chloride and *n*-butylmagnesium bromide to pyridine, concomitant with 1,2 addition has been reported: R. A. Benkeser and D. S. Holton, *J. Amer. Chem. Soc.*, **73**, 5861 (1951); W. von E. Doering and V. Z. Pasternak, *ibid.*, **72**, 145 (1950). The formation of I and III in a similar reaction is consistent with such a 1,2 and 1,4 addition.

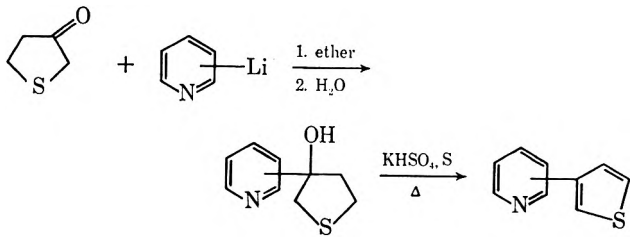
chloro-1,4-dihydropyridine was also carried out.[6] Although yields were low (2%), the product (III), mp 92.5–93.5°, was identical in all respects with that obtained *via* the 1,4 addition of the Grignard reagent.[7]

B. 2-(3′-Pyridyl)thiophene (II).—This substance was prepared using a modified Gomberg reaction generating the 3-pyridyl radical in thiophene.[8] Two



components in a ratio of 6:1 were obtained in a combined yield of 47%. Separation by preparative thin layer chromatography (tlc) yielded two pyridylthiophenes: an oil, bp 121–122° (0.4 mm), as the main product, and a solid of mp 72–74°. We assigned structure II, 2-(3′-pyridyl)thiophene, to the oil and structure V, 3-(3′-pyridyl)thiophene, to the solid on the basis of their spectral data and the desulfurization of II to 3-*n*-butylpyridine.

C. 3-(2′-Pyridyl)thiophene (IV), 3-(3′-Pyridyl)thiophene (V), and 3-(4′-Pyridyl)thiophene (VI).—A rational method for the preparation of the three substituted thiophene isomers in this series[9a,b] was found to be the reaction between 3-ketotetrahydrothiophene and the lithiopyridines.[9c,d] The crude inter-



mediate carbinols obtained in yields of 50–70% were dehydrated and aromatized in one step by heating with potassium hydrogen sulfate and sulfur.[9a]

The pyridylthiophene, mp 27–28°, obtained from 2-lithiopyridine[9c] in an over-all yield of 10% showed spectral properties consistent with an α-substituted pyridine ring. On the basis of spectral data (see Structure Proofs and Spectra) we assigned structure IV, 3-(2′-pyridyl)thiophene, to it.

Another isomer, mp 75–76.5°, was isolated in the same over-all yield starting from 3-lithiopyridine.[9c] This material was identical in all respects with the minor product obtained from synthesis B and gave spectra agreeing with V, 3-(3′-pyridyl)thiophene. Desulfurization produced 3-*sec*-butylpyridine.

When 4-lithiopyridine[9d] was used as a starting material a pyridylthiophene, mp 138.5–139°, was obtained in an over-all yield of 2%. Its spectral properties were characteristic for a 4-substituted pyridine ring and were consistent with those expected for 3-(4′-pyridyl)-thiophene (VI).

Structure Proofs and Spectra.—The assignment of the structures to the six isomers (I–VI) is based on three pieces of evidence: (a) the method of synthesis, (b) the identification of the desulfurization products, and (c) the spectra—especially pmr spectra—of the pyridylthiophenes themselves.

Identification of the Desulfurization Products.—The desulfurization products of I, II, and III (2-, 3-, and 4-*n*-butylpyridine, respectively) showed aliphatic pmr absorptions identical with those of separately prepared 2-*n*-butylpyridine[3] and aromatic absorption patterns identical with those reported for 2-, 3-, and 4-methylpyridine,[10a] respectively. Upon desulfurization V furnished 3-*sec*-butylpyridine. Its pmr spectrum was compared with that of 3-methylpyridine (aromatic region identical) and *sec*-butyl alcohol and *sec*-butylamine (aliphatic region identical).

The ultraviolet (uv) spectra of these four desulfurization products were virtually indistinguishable from one another.

Pmr Spectra (Table I).—The chemical shift and splitting patterns of the α-pyridyl hydrogen atoms of a monosubstituted pyridine ring are characteristic for the

TABLE I

PROTON MAGNETIC RESONANCE SPECTRA[a]

Compd	α-Pyridyl hydrogen atoms	Other hydrogen atoms
I	1.4[b] (t[c]–t) (1)[d]	2.3–3.1 (m) (6)
II	1.1 (d) (1)	2.2–2.4 (t–t) (1)
	1.5 (d–d) (1)	2.7–3.1 (m) (4)
III	1.5 (d–d) (2)	2.5–2.7 (m) (4)
		2.8–3.1 (d–d) (1)
IV	1.5 (t–t) (1)	2.1–3.1 (m) (6)
V	1.3 (d) (1)	2.1–2.4 (t–t) (1)
	1.6 (d–d) (1)	2.5–3.0 (m) (4)
VI	1.6 (d–d) (2)	2.4–2.8 (m) (5)
2-Phenylpyridine[e]	1.4 (t–t) (1)	2.1–2.3 (m) (8)
3-Phenylpyridine[f]	1.4 (d) (1)	2.1–2.3 (t–t) (1)
	1.6 (d–d) (1)	2.4–2.9 (m) (6)
4-Phenylpyridine[g]	1.5 (d–d) (2)	2.3–2.7 (m) (7)

[a] Measured in carbon tetrachloride against tetramethylsilane as an internal standard. [b] τ values. [c] t, triplet; m, multiplet; d, doublet; s, singlet. [d] Number of hydrogen atoms. [e] Reference 3. [f] Reference 8. [g] Reference 6.

place of the substituent.[10] Therefore we compared these absorptions of the pyridylthiophenes with those of the phenylpyridines[3,6,8] prepared in our laboratory (see Table I). A close similarity between the spectra of I and IV, II and V, and III and VI with 2-, 3-, and 4-phenylpyridine, respectively, is evident.

Uv Spectra (Table II).—Interesting changes are apparent when the uv spectra of the pyridylthiophenes and their pyridinium ions are compared. In accordance with expectations and the spectral changes in the

(6) This is a method for the preparation of 4-phenylpyridine: J. E. Lowman, Doctoral dissertation, Columbia University, 1948, cited in E. Klingsberg, "Heterocyclic Compounds, Pyridine," Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1961, p 220.

(7) These structure proofs make it clear that the conclusions of Kahmann, *et. al.*, concerning the ability of aromatic bonded sulfur to participate in chelate formation[4] need revision.

(8) 3-Phenylpyridine was obtained in 39% yield from an identical procedure carried out in benzene: H. Rapoport, M. Look, and G. J. Kelly, *J. Amer. Chem. Soc.*, **74**, 6293 (1952).

(9) (a) H. Wynberg, A. Logothetis, and D. Verploeg, *ibid.*, **79**, 1972 (1957); (b) J. Szmuszkovicz and E. J. Modest, *ibid.*, **72**, 571 (1950); (c) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951); (d) J. P. Wibaut and L. G. Heeringa, *Rec. Trav. Chim. Pays Bas*, **74**, 1003 (1955).

(10) (a) H. J. Bernstein and W. G. Schneider, *J. Chem. Phys.*, **24**, 469 (1956). (b) A 2-pyridyl ring shows one α-pyridyl hydrogen atom; a 3-pyridyl ring has two low-field protons with different chemical shifts and splitting patterns; two α-pyridyl hydrogen atoms with a clear doublet–doublet pattern are characteristic for a 4-substituted pyridine ring. (c) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book, Co., New York, N. Y., 1959, p 266.

TABLE II
ULTRAVIOLET ABSORPTION SPECTRA

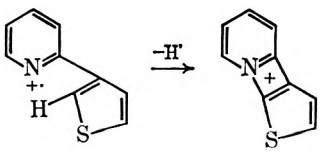
Compd	In 96% ethanol, λ_{max}, mμ (ϵ)	In 2 *N* hydrochloric acid, λ_{max}, mμ (ϵ)
I	303 (13,200)	334 (15,300)
	262 (7,800)	268 (6,700)
II	287 (13,100)	295 (10,700)
	262 (sh)[a] (8,600)	242 (8,400)
III	295 (15,900)	335 (20,300)
	266 (8,400)	275 (5,400)
	226 (5,200)	239 (5,200)
IV	285 (8,500)	312 (11,800)
	255 (10,100)	253 (7,200)
	228 (11,200)	
V	259 (13,700)	305 (sh) (4,600)
	227 (12,900)	265 (13,200)
		228 (sh) (12,800)
		221 (14,800)
VI	268 (16,400)	307 (17,100)
	228 (11,300)	270 (sh) (8,000)
		245 (3,800)
2-Phenylpyridine[b]	277 (8,900)	295 (13,800)
	244 (11,100)	242 (8,700)
3-Phenylpyridine[c]	275 (sh) (6,100)	285 (sh) (5,900)
	246 (13,700)	255 (11,100)
		232 (13,400)
4-Phenylpyridine[d]	256 (16,000)	288 (16,900)

[a] sh, shoulder. [b] Reference 3. [c] Reference 8. [d] Reference 6.

phenylpyridines,[11] a considerable greater bathochromic shift is observed for the 2 and 4 isomers than for the 3 isomer upon going from the pyridyl compounds to the pyridinium ions. Conjugation interaction between the nitrogen atom and the second aryl ring is not possible for 3-substituted pyridines. This effect becomes more important in the protonated species owing to a more electron-attracting nitrogen center. In addition this effect is more pronounced in the pyridylthiophenes than in the phenylpyridines because of a greater electron-donating effect of the thiophene ring.

Mass Spectra.—All of the pyridylthiophenes show very similar mass spectra with the parent peak (is base peak) at *m/e* 161 and the same degradation fragments.

Hydrogen abstraction leads to the most intense fragmentation peak with intensities of 12–20% with the exception of IV, which shows an intensity of 51%. This difference is caused possibly through the presence of a reactive α-thienyl center near the nitrogen atom.[12]



Other fragments in less than 15% of the highest intensity are found at *m/e* 135 (M − C_2H_2), 134 (M − HCN), 128 (M − HS), 117 (M − CS), 108 (M − C_3H_3N), and 116 (M − HCS or 160 − CS). Correct metastable peaks are present for the formation of the first five fragments out of the parent ion.

(11) F. Krumholz, *J. Amer. Chem. Soc.*, **73**, 3487 (1951); G. Favini, *Gazz. Chim. Ital.* **93**, 635 (1963).

(12) In comparison with 2-alkylpyridines: H. Budzikiewicz, C. Djerassi, and D. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 566.

Experimental Section

Melting points were determined with a Reichert melting point microscope and are uncorrected. Ultraviolet spectra were recorded on a Zeiss PMQ II spectrophotometer. Pmr spectra were taken on a Varian A-60 spectrometer in carbon tetrachloride with tetramethylsilane as an internal standard and are reported in τ values. An A.E.I. MS 902 mass spectrometer equipped with an all-glass heated inlet system at 150° was used. The ionization potential and current were 70 eV and 100 μA. Microanalysis were performed by the analytical department of our laboratory under the supervision of Mr. W. M. Hazenberg.

A. 2-(2′-Pyridyl)- and 2-(4′-Pyridyl)thiophene (I and III).—A Grignard solution free from magnesium turnings was prepared in the usual manner using 42 g (0.22 mol) of 2-iodothiophene[13] in 130 ml of dry ether. To this well-stirred solution under nitrogen atmosphere kept at room temperature was added dropwise a solution of 20.5 g (0.25 mol) of dry pyridine in 100 ml of dry ether. A white precipitate formed immediately. Stirring was continued for 20 min and the ether was evaporated while keeping the volume constant by adding 250 ml of dry xylene. Refluxing the mixture for 20 hr yielded two separate layers. Hydrolysis with a concentrated ammonium chloride solution, extraction of the organic layer with dilute hydrochloric acid, and subsequent steam distillation removed all volatile nonbasic components. The residue was made alkaline and a second steam distillation yielded 1.4 g (4%) of colorless crystals. Glpc and tlc showed that even after recrystallization from petroleum ether (bp 40–60°) a mixture of to components was present in a ratio of 1:3. Chromatography over a silica gel column yielded 2-(2′pyridyl)-thiophene (I), mp 60.5–62° [recrystallized from petroleum ether (bp 40–60°)], with benzene as eluent and 2-(4′-pyridyl)thiophene (III), mp 92–92.5° [recrystallized from petroleum ether (bp 40–60°)] as the major product with ether as eluent.

Anal. Calcd for C_9H_7NS: C, 67.12; H, 4.38; N, 8.68; S, 19.92. Found for I: C, 66.61; H, 4.31; N, 8.46; S, 19.84. Found for III: C, 66.71; H, 4.27; N, 8.59; S, 19.92.

2-(4′-Pyridyl)thiophene (III).—A Grignard solution free from magnesium turnings was prepared using 72 g (0.34 mol) of 2-iodothiophene[13] and 9.7 g (0.34 g-atom) of magnesium, both in 100 ml of dry ether. This solution was kept under a dry nitrogen atmosphere and added dropwise to ice-cooled, well-stirred crude 1-benzoyl-4-chloro-1,4-dihydropyridine obtained by heating 27 g (0.34 mol) of dry pyridine, 49 g (0.34 mol) of freshly distilled benzoylchloride, and 0.7 g of copper powder.[14] A thick green precipitate was formed which prevented further stirring. The mixture was refluxed for 14 hr, hydrolyzed, and extracted with dilute hydrochloric acid solution. The acid layers were steam distilled to remove all nonbasic volatile organic components and the residue was made alkaline. Another steam distillation yielded 1 g (2%) of 2-(4′-pyridyl)thiophene (III), mp 92.5–93.5° [recrystallized from petroleum ether (bp 40–60°)]. The mixture melting point with the material obtained above was 92.5–93.5°.

B. 2-(3′-Pyridyl)thiophene (II).—The reaction was carried out as described by Rapoport, *et al.*, for 3-phenylpyridine[8] replacing benzene by thiophene. The thiophene was removed by distillation and the residue was extracted with dilute hydrochloric acid solution. The acid extracts were steam distilled to remove all volatile nonbasic compounds. The residue was made alkaline with sodium hydroxide and submitted to a second steam distillation. The distillate was extracted with ether and the extracts were dried ($CaCl_2$). After evaporation of the solvent the residue upon distillation furnished 13.9 g (0.08 mol, 47%) of an oil [bp 102–111° (1.9 mm)] consisting of two components (ratio of 1:6, glpc). With preparative tlc on silica gel (Merck, PF-254) and a petroleum ether (bp 40–60°)–acetone mixture (4:1) as eluent, pure 2-(3′-pyridyl)thiophene (II), bp 121–122° (4.0 mm), $n^{20}D$ 1.6502, could be obtained as the major product. A second fraction consisting of a 1:1 mixture of both components yielded 3-(3′-pyridyl)thiophene (V), mp 72–74°, upon two recrystallizations from an excess of petroleum ether (bp 40–60°). This material still contained 2.5% II (estimated from glpc).

Anal. Calcd for C_9H_7NS: C, 67.12; H, 4.38; N, 8.68; S, 19.92. Found for II: C, 67.11; H, 4.42; N, 8.53; S, 20.09. Found for V: C, 67.01; H, 4.46; N, 8.48; S, 19.60.

(13) W. Minnis, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1950, p 35 ff.

(14) E. Koenigs and E. Ruppolt, *Liebigs Ann. Chem.*, **509**, 142 (1934).

C. 3-(2′-Pyridyl)-, 3-(3′-Pyridyl)-, and 3-(4′-Pyridyl)thiophene (IV, V, and VI).—Over a period of 15 min a solution of 10 g (0.063 mol) of bromopyridine in 25 ml of dry ether was added to a well-stirred solution of 0.063 mol of *n*-butyllithium in 32 ml of hexane diluted with 100 ml of dry ether under a nitrogen atmosphere. During the addition the temperature was maintained between −75 and −60°. After a second 15-min period of stirring, a solution of 6.4 g (0.063 mol) of 3-ketotetrahydrothiophene[15] in 25 ml of dry ether was added in 15 min. The stirring of the gray suspension was continued for another 15-min period raising the temperature to −40°. The reaction mixture was poured into 100 ml of water and the aqueous layer was extracted with ether (in the case of the 4-pyridyl compound chloroform must be used). The combined organic layers were dried ($CaCl_2$) and the solvent was evaporated. Removal of unused ketone through distillation at the water pump [up to 85° (20 mm)] left 6.0–8.0 g (0.033–0.044 mol, 52–70%) of a viscous oil (for the 4-pyridyl compound a solid), mainly the tertiary carbinol.

This oil was heated with 2.5 g of sulfur and 2.0 g of $KHSO_4$. At 160° water began to distil from the reaction mixture and hydrogen sulfide was evolved. The heating was continued for 30 min and the temperature was slowly raised to 225°. Steam distillation of the reaction mixture yielded crystalline plates of 3-(3′-pyridyl)- and 3-(4′-pyridyl)thiophene (V and VI). With the 2-pyridyl compound an oil was obtained, which was further purified through preparative tlc on silica gel (Merck PF-254) with chloroform as eluent to remove some unchanged carbinol. Distillation furnished an analytical sample of 3-(2′-pyridyl)-thiophene (IV), bp 93–95° (0.45 mm). See Table III for analytical data.

TABLE III

Compd	Mp, °C	Overall yield, %	Analysis, % Found C	H	N	S
IV	27–28	10	67.16	4.50	8.59	19.71
V	75–76.5	10	66.70	4.39	8.59	19.94
VI	138.5–139	2	66.99	4.41	8.62	19.75
			Calcd for C_9H_7NS			
			67.12	4.38	8.68	19.92

(15) F. A. Buiter, J. H. Sperna Weiland, and H. Wynberg, *Rec. Trav. Chim.*, **83**, 1160 (1964).

Bromopyridines.—The 2- and 3-bromopyridines were commercially available. The unstable[16] 4-brompyridine was obtained from the commercially available hydrogen chloride salt through addition of an equimolar amount of concentrated sodium hydroxide solution at 0°. Extraction with ether, drying of the organic layers (Na_2SO_4), and evaporation of the solvent below 30° yielded almost pure 4-bromopyridine. Because of its instability, it was used immediately for further reactions.

Desulfurizations.—The desulfurizations were accomplished by refluxing the individual highly purified pyridylthiophenes (I, II, III, and V) with 10 times their weight of Raney nickel W-5[17] in absolute ethanol for 30 min. The Raney nickel was removed by filtration through a glass filter and was washed carefully with absolute ethanol. The concentrated filtrates were dissolved in ether and dried ($CaCl_2$). Evaporation of the solvent yielded a crude oil giving pmr spectra (Table IV) consistent with butylpyridines (25–70%).

TABLE IV

Desulfurization product of	Pmr spectra Aromatic	Alkyl
I	1.7 (t–t) (1), 2.2–3.2 (m) (3)	7.2 (t) (2), 8.0–8.9 (m) (4), 9.0 (t) (3)
II	1.7 (s) (2), 2.5–3.2 (m) (2)	7.5 (t) (2), 8.2–8.9 (m) (4), 9.1 (t) (3)
III	1.7 (d) (2), 3.1 (d) (2)	7.6 (t) (2), 8.1–8.8 (m) (4), 9.1 (t) (3)
V	1.7 (s) (2), 2.4–3.1 (m) (2)	7.2 (m) (1), 8.0–8.8 (m) (5), 9.0 (t) (3)

Registry No.—I, 3319-99-1; II, 21298-53-3; III, 21298-54-4; IV, 21298-55-5; V, 21308-81-6; VI, 21308-82-7; 2-phenylpyridine, 1008-89-5; 3-phenylpyridine, 1008-88-4; 4-phenylpyridine, 939-23-1.

(16) J. P. Wibaut, J. Overhoff, and H. Geldof, *ibid.*, **54**, 807 (1935).

(17) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., p 176.

An Unusually Facile Anilide Ethanolysis

SAUL B. KADIN

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut 06340

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Refluxing ethanol promptly converts the 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilides (Ia–e) into ethyl 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxylate (II) in good yields. The facility with which this ethanolysis occurs appears to be related to the higher energy state of I relative to II. Lack of enol character of I, presumably due to steric hindrance, and the hydrogen-bonded stabilization of its enolate anion (V) impart substantial acidic character to this molecule, and this property provides the proton which is believed to catalyze the ethanolysis.

Treatment of carboxylic acid esters with amines is generally a convenient method for the preparation of amides.[1] Alcohols, which often facilitate this reaction,[2,3] are generally considered to be sufficiently poor nucleophiles as to allow the intermediate tetrahedral complex formed by nucleophilic attack of an amine on carbonyl carbon to lead, irreversibly, to amide formation.[4] Furthermore, the inertness of alcohols toward amides and anilides frequently suggests their use as recrystallization solvents.[5]

Quite unexpectedly, therefore, in the course of purifying 2′-chloro-2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ib) it was discovered that refluxing ethanol converted this substance into ethyl 2-methyl-1,3-(2H,4H)-dioxoisoquinoline-4-carboxylate (II) in a yield of better than 90% and this unusual alcoholysis was subsequently found to be characteristic for related anilides (Table I). To gain insight into the mechanism of this uncommon and extraordinarily facile reaction, the physical properties of these anilides and related substances were investigated.

The 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-car-

(1) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1953, p 568.

(2) R. L. Betts and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1568 (1937).

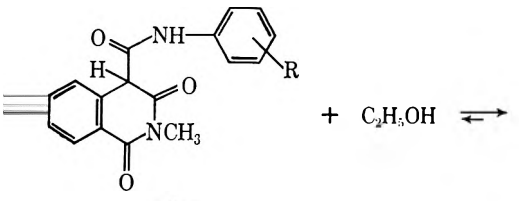
(3) R. Baltzly, I. M. Berger, and A. A. Rothstein, *ibid.*, **73**, 4149 (1950).

(4) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 665 (1960).

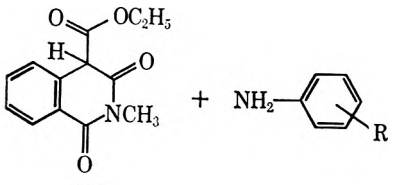
(5) S. M. McElvain, "The Characterization of Organic Compounds," Rev. Ed., The Macmillan Co., New York, N. Y., 1945, pp 141, 189.

TABLE I

pK_a' VALUES AND ETHANOLYSIS RESULTS OF SUBSTITUTED 2-METHYL-1,3(2H,4H)-DIOXOISOQUINOLINE-4-CARBOXANILIDES



I



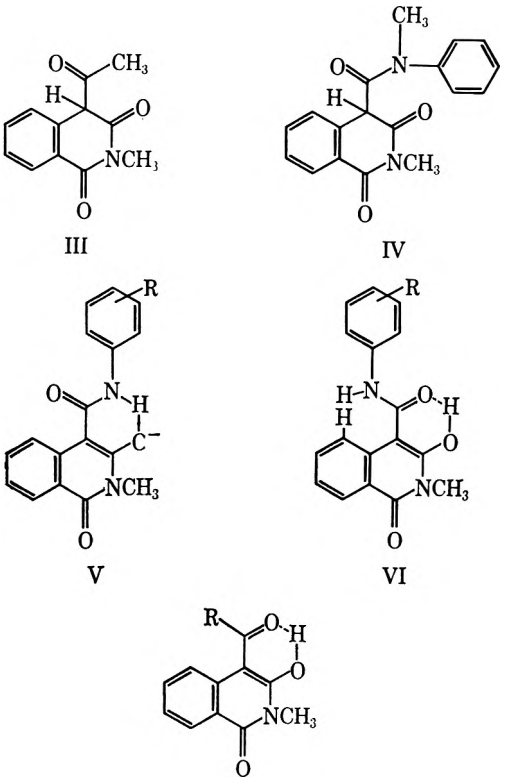
II

Compound	R	pK_a' [a]	Yield of II, %
Ia	H	5.68	42
Ib	2-Cl	4.38	94
Ic	2-OCH_3	5.49	71
Id	2-CH_3	5.36	64
Ie	4-NO_2	insoluble	81

[a] See Experimental Section.

boxanilides are unexpectedly strong acids (Table I). Specifically, they are substantially more acidic than II ($pK_a' = 7.15$) or 4-acetyl-2-methylisoquinoline-1,3-(2H,4H)-dione (III) ($pK_a' = 6.60$). Since a carbamoyl moiety is inferior to an acetyl or a carbethoxy function in its electron-withdrawing properties,[6,7] it appeared that the reasons for the acidity of compounds of type I might be related directly to the facility with which they undergo ethanolysis.

The nmr spectra of the carboxanilides are consistent with a keto rather than an enol configuration. For example, the spectrum of Ia exhibits a singlet at τ 6.75 (N-methyl), a singlet at 4.5 (methine hydrogen), an aromatic multiplet, and a signal at −0.5 (amide hydrogen). That the assignments of the methine and amide hydrogens are as indicated was confirmed by the nmr spectrum of N,2-dimethyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (IV) which is quite similar to that of Ia except that there is no signal downfield from the aromatic multiplet. Although the spectra were generally obtained, for solubility purposes, in deuterated dimethyl sulfoxide, a solvent which, in comparison with less polar solvents, is not expected to favor an intramolecularly hydrogen-bonded enolic configuration,[8] a few compounds were sufficiently soluble to be examined in deuterated chloroform in which case the nmr spectra showed little change from those obtained in the former solvent. Contrary to those of the carboxanilides, the nmr spectra of II and III exhibit chemical shifts which are expected for compounds having strongly bonded enolic configurations. The enolic proton of the former appears at τ −5.9 (CCl_4) and that of the latter at −6.8 (CCl_4). Evidently, part of the reason for the enhanced acidity of I compared with that of II and III is that ionization of I results in the formation of a planar, conjugated anion (V) in which π-orbital overlap is maximal. This contrasts with the nonplanar keto configuration of I which, because of the steric effect which would be engendered between the hydrogen on the anilide nitrogen and the hydrogen at position 5 of the isoquinolinedione moiety, cannot assume the low energy, resonance-stabilized enol configuration (VI) similar to that which occurs in II and III (VII).



III IV V VI

VII, R = CH_3, OC_2H_5

Therefore, in the case of I, but not of II and III, ionization is probably enhanced by the formation of an anion which is configurationally more stable than its conjugate acid.

When II was refluxed with aniline or *o*-chloroaniline in ethanol, the corresponding carboxanilides were detected (tlc) in trace amounts although the ester was recovered almost quantitatively. Thus, II is the favored product under equilibrating conditions despite the greater nucleophilicity of aniline compared with that of ethanol,[9,10] lending additional credence to the postulated energy differences between I and II. As anticipated, conventional aminolysis of II in xylene proved to be a successful route to the synthesis of compounds of type I provided that ethanol was removed from the reaction mixture.

A second feature contributing to the enhanced acidity of I is noted when the pK_a' values of 23 anilides of structure I substituted in the *ortho*, *meta*, and *para* positions of the anilide moiety are plotted against the pK_a values of the correspondingly substituted anilines.[11] A straight line of slope 0.48 (correlation coefficient,

(6) F. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).
(7) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(8) M. T. Rogers and J. L. Burdett, *Can. J. Chem.*, **43**, 1516 (1965).
(9) C. G. Swain, D. C. Dittmer, and L. E. Kaiser, *J. Amer. Chem. Soc.*, **77**, 3737 (1955).
(10) Although Wepster and Verkade [*Rec. Trav. Chim.*, **67**, 425 (1948)] showed that 2′-nitroacetanilide undergoes methoxide ion catalyzed methanolysis, we have found that 2′-chloroacetoacetanilide [H. E. Fierz-David and E. Ziegler, *Helv. Chim Acta*, **11**, 776 (1928)], a β-ketoanilide bearing some structural similarity to Ib, is recovered unchanged after refluxing in ethanol for 5 hr; no trace (tlc) of ethyl acetoacetate was detected.
(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 7.

0.97) is obtained. This indicates that the substituent effect upon the electron density about the aniline nitrogen is proportional to its effect upon the acidity of I, and that the latter effect is probably manifested by means of a hydrogen bond from the enolate anion oxygen to the hydrogen on the anilide nitrogen (V). A similar type of enolate anion stabilization has been proposed to explain the difference in acidity between N-salicoylmesitamide and salicylamide.[12] The fact that IV ($pK_a' = 7.57$) is much less acidic than Ia–d also emphasizes the acid-enhancing effect of the hydrogen on the anilide nitrogen.

In conclusion, the unusual ease with which compounds of type I undergo ethanolysis seems to be related to the substantially higher energy state in which they exist relative to the reaction product. The lack of enol character of I, presumably due to steric hindrance, and the relatively greater stability of the planar, conjugated anion (V) resulting upon ionization of I impart substantial acidic character to this molecule, and this intrinsic acidity provides the proton which is probably required to catalyze the ethanolysis.[13]

Experimental Section

Nmr spectra were recorded on a Varian A-60 spectrometer and are reported as τ values relative to tetramethylsilane as an internal standard. Melting points are uncorrected. pK_a' determinations were performed in 1:2 water–dioxane using a Metrohm Potentiograph. Isocyanates used were commercial materials. Each of the carboxanilides gave a positive ferric chloride test.

2-Methylisoquinoline-1,3(2H,4H)-dione.[14]—A solution of homophthalic acid in aqueous methylamine was evaporated to dryness under reduced pressure and the residue was heated for 1 hr in an oil bath at 180–190°. The melt was poured into ethanol from which crystals, mp 122–124°, were obtained (lit.[15] mp 123°).

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ia).—A refluxing solution of 35.0 g (0.2 mol) of 2-methylisoquinoline-1,3(2H,4H)-dione and 21.2 g (0.21 mol) of triethylamine in 250 ml of dry tetrahydrofuran was treated, dropwise, with a solution of 25.0 g (0.21 mol) of phenyl isocyanate in 10 ml of dry tetrahydrofuran. Refluxing was continued for 1.5 hr after addition of the isocyanate was complete. The red-brown solution was poured into a stirred ice–water mixture containing 28 ml of hydrochloric acid. The resulting precipitate was filtered, washed with water, dried, and recrystallized from acetonitrile to yield 32.0 g (55%) of white crystals, mp 243–244° dec.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.52; H, 4.81; N, 9.51.

2'-Chloro-2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ib).—Ib was prepared in 54% yield as described for Ia except that *o*-chlorophenyl isocyanate was employed: mp 212–213° dec (acetonitrile).

Anal. Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.10; H, 3.98; N, 8.52. Found: C, 61.99; H, 3.97; N, 8.47.

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carbox-*o*-anisidide (Ic).—Ic was prepared in 42% yield as described for Ia except that *o*-methoxyphenyl isocyanate was employed: mp 197–199° dec (acetonitrile).

Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.69; H, 5.02; N, 8.71.

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carbox-*o*-toluidide (Id).—A mixture of 4.4 g (0.025 mol) of 2-methylisoquinoline-1,3(2H,4H)-dione and 2.6 g (0.026 mol) of triethylamine in 25 ml of dry dimethyl sulfoxide was treated, dropwise, with 3.5 (0.026 mol) of *o*-tolyl isocyanate. The resulting solution was stirred at room temperature for 3 hr and then poured into an ice–water mixture containing 5 ml of 6 *N* hydrochloric acid. The precipitate which formed was filtered, dried, and recrystallized from acetonitrile to yield 5.1 g (73%) of white crystals, mp 221–223° dec.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.45; H, 5.19; N, 9.17.

4'-Nitro-2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ie).—A solution of 4.94 g (0.02 mol) of ethyl 2-methyl-1,3-(2H,4H)-dioxoisoquinoline-4-carboxylate and 3.0 g (0.022 mol) of *p*-nitroaniline in 100 ml of xylene was refluxed for 4.5 hr during which time solvent was slowly removed by means of a still head. A precipitate began to form as the mixture approached reflux temperature and became heavier with time. When the mixture had cooled, the precipitate was filtered and dried to yield 6.0 g (88%), mp 235–236° dec. Attempted recrystallizations were unsuccessful.

Anal. Calcd for $C_{17}H_{13}N_3O_5$: C, 60.17; H, 3.86; N, 12.39. Found: C, 60.45; H, 3.88; N, 12.74.

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carbox-N-methylanilide (IV).—A solution of 2.5 g (0.01 mol) of ethyl 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxylate and 1.1 g (0.01 mol) of N-methylaniline in 25 ml of xylene was refluxed for 1 hr during which time solvent was slowly removed by means of a still head. The reaction mixture was chilled in an ice bath while 15 ml of hexane was added. The resulting precipitate was filtered, dried, and recrystallized from benzene–hexane to yield 1.8 g (58%) of white crystals, mp 160–162°.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.86; H, 5.22; N, 9.06.

Ethyl 2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxylate (II).—A solution of 16.4 g (0.05 mol) of Ib in 125 ml of ethanol was refluxed for 4 hr after which time *ca.* half of the ethanol was allowed to evaporate. Cooling produced white needles which were recrystallized from ethanol to yield 11.5 g (94%) of material, mp 113–115° (positive ferric chloride test).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.07; H, 5.33; N, 5.65.

Ethanolyses of other compounds in Table I were effected by a similar procedure, using tlc to follow the course of the reaction.

A solution of 8.75 g (0.05 mol) of 2-methylisoquinoline-1,3-(2H,4H)-dione in 80 ml of dry tetrahydrofuran was added to a stirred suspension of 4.45 g of a 59.5% mineral oil dispersion of sodium hydride in 15 ml of dry tetrahydrofuran and the resulting suspension was treated over 45 min with a solution of 6.0 g (0.055 mol) of ethyl chloroformate in 10 ml of the same solvent. A tan suspension developed during 19 hr of stirring at room temperature after which time the reaction mixture was poured into an ice–water mixture containing 20 ml of 6 *N* hydrochloric acid. The resulting precipitate was filtered, dried, and recrystallized three times from ethanol to yield 2.0 g (16%) of white crystals, mp 111–113° (positive ferric chloride test) whose infrared spectrum was superimposable on that of the material obtained by anilide ethanolysis.

4-Acetyl-2-methylisoquinoline-1,3(2H,4H)-dione (III).—This compound was prepared by the method of Bailey and Swallow:[15] mp 115–117° (lit.[15] mp 115°).

Registry No.—Ia, 21389-75-3; Ib, 21389-76-4; Ic, 21389-77-5; Id, 21389-78-6; Ie, 21389-79-7; II, 21389-80-0; IV, 21389-81-1.

(12) R. M. Topping and D. E. Tutt, *J. Chem. Soc., B*, 1346 (1967).

(13) The possibility also exists that the ethanolysis proceeds through a ketene intermediate similar to that recently proposed by Bruice and Holmquist [*J. Amer. Chem. Soc.*, **90**, 7136 (1968)] for the hydrolysis of malonate and cyanoacetate esters.

(14) S. Gabriel, *Ber.*, **19**, 2363 (1886).

(15) A. S. Bailey and D. L. Swallow, *J. Chem. Soc.*, 2477 (1956).

The Stability, Decomposition, and Reactivity of a 1,2-Diazacyclopentene-3,5-dione. 4,4-Diethylpyrazoline-3,5-dione[1]

BERNARD T. GILLIS AND ROBERT A. IZYDORE

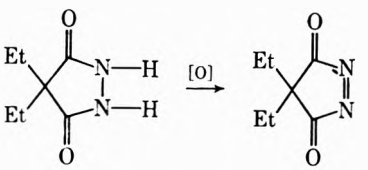
Chemistry Department, Duquesne University, Pittsburgh, Pennsylvania 15219

Received December 26, 1968

The diazacyclopentene-3,5-dione, 4,4-diethylpyrazoline-3,5-dione (2), was prepared by the oxidation of 4,4-diethylpyrazolidine-3,5-dione (1) with either nitrogen tetroxide or lead tetraacetate (LTA). Dilute solutions of 2 proved to be more stable when nitrogen tetroxide was used to oxidize 1 and could be stored for indefinite periods at −15°. On warming to room temperature, 2 decomposed readily to give products which depended on the nature of the oxidant and decomposition conditions. Oxidation of 1 with nitrogen tetroxide and decomposition gave nitrogen, 2,2,6,6-tetraethylpyrazolo[1,2-*a*]pyrazole-1,3,5,7-tetraone (3), 1-(diethylcarboxyacetyl)-4,4-diethylpyrazolidine-3,5-dione (4), and diethylmalonic acid (5) as products. Oxidation of 1 with LTA and decomposition gave nitrogen, 3, lead diethylmalonate (9), 3-acetoxy-4,4-diethyl-2-pyrazolin-5-one (10), 3,5-diacetoxy-4,4-diethylpyrazole (11), and diacetoxy diethylmalonate (13) as products. The *in situ* reaction of 2 with dienes yielded a series of Diels–Alder adducts. Adducts were obtained by the reaction of 2 with 2,3-dimethyl-1,3-butadiene, isoprene, 1,4-diphenyl-1,3-butadiene, cyclopentadiene, 1,3-cyclohexadiene, α-phellandrene, 1,3-cyclooctadiene, and anthracene. Higher yields of the adducts resulted when LTA was used to oxidize 1. The nmr and uv spectra of the adducts gave a considerable amount of information about their geometry.

The preparation of diazabicyclic systems by the reaction of electron-deficient *cis*-azo dienophiles and conjugated dienes in 1,4 cycloaddition has been reported.[2-5] These *cis*-azo dienophiles were found to be generally more reactive than *trans*-azo dienophiles.[2-8] The purpose of this investigation was to develop and study new *cis*-azo compounds which may be useful as dienophiles in 1,4-cycloaddition reactions.

Oxidation of the hydrazide, 4,4-diethylpyrazolidine-3,5-dione (1), was found to yield the 1,2-diazacyclopentene-3,5-dione 2.[9]

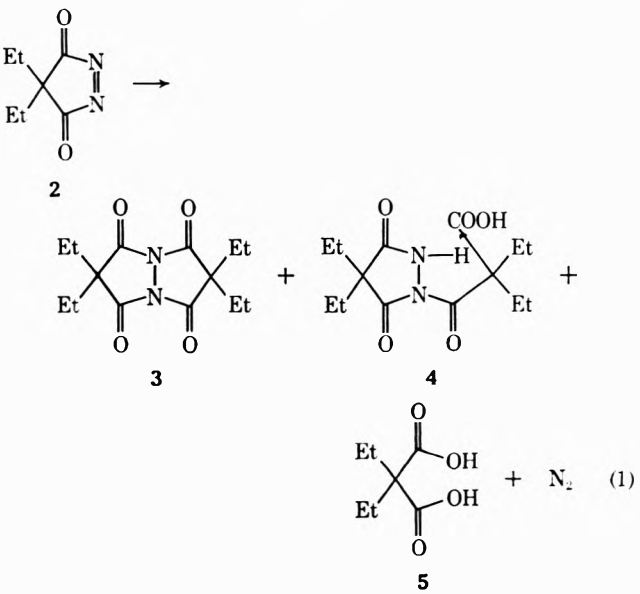


1 2

The presence of 2 could easily be detected by the deep color of its methylene chloride solutions. When lead tetraacetate (LTA) was used as the oxidizing agent, the solution containing 2 appeared green. When nitrogen tetroxide was used to oxidize 1, a transient green solution formed which gave way to a deep blue solution containing 2. Since the addition of LTA to commercial methylene chloride gave an orange solution, the blue color of 2 produced by this oxidizing agent was probably masked.[10]

At any rate, the visible spectrum of 2 was found to be independent of the oxidizing agent. In general, solutions of 2 were more stable when nitrogen tetroxide was used as an oxidant. Dilute solutions of 2 were 29% decomposed after standing at room temperature for 72 hr, as measured by the decrease of molar absorptivity when nitrogen tetroxide was used, but, when LTA was used, 50% decomposition at room temperature had taken place after 72 hr. The visible spectrum of 2 is summarized in Table I. It can be seen that little decomposition had taken place after 32 weeks.

The ultraviolet spectrum showed only end absorption. Attempts were made to obtain pure 2 by the isolation method of Stickler and Pirkle.[11] In all cases, a deep blue liquid was obtained, which, on warming to room temperature, decomposed rapidly with gas evolution. This decomposition, which gave nitrogen, 2,2,6,6-tetraethylpyrazolo[1,2-*a*]pyrazole-1,3,5,7-tetraone (3), 1-(diethylcarboxyacetyl)-4,4-diethylpyrazolidine-3,5-dione (4), and diethylmalonic acid (5), can be represented by eq 1.



When the decomposition of 2 was allowed to proceed in methylene chloride solution, it was noted that the solution remained strongly acidic even in the presence of excess sodium sulfate. The solution was therefore neutralized by adding sodium bicarbonate and filtered

(1) This investigation was supported by Grant GP-7680 from the National Science Foundation.

(2) B. T. Gillis and R. Weinkam, *J. Org. Chem.*, **32**, 3321 (1967).

(3) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc., C*, 19, 1905–1909 (1967).

(4) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).

(5) B. T. Gillis, "1,4-Cycloaddition Reactions," Academic Press Inc., New York, N. Y., 1967, Chapter 6.

(6) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962).

(7) T. J. Kealy, *J. Amer. Chem. Soc.*, **84**, 966 (1962).

(8) R. A. Clement, *J. Org. Chem.*, **25**, 1724 (1960).

(9) Sulfo derivatives of pyrazoline-3,5-dione have previously been reported; see A. M. Khaletskii and B. L. Moldover, *Materialy 1-go (Pervogo) Vseros. Sezda Farmatsevtov* (Moscow: Med.) *Sb.*, 330 (1962), *Chem. Abstr.*, **63**, 5625*f* (1965).

(10) Under anhydrous conditions, LTA oxidation of 1 also gave a blue color.

(11) J. C. Stickler and W. H. Pirkle, *J. Org. Chem.*, **31**, 3444 (1966).

TABLE I

VISIBLE SPECTRUM OF 4,4-DIETHYLPYRAZOLINE-3,5-DIONE[a]

λ_{max}, mμ, in methylene chloride[c]	Molar absorptivity, ε			
	Initial	1 week[b]	14 weeks	32 weeks
724	37	36	32	26
680	111	109	102	82
644	154	150	127	110
621	139	136	117	94

[a] Nitrogen tetroxide was used as the oxidant of **1**. [b] The solution was stored at −15°. [c] Oxidation of **1** with LTA gave the same four peaks with comparable absorptivities.

before allowing the decomposition to proceed. Compounds **3**, **4**, **5**, and nitrogen were again obtained. Table II shows that the yields of the decomposition products were dependent on the mode of decomposition.

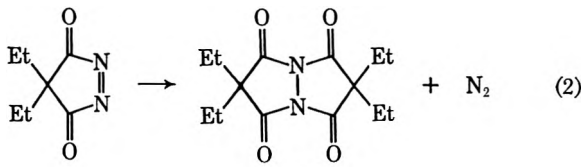
TABLE II

DECOMPOSITION PRODUCTS OF 4,4-DIETHYLPYRAZOLINE-3,5-DIONE[a]

Product	Yield, %: No solvent	Neutral methylene chloride solution
3	26.8	50.0
4	41.9	29.4
5	10.3	2.1

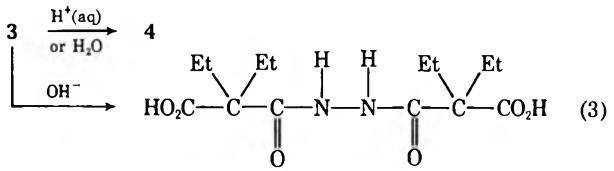
[a] Nitrogen tetroxide was used as the oxidant of **1**.

The formation of **3** can be represented simply by eq 2. Similar reactions have been reported by Kealy.[7]



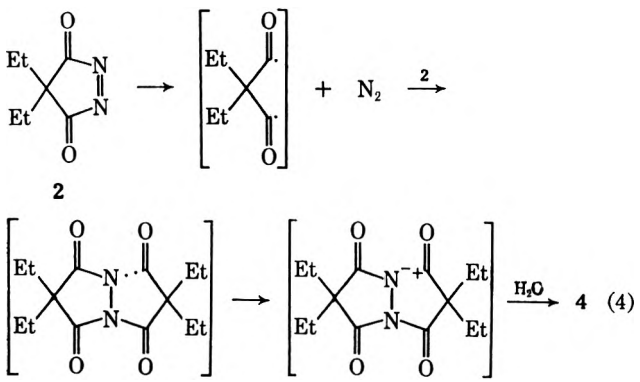
2 **3** (2)

It was found that **3** reacted with acid or water to give the carboxylic acid **4**, but that it reacted with base to furnish the further opened dicarboxylic acid **6**, as shown in eq 3.



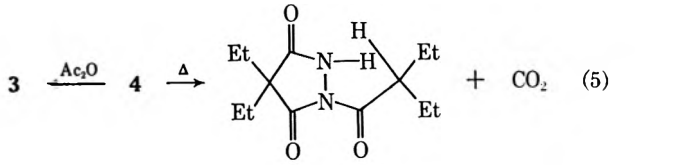
6 (3)

Since **3** was found to be indefinitely stable to atmospheric moisture, the formation of **4** by decomposition of **2** can be ascribed to sequence 4.



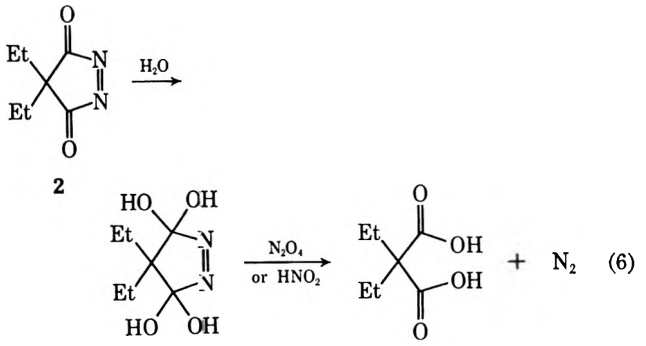
2 (4)

The acid **4** was thermally unstable and decarboxylated readily on heating under reduced pressure to give 1-(diethylacetyl)-4-4-diethylpyrazolidine-3,5-dione (**7**). Dehydration of **4** using acetic anhydride quantitatively furnished **3**. These latter two conversions of **4** are summarized by eq 5.



7 (5)

The presence of diethylmalonic acid (**5**) can be accounted for either by the presence of excess nitrogen tetroxide or by the presence of nitrous acid, as shown by eq 6.



2 **8** **5** (6)

Table II shows that, when the decomposition of **2** was carried out in neutral methylene chloride solution, only 2.1% diethylmalonic acid (**5**) was isolated. It is noteworthy to mention that, when the decomposition of **2** was allowed to proceed in methylene chloride solution without the addition of sodium bicarbonate solution, the yield of diethylmalonic acid (**5**) increased to 35%, even when only 1 equiv of nitrogen tetroxide was used. In this case, it appears that the nitrous acid formed in the oxidation of **1** is acting as a further oxidant of **2**. This latter mode of decomposition also yielded a little diethylacetic acid, which was probably formed from decarboxylation of diethylmalonic acid in the acidic media.

When LTA was used as the oxidizing agent, the decomposition of **2** gave **3**, lead diethylmalonate (**9**), 3-acetoxy-4,4-diethyl-2-pyrazolin-5-one (**10**), 3,5-diacetoxy-4,4-diethylpyrazole (**11**), and diacetoxy diethylmalonate (**13**). The products were possibly formed as shown in Scheme I.

The dianhydride **13** was characterized by its elemental analysis, infrared spectra, and nmr spectra. It reacted readily with aniline to give acetanilide and diethylmalonic acid, and it reacted slowly over a period of several days with lead acetate to give lead diethylmalonate (**9**).

The acetoxy derivatives **10** and **11** were characterized by their elemental analysis and by ultraviolet, infrared, and nmr spectra, as well as by comparison with authentic samples of **10** and **11** which were prepared from the reaction of the hydrazide **1** with acetic anhydride.

The high stability of **2** at 0°, in addition to the fact that it is readily available, made it a potentially at-

SCHEME I

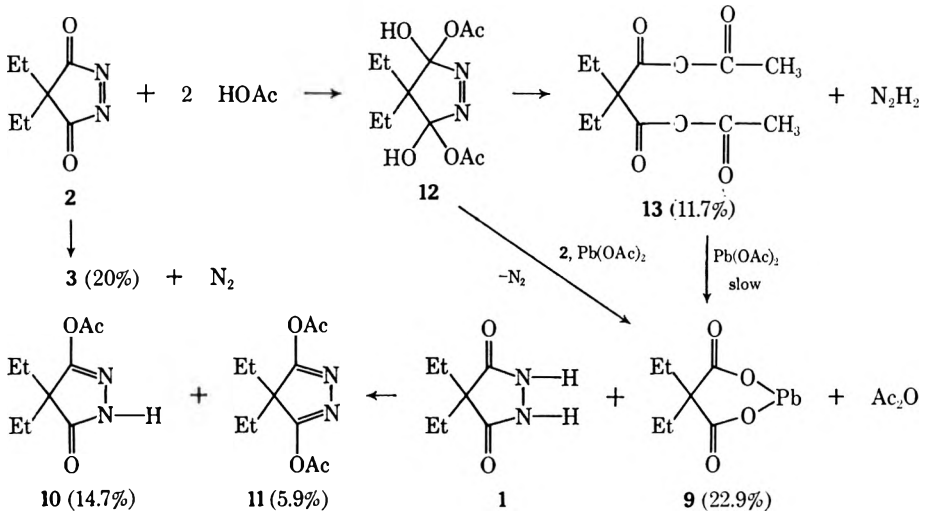
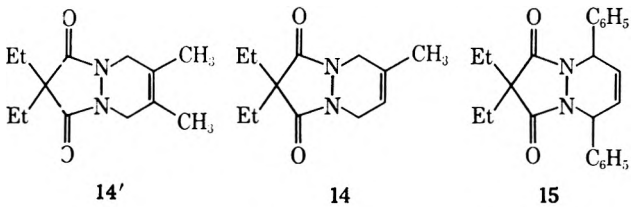


TABLE III

Diene	Adduct	Mp, °C (bp, mm)	Yield, %[a]	λ_{max} mμ, (solvent)	ε
2,3-Dimethylbutadiene	14′	107–108	94.3 (55.3)[b]	256 (cyclohexane)	2040
				257 (95% ethanol)	2250
Isoprene	14	58.5–60	46.6	256 (cyclohexane)	2210
				256 (95% ethanol)	2850
1,4-Diphenylbutadiene	15	147–148	51.9	259 (cyclohexane)	2170
				259 (95% ethanol)	2270
Cyclopentadiene	16	76–77	40.0	269 (cyclohexane)	3030
			(15.9)[b]	254 (95% ethanol)	4150
Cyclohexadiene	17	105–106	76.1	268 (cyclohexane)	3900
				256 (95% ethanol)	4520
α-Phelladrene	18	(141–143, 0.2)	41.4	256 (cyclohexane)	3810
				247 (95% ethanol)	4180
1,3-Cyclooctadiene	19	134–136	21.0	261 (cyclohexane)	3790
				257 (methanol)	2820
Anthracene	20	224–226	13.6	262 (methanol)	5740
Diethylmalonic acid cyclic hydrazine	1			253 (water)	3600

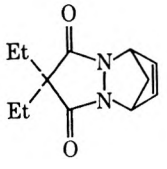
[a] LTA was used as the oxidant of 1. [b] Nitrogen tetroxide was used as the oxidant of 1.

tractive dienophile. When 2 was generated by LTA oxidation in the presence of a 1,3-diene, the characteristic green color of 2 was completely absent after 5 min to 3 hr or longer, depending on the reactivity of the diene towards Diel–Alder addition. The results are summarized in Table III.


14′

14

15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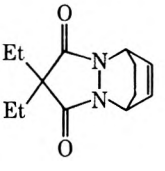
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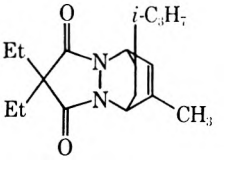
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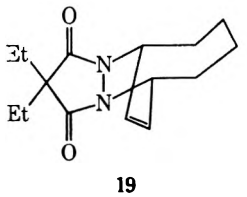
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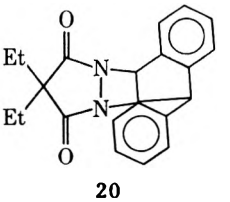

20

It can be seen from the yields of compounds 14′ and 1 that far higher yields of Diels–Alder adducts resulted when LTA was used to oxidize 1. Nitrogen tetroxide oxidations always led to large amounts of polymeric materials. Norbornadiene gave no adduct with 2. Instead, the mixed acetates of norbornadiene (LTA oxidation) that were reported by Alder,[12] or polymeric materials (nitrogen tetroxide oxidation), were isolated.

Thus, 4,4-diethylpyrazoline-3,5-dione is one of the more reactive *cis*-azo dienophiles. It is more reactive than 5-substituted pyrazol-3-one derivatives[2] but a little less reactive than 4-phenyl-1,2,4-triazoline-3,5-dione, which gives an adduct with norbornadiene.[4,7,8]

Each of the adducts was identified by its nmr, infrared, and ultraviolet spectra as well as by elemental analysis. The main feature of their infrared spectra was a split carbonyl absorption of unequal intensity at about 5.95 and 5.80 μ with the former being more intense. The degree of rigidity of the various adducts about the N,N ring fusion was illustrated by their nmr and ultraviolet spectra. Those adducts with 1,4 substitution as a bridge showed nonequivalent C-

(12) K. Alder, F. H. Flock, and H. Wirtz, *Chem. Ber.*, **91**, 609 (1958).

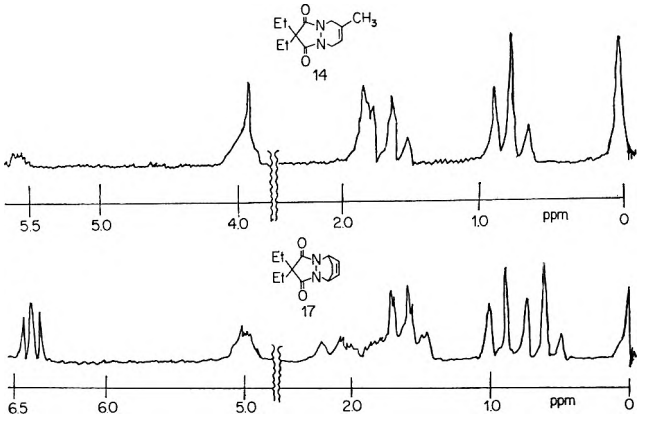
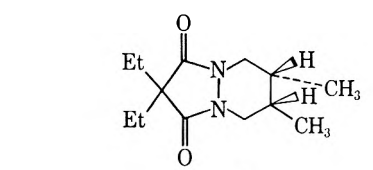


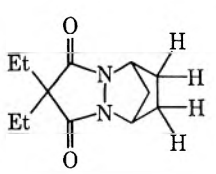
Figure 1.–Nmr spectra of adducts **14** and **17**.

methyl proton absorptions for the two ethyl groups in the nmr.

Those adducts with no bridge at the 1,4 positions showed only an average C-methyl absorption due to the free inversion about the 1,4-carbon atoms. This distinction is shown by the nmr spectra of **14** and **17**, which are illustrated in Figure 1. The nmr data is complemented by the ultraviolet data, which is tabulated in Table III. The table shows that those adducts with no 1,4 bridge exhibit no shift in wavelength with a change in the polarity of the solvent. However, those adducts with a 1,4 bridge, with the exception of **15**, which is not nearly so strained as the other 1,4-bridged adducts, show an increase in the wavelength of absorption with a decrease in solvent polarity. This bathochromic shift is probably due to an interaction between the endocyclic double bond and the nonbonded electrons on the two nitrogen atoms, even though they are shielded by the nitrogen nuclei. The table shows a correlation between the magnitude of the bathochromic shift and the rigidity of the various bridged adducts. In polar solvents, the lone pair of electrons on the two nitrogen atoms form a hydrogen bond with the solvent, and no bathochromic shift is observed. To investigate further the difference in the ultraviolet behavior between the bridged and nonbridged adducts, the endocyclic double bond of adducts **14′**, **16**, and **17** were hydrogenated to give **21**, **22**, and **23**, respectively.



21



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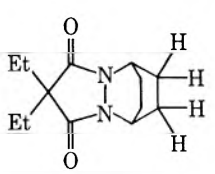

23

Table IV summarizes the ultraviolet spectral data of compounds **14′**, **16**, **17**, **21**, **22**, and **23** in both cyclohexane and 95% ethanol. From the table it can be seen that in a given solvent system, the nonbridged adduct shows little or no change in wavelength on saturation of the endocyclic double bond. However, the bridged adducts show a significant increase in wavelength on saturation, with the increase being proportional to the rigidity of the adduct. It is apparent that an interaction between the endocyclic double bond and the two nitrogen atoms stabilizes the ground state of the bridged adducts. It should also be noted that the solvent effect on **21**, **22**, and **23** is proportional to the rigidity of the compound.

TABLE IV

Compd	$\lambda_{max}^{cyclohexane}$, mμ (ε)	$\lambda_{max}^{95\%\ ethanol}$, mμ (ε)
14′	256 (2040)	257 (2250)
21	256 (2520)	258 (2570)
17	268 (3900)	256 (4520)
23	270 (2780)	264 (3600)
16	269 (3030)	254 (4150)
22	277 (2140)	266 (2420)

The high stability and reactivity of **2** at 0°, in addition to the fact that it is readily available, make it an efficient reagent for obtaining derivatives of the pyrazolo[1,2-*a*]pyridazine ring system. An investigation of the chemistry of this ring system is currently in progress.

Experimental Section[13]

Synthesis of 4,4-Diethylpyrazolidine-3,5-dione (**1**).—A mixture of 86.4 g of diethyl diethylmalonate and 283 g of an 85% solution of hydrazine hydrate was heated at reflux for 8 days. The reaction mixture was distilled to dryness at atmospheric pressure. The first fraction, consisting mainly of ethanol, water, and a little hydrazine hydrate, was discarded, but the remaining distillate, consisting mainly of hydrazine hydrate plus a little unreacted ester, was saved for recycling in future preparations of **1**. The crude crystals of **1** were recrystallized from water to give 43.0 g (69%) of **1** as white crystals, mp 266–267° (lit.[14] mp 270°).

Oxidation of 1 with Nitrogen Tetroxide.—A mixture of 1.400 g (0.089 mol) of **1** and 10 g of anhydrous sodium sulfate in 100 ml of methylene chloride was oxidized with nitrogen tetroxide according to the procedure of Stickler and Pirkle.[11] A deep blue solution of 4,4-diethylpyrazoline-3,5-dione (**2**) was obtained. A 1-ml aliquot of the solution was transferred to a 100-ml volumetric flask and diluted to volume with cold methylene chloride: concn 8.9×10^{-4} *M*, visible λ_{max} (methylene chloride) 724 (ε 37), 680 (ε 111), 644 (ε 154), and 621 mμ (ε 139).

In a similar manner, 18.6 g (0.12 mol) of **1** was oxidized. The solvent was removed under reduced pressure at 0° to give **2** as a blue liquid. On warming to room temperature, the liquid decomposed with gas evolution. The decomposed mixture was dissolved in 100 ml of methylene chloride and washed twice with 100-ml portions of water. The aqueous washings were washed twice with 50-ml portions of methylene chloride, and these washings were added to the methylene chloride solution containing the non-water-soluble materials. To the aqueous solution was added 150 ml of 1 *M* lead diacetate trihydrate to precipitate 4.5 g (10.3%) of lead diethylmalonate (**9**).

The lead salt **9** was characterized as follows. A quantity of **9** weighing 6.2 g was dissolved in 90% acetic acid. Concentrated hydrochloric acid was added dropwise until no more lead chloride precipitated. The mixture was filtered and washed with water to give 3.5 g of lead chloride (56.5% lead in **9**). The acetic acid solution was distilled to dryness under reduced pressure, and the residue was sublimed three times to give pure diethylmalonic acid (**5**): mp 126–127° (lit.[15] mp 125°); nmr ($CDCl_3$) δ 2.36 (m,

(13) Melting points are corrected. Microanalyses were performed by Dr. Alfred Bernhardt, Mulheim, Germany. Infrared spectra were taken with a Perkin-Elmer Model 137 double-beam spectrophotometer. The nmr spectra were taken with a Varian Model A-60 using either carbon tetrachloride, deuterochloroform, or deuterium oxide as a solvent and tetramethylsilane as a reference standard. The ultraviolet spectra were taken with a Cary Model 14 Spectrophotometer.

(14) H. Ruhkopf, *Chem. Ber.*, **73B**, 820 (1940).

(15) N. A. Lange, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 1949, p 464.

2) 1.29 (t, 3); mol wt (potentiometric titration) 160; mp of *p*-nitrobenzyl ester, 91–91.5° (lit.[16] mp 91°).

A solution of the water-insoluble materials in 300 ml of methylene chloride was washed three times with 100-ml portions of 10% sodium bicarbonate. The bicarbonate washings were acidified with excess hydrochloric acid and back-extracted three times with methylene chloride. These latter methylene chloride extracts were dried (Na_2SO_4) and the solvent was removed to give 7.5 g (41.9%) of 1-(diethylcarboxyacetyl)-4,4-diethylpyrazolidine-3,5-dione (**4**). The crude acid was recrystallized from benzene–petroleum ether (low boiling) to give pure **4**: mp 180–181° dec; uv λ_{max} (95% ethanol) 255 mμ (ε 2100).

Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.57; H, 7.47; N, 9.40.

The methylene chloride containing the neutral component[17] was dried (Na_2SO_4) and the solvent was removed to give 4.5 g (26.8%) of 2,2,6,6-tetraethylpyrazolo[1,2-*a*]pyrazole-1,3,5,7-tetraone (**3**), which may be recrystallized from ethanol–water: mp 206–207.5°; uv λ_{max} (95% ethanol) 270 (ε 1000), 260 (ε 1100), and 233 mμ (ε 11,200); ir (Nujol) 1755 and 1786 cm^{-1} (ring C=O); nmr ($CDCl_3$) δ 1.96 (m, 8, CH_2C), and 0.96 (t, 12, CH_3C).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.87; H, 7.13; N, 10.13.

When **2** was prepared as above and allowed to decompose in its methylene chloride solution which had been neutralized with solid sodium bicarbonate, 7.4 g (50.0%) of **3**, 5.25 g (29.4%) of **4**, and 0.9 g (2.1%) of **5** was obtained. The same isolation procedure of the decomposition products as above was employed.

When the decomposition of **2** was allowed to proceed in its methylene chloride solution without neutralization, a 35% yield of diethylmalonic acid was obtained; also isolated was a little diethylacetic acid.

Sublimation of the acid **4** at 80° gave the decarboxylated product 1-(diethylacetyl)-4,4-diethylpyrazolidine-3,5-dione. Recrystallization from ethanol–water gave a pure sample of **7**: mp 113–113.5°; uv$_{max}$ (95% ethanol) 260 mμ (ε 3500; ir (Nujol) 3175 (N–H), 1755, and 1786 cm^{-1} (ring C=O); nmr ($CDCl_3$) δ 3.56 (m, 1, Et_2CHCO), 1.80 (m, 8, CH_2C), and 0.86 (t, 12, CH_3C).

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.40; H, 8.69; N, 11.02.

Reaction of 3 with Sodium Hydroxide.—To 25 ml of 10% sodium hydroxide at 40° was added 1.0 g (0.0036 mol) of **3** with stirring. All of compound **3** had gone into solution after 10 min. Acidification with hydrochloric acid caused the precipitation of 1.1 g (100%) of the dicarboxylic acid **5**, which was recrystallized from ethanol–water: mp 236–236.5°; uv λ_{max} (95% ethanol) 233 mμ (ε 4900); nmr (D_2O, Na salt) δ 2.19 (m, 8, CH_2C) and 1.24 (t, 12, CH_3C).

Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86. Found: C, 53.18; H, 7.70; N, 8.84.

Reaction of 3 with Dilute Hydrochloric Acid.—To 0.5 g (0.0018 mol) of **3** in 20 ml of 95% ethanol was added enough 3 *M* hydrochloric acid to give pH 1. The solution was allowed to stand at room temperature for 6 days. To the solution was added 50 ml of methylene chloride, after which it was washed twice with 25-ml portions of 5% sodium bicarbonate. The bicarbonate washings were acidified (HCl) and back-extracted twice with 25-ml portions of methylene chloride. The methylene chloride extracts were dried (Na_2SO_4) and the solvent was removed to give 0.35 g (66.0%) of the acid **4**, mp 176–182° dec.

Reaction of 3 with Water.—To 0.5 g (0.0018 mol) of **3** in 40 ml of 95% ethanol was added 5 ml of water, and the resulting solution was allowed to stand at room temperature for 5 days. To the solution was added 50 ml of methylene chloride, after which it was washed twice with 25-ml portions of 5% sodium bicarbonate. The bicarbonate washings were acidified (HCl) and back-extracted twice with 25-ml portions of methylene chloride. The methylene chloride extracts were dried (Na_2SO_4) and the solvent was removed to give 0.2 g (38%) of **4**, mp 179–181° dec.

Reaction of 4 with Acetic Anhydride.—To 2.1 g (0.007 mol) of the acid **4** in 50 ml of methylene chloride at room temperature was added 2.2 g of acetic anhydride with stirring. Stirring was continued for 3 days, after which the reaction mixture was filtered to remove a trace of the starting acid. The solvent was removed to give 1.9 g (97.0%) of **3**, mp 206–207.5°.

Reaction of 1 with Lead Tetraacetate.—To 18.6 g (0.12 mol) of the hydrazine **1** in 400 ml of methylene chloride was added 66 g (0.126 mol) of an 85% solution of lead tetraacetate with stirring. During the lead tetraacetate addition, a deep green color appeared. The reaction mixture was allowed to warm to room temperature, after which 2 days were required for the complete decomposition of **2** as evidenced by the absence of any green color. The reaction mixture was filtered, and the filtered solids were placed in 1 l. of water. The insoluble solids were filtered to give 10.3 g (1[illegible].9%) of the lead salt **9**.

The methylene chloride solution was washed twice with 150-ml portions of water and three times with 100 ml of 10% sodium bicarbonate. The bicarbonate washings were acidified to precipitate 3.5 g (14.7%) of **10**: mp 174–175°; uv λ_{max} (95% ethanol) 275 (ε 4100) and 219 mμ (ε 9000); ir (Nujol) 3260 (NH), 1748 (ester C=O), and 1700 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 2.52 (s, 3, CH_3CO) and 1.83 (m, 4, CH_2C).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.46; H, 6.98; N, 14.27.

The methylene chloride solution was dried (Na_2SO_4) and the solvent was removed to give a solid–liquid mixture. The mixture was dissolved in 25 ml of benzene, and an excess of petroleum ether was added to precipitate 3.4 g (20.0%) of **3**, mp 206–207.5°.

The benzene was removed under reduced pressure to give 5.5 g of a liquid mixture containing 1.8 g (5.9%) of 3,5-diacetoxy-4,4-diethylpyrazole (**11**) and 3.7 g (11.7%) of diacetoxy diethylmalonate (**13**), as shown by vpc data and elemental nitrogen analysis. The presence of **11** was confirmed by comparison of its properties with that of an authentic sample of **11** whose synthesis is described below. Three distillations gave an analytical sample of the dianhydride **13**: bp 96–96.5° (0.16 mm); $n^{24.5}D$ 1.4510; uv λ_{max} (95% ethanol) end absorption; nmr ($CDCl_3$) δ 2.05 (s, 6, CH_3C), 2.00 (m, 4, CH_2C), and 0.97 (m, 6, CH_3C); mol wt (vapor phase osmometry) 240.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 5418; H, 6.38.

The dianhydride **13** was further characterized as follows. To 2 drops of **13** on a watch glass was added 4 drops of acetic anhydride. The reaction mixture was mixed and heated on the steam bath for 10 min, and on cooling it solidified. The solidified product was washed with water, and to the washings were added a few drops of 1 *M* lead diacetate trihydrate. An immediate precipitate of the lead salt **9** appeared. The water-insoluble solid was found to be identical with acetanilide. A few drops of the dianhydride **13** were placed in 5 ml of 1 *M* lead diacetate trihydrate at room temperature. Partial conversion to the lead salt **9** had taken place after 72 hr.

Reaction of 1 with Acetic Anhydride.—To 9.3 g (0.06 mol) of **1** in 50 ml of methylene chloride at room temperature was added 10 ml of acetic anhydride with stirring. Stirring was continued for 3 days, after which the reaction mixture was filtered to give 7.8 g (65.6%) of **10**, mp 173–174°. The methylene chloride and excess acetic anhydride were removed by distillation. The residue was distilled to give 2.5 g (17.4%) of **11**, bp 88–98° (0.1 mm). Redistillation gave an analytical sample of **11** which solidified on standing: bp 86–88° (0.12 mm); mp 54–54.5°; uv λ_{max} (95% ethanol) 217 mμ (ε 9500); nmr ($CDCl_3$) δ 2.58 (s, 6, CH_3CO), 1.88 (m, 4, CH_2C), and 0.86 (t, 6, CH_3C). The solid **11** can be recrystallized from ethanol–water.

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.34; H, 6.41; N, 11.65.

General Procedure for the Diels–Alder Reactions (LTA Oxidation).—To a mixture of 0.04 mol of **1** and 0.04 mol of the 1,3-diene in 200 ml of methylene chloride at 0° was added 22.0 g (0.042 mol) of an 85% solution of LTA with stirring. Stirring was continued at 0° until the characteristic green color had faded. The reaction mixture was filtered and washed with 100 ml of water and two 100-ml portions of 10% sodium bicarbonate solution. The methylene chloride solution was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude Diels–Alder adduct. Purification was accomplished by recrystallization, sublimation, or distillation.

1,4-Dihydro-2,3-dimethyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (14′).—From a mixture of 0.12 mol each of 2,3-dimethyl-1,3-butadiene, **1**, and LTA was obtained 26.7 g (94.3%) of **13** after removal of the solvent and drying. Recrystallization

(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1964, p 313.

(17) Also obtained with the neutral component was a little bis(2-ethylhexyl)phthalate, which was identified by comparison of its ir and nmr spectra with that of an authentic sample. It was possibly leached out of the plasticized tubing employed in the oxidation of **1** by nitrogen tetroxide.

from water gave an analytical sample of **14'**: mp 107–108°; nmr (CCl_4) δ 3.86 (s, 4, bridgehead CH_2), 1.71 (m, 4, CH_2C), 1.78 (s, 6, CH_3), and 0.78 (t, 6, CH_3C).

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.93; H, 8.33; N, 12.02.

1,4-Dihydro-2-methyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (14).—From a mixture of 0.09 mol of isoprene and 0.06 mol each of **1** and LTA was obtained 8.4 g of a viscous liquid. Distillation gave a fraction, bp 110–125° (0.2 mm), yield 6.2 g (46.6%), of **14** which solidified on standing. Repeated sublimations gave **14** as white crystals: mp 58.5–60°; nmr (CCl_4) δ 5.58 (s, 1, vinylic H), 3.93 (s, 4 bridgehead CH_2), 1.71 (m, 4, CH_2C), 1.86 (s, 3, allylic CH_3C), and 0.79 (t, 6, CH_3C).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.70; H, 8.14; N, 12.48.

1,4-Dihydro-1,4-diphenyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (15).—From a mixture of 0.02 mol each of 1,4-diphenyl-1,3-butadiene, **1**, and LTA was obtained **15** as a crude solid which was washed with petroleum ether and recrystallized from 95% ethanol to give 3.8 g (51.9%) of pure **15**: mp 147–148°; nmr ($CDCl_3$) δ 7.41 (m, 10, aromatic H), 5.93 (d, 2, vinylic H), 5.61 (d, 2, bridgehead H), 1.60 (m, 4, CH_2C), 0.88 (t, 3, CH_3C), and 0.33 (t, 3, CH_3C).

Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.85; H, 6.80; N, 7.65.

1,4-Dihydro-1,4-methanol-7,7-diethylpyrazolo[1,2-]pyridazine-6,8(7H)-dione (16).—From a mixture of 0.08 mol each of 1,3-cyclopentadiene, **1**, and LTA was obtained a viscous liquid. Distillation gave a fraction, bp 120–140° (0.2 mm), yield 6.9 g (40.0%), of **16** which solidified on standing. Sublimation gave a pure sample of **16**: mp 76–77°; nmr (CCl_4) δ 6.50 (m, 2, vinylic H), 5.20 (m, 2, bridgehead H), 2.07 (m, 2, bridging CH_2), 1.70 (m, 4, CH_2), 0.98 (m, 3, CH_3C), and 0.66 (t, 3, CH_3C).

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.33; H, 7.13; N, 12.61.

1,4-Dihydro-1,4-ethanol-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (17).—From a mixture of 0.08 mol each of 1,3-cyclohexadiene, **1**, and LTA was obtained 21.4 g (76.1%) of **17** after washing with petroleum ether and drying. Sublimation at 0.1 mm pressure gave an analytical sample of **17**: mp 105–106°; nmr (CCl_4) δ 6.55 (m, 2, vinylic H), 5.03 (m, 2, bridgehead H), 1.60 (m, 8, CH_2C), 0.89 (t, 3, CH_3C), and 0.61 (t, 3, CH_3C).

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.83; H, 7.87; N, 11.77.

1,4-Dihydro-1,4-(1-isopropylethano)-3-methyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (18).—From a mixture of 0.12 mol each of α-phellandrene, **1**, and LTA was obtained 22.5 g of a liquid. Distillation gave a fraction, bp 141–143° (0.2 mm), yield 14.4 g (41.4%), of **18**. Redistillation gave an analytical sample of **18**: $n^{23}D$ 1.5071; nmr (CCl_4) δ 6.01 (m, 1, vinylic H), 4.85 (m, 2, bridgehead H), 1.93 (s, 3, allylic CH_3) 1.90 [s, 1, $(CH_3)_2CH$)], 1.6 (m, 4, CH_2C), 1.2–0.8 [m, 9, $(CH_3)CH$ and CH_3CH_2], and 0.60 (t, 3, CH_3-CH_2).

Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.21; H, 9.17; N, 9.54.

1,6-Etheno-1,2,3,4,5,6-hexahydro-9,9-diethylpyrazolo[1,2-*a*]-[1,2]diazocine-8,10(9H)-dione (19).—From a mixture of 0.06 mol each of 1,3-cyclooctadiene, **1**, and LTA was obtained 4.8 g of a liquid. After the liquid was allowed to stand for 3 months, a quantity of crystals appeared. These crystals were filtered and dried to yield 3.3 g (21.0%) of **19**. Sublimation gave an analytical sample of **19**: mp 134–136°; nmr ($CDCl_3$) δ 6.13 (m, 2, vinylic H), 0.97 (t, 3, CH_3C), and 0.80 (t, 3, CH_3C).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.56; H, 8.16; N, 10.82.

5,10-*o*-Benzo-5,10-dihydro-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (20).—From a mixture of 0.02 mol each of anthracene, **1**, and LTA was obtained a solid residue. The residue was washed with methanol and filtered to give 2.3 g of anthracene (63.9% recovery). The filtrate was evaporated under reduced pressure and the residue was sublimed to give 0.9 g of **20** (13.6%) which contained a trace of anthracene. Preparative thin layer chromatography (Mallinckrodt Chromosorb Ar Sheet 1000) gave an analytical sample of **20**: mp 222–224° dec; nmr ($CDCl_3$) δ 7.28 (m, 8, aromatic H), 6.41 (s, 2, bridgehead H), 1.61 (m, 4, CH_2C), and 0.38 (t, 6, CH_3C).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.90; H, 6.06; N, 8.43. Found: C, 75.83; H, 6.21; N, 8.32.

1,4-Dihydro-2,3-dimethyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (13) (Nitrogen Tetroxide Oxidation).—To a mixture of 0.02 mol of **1** and 20 g of anhydrous sodium sulfate in 150 ml of methylene chloride at 0° was added gaseous nitrogen dioxide with stirring until all of the hydrazide **1** had dissolved. The reaction mixture was neutralized by the addition of 35 g of sodium bicarbonate and filtered into a stirred solution of 0.03 mol of 2,3-dimethyl-1,3-butadiene in 50 ml of methylene chloride at 0°. The resulting solution was stirred at 0° until the characteristic color of **2** had faded. The solution was filtered, and the solvent was evaporated under reduced pressure to give 2.6 g (55.3%) of **13**.

1,4-Dihydro-1,4-methano-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (16) (Nitrogen Tetroxide Oxidation).—To a mixture of 0.04 mol of **1** and 30 g of anhydrous sodium sulfate in 200 ml of methylene chloride at 0° was added gaseous nitrogen dioxide with stirring until all of the hydrazide **1** has dissolved. The reaction mixture was neutralized with 50 g of sodium bicarbonate and filtered into a stirred solution of 0.06 mol of freshly distilled cyclopentadiene in 50 ml of methylene chloride at 0°. The resulting solution was stirred at 0° until the characteristic color of **2** had faded. The solution was filtered and the solvent was evaporated under reduced pressure to give a dark liquid. The liquid was distilled to give a fraction, bp 135–148° (0.75 mm), yield 1.4 g (15.9%), of **16**.

Attempted Preparation of 1,10,4-ethylidene-7,7-diethyl-1,2,3,4-tetrahydropyrazolo[1,2-*a*]cyclopropa[*d*]pyridazine-6,8(7H)-dione. LTA Oxidation.—From a mixture of 0.1 mol each of norbornadiene, **1**, and LTA was obtained a 11.5-g mixture of the oxidized diene,[15] bp 94–114° (0.6 mm), and 1.9 g of **3**.

Nitrogen Tetroxide Oxidation.—To 0.04 mol of **1** and 40 g of anhydrous sodium sulfate in 20 ml of methylene chloride at 0° was added gaseous nitrogen dioxide with stirring until all of the hydrazide **1** had dissolved. The reaction mixture was neutralized with 50 g of sodium bicarbonate and filtered into a solution of 0.06 mol of norbornadiene in 50 ml of methylene chloride at 0°. The resulting solution was stirred at 0° until the characteristic color of **2** had faded (2 weeks). The solution was filtered and the solvent was evaporated under reduced pressure to give 2.0 g of **3** plus polymeric material.

***cis-endo*-2,3-Dimethyl-1,2,3,4-tetrahydro-7,7-diethylpyrazolo-[1,2-*a*]pyridazine-6,8(7H)-dione (21).**—To a slurry of 0.1 g of 5% palladium on carbon in 25 ml of 95% ethanol was added a solution of 2.44 g (0.01 mol) of **13** in 25 ml of 95% ethanol. The slurry was stirred under hydrogen at 25° and 1 atm until the theoretical amount of hydrogen had been absorbed (14 hr). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give 2.3 g (96.6%) of **21** as a viscous oil. Evaporative distillation gave pure **21**: nmr ($CDCl_3$) δ 3.48 (d, 4, NCH_2), 2.18 (m, 4, CH_2), 1.02 (d, 6, CH_3C), and 0.80 (t, 6, CH_3CH_2).

Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75. Found: C, 65.48; H, 9.04; N, 11.89.

1,4-Methano-1,2,3,4-tetrahydro-7,7-diethylpyrazolo[1,2-*a*]-pyridazine-6,8(7H)-dione (22).—To a slurry of 0.1 g of 5% palladium on carbon in 25 ml of 95% ethanol was added a solution of 1.74 g (0.0079 mol) of **16** in 25 ml of 95% ethanol. The slurry was stirred under hydrogen at 25° and 1 atm until the theoretical amount of hydrogen had been absorbed (30 min). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give 1.60 g (91.4%) of **27** as a viscous oil. Evaporative distillation gave pure **22**: nmr ($CDCl_3$) δ 4.83 (s, 2, bridgehead H), 1.5–2.0 (m, 10), and 0.93 (t, 6, CH_3CH_2).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.86; H, 8.16; N, 12.60. Found: C, 64.67; H, 8.13; N, 12.65.

1,4-Ethanol-1,2,3,4-tetrahyro-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (23).—To a slurry of 0.1 g of 5% palladium on carbon in 25 ml of 95% ethanol was added a solution of 1.0 g (0.0043 mol) of **17** in 25 ml of 95% ethanol. The slurry was stirred under hydrogen at 25° and 1 atm until the theoretical amount of hydrogen had been absorbed (30 min). The catalyst was evaporated under reduced pressure to give 0.95 g (94.1%) of **23** as a white solid. Sublimation gave pure **23**: mp 98–98.5°; nmr ($CDCl_3$) δ 4.50 (s, 2, bridgehead H), 1.97 (s, 8, ethanol H), 1.77 (m, 4, CH_3CH_2), and 0.86 (t, CH_3CH).

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.28; H, 8.30; N, 12.05.

Registry No.—**1**, 4744-72-3; **2**, 21367-52-2; **3**, 6495-34-7; **4**, 21367-54-4; **5**, 510-20-3; **7**, 21367-56-6; **10**, 21367-57-7; **11**, 21367-58-8; **13**, 21367-59-9; **14**,

21367-60-2; **15**, 21367-61-3; **16**, 21367-62-4; **17**, 21367-63-5; **18**, 21367-64-6; **19**, 21367-65-7; **20**, 21367-66-8; **21**, 21449-60-5; **22**, 21367-67-9; **23**, 21367-68-0; 1-(diethylacetyl)-4-4-diethylpyrazolidine-3,5-dione, 21367-56-6.

Acknowledgment.—The authors wish to acknowledge the assistance of the National Science Foundation in providing for departmental use a Cary 14 spectrophotometer, upon which all ultraviolet spectra were taken.

Notes

The Condensation of Succinic Anhydride with Benzylidinemethylamine. A Stereoselective Synthesis of *trans*- and *cis*-1-Methyl-4-carboxy-5-phenyl-2-pyrrolidinone

NEAL CASTAGNOLI, JR.

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco Medical Center, San Francisco, California 94122

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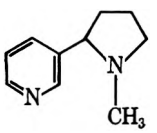
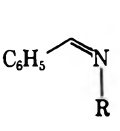
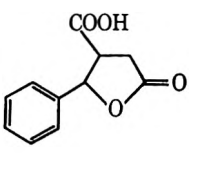
Our interest in examining structural parameters associated with the peripheral and central activities of the tobacco alkaloid nicotine (**1**) has led to a consideration of potentially versatile synthetic routes to substituted 2-arylpyrrolidines. As part of this program, we wish to report our studies on the condensation of benzylidinemethylamine (**2**) with succinic anhydride. By analogy with the Perkin condensation[1] of benzaldehyde and succinic anhydride to form the phenylparaconic acid (**3**), this reaction would be expected to yield the carboxypyrrolidinone system (**4**) and thus provide a facile entry to uniquely substituted nicotine analogs.



1



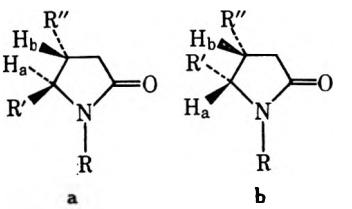
2, R = CH_3
12, R = C_6H_5



3

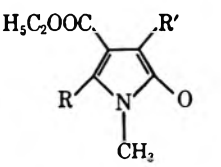
The spectral data of the crude isolate obtained from this reaction corresponded to the lactam system, **4**. Fractional crystallization separated the reaction product into two $C_{12}H_{13}NO_3$ acids, A (major) and B (minor). The nmr spectra of the two isomers can be readily interpreted in terms of the *trans*- and *cis*-carboxypyrrolidinones, **4a** and **4b**, respectively. A doublet centered near 5.0 ppm in both spectra is attributed to proton H_a based on its coupling with H_b and by analogy with the corresponding assignments reported for related 5-substituted-2-pyrrolidinones.[2] From the estimated dihedral angles, H_{a-b} (120°, *trans* isomer, and 0°, *cis* isomer), and the Karplus relationship,[3] the coupling constants, J_{a-b} (5 Hz, isomer A, and 9 Hz, isomer B) support the assignments of compound A as the *trans* isomer, **4a**, and compound B as the *cis* isomer, **4b**. Similar stereochemical conclusions were recently reported for the related 4-aryl-5-ethoxycarbonyl-2-pyrrolidinone system, **5**.[2b,c] Protons $H_{b,c,d}$ of **4a** form a complex multiplet centered near 3.4 ppm while the corresponding signals for **4b** are separated into three quartets; the lowest field quartet (3.85 ppm) can be assigned to H_b since irradiation of the low field doublet (due to H_a) caused the quartet to collapse to a triplet (J = 9 Hz).

Confirmation of the above structure assignments was obtained by an independent synthesis of the *cis* acid. The condensation[4] of diethyl oxalacetate with benzaldehyde and methylamine gave the pyrrolinone, **6**. Attempted borohydride and catalytic reductions of **6**

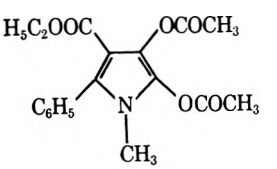


a **b**

4, R = CH_3; R′ = C_6H_5; R″ = COOH
5, R = H; R′ = $COOC_2H_5$; R″ = Aryl
8, R = CH_3; R′ = H; R″ = $COOC_2H_5$
11, R = CH_3; R′ = C_6H_5; R″ = $COOC_2H_5$
14, R = R′ = C_6H_5; R″ = COOH



6, R = C_6H_5; R′ = OH
7, R = H; R′ = $OCOCH_3$
9, R = C_6H_5; R′ = $OCOCH_3$



10

(1) M. Anteunis, *Bull. Soc. Chem. Belges.*, **69**, 356 (1960).

(2) (a) A. M. Duffield, H. Budzikiewicz, and Carl Djerassi, *J. Amer. Chem. Soc.*, **87**, 2026 (1965); (b) F. Zymalkowski and P. Pachaly, *Chem. Ber.*, **100**, 1137 (1967); (c) P. Pachaly, *ibid.*, **101**, 2176 (1968).

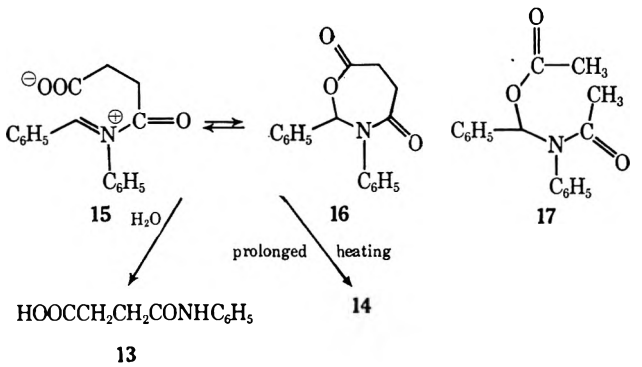
(3) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(4) J. R. Merchant and V. Srinivasan, *Rec. Trav. Chim. Pays-Bas*, **81**, 144 (1962).

afforded only unreacted starting material. The related enol acetate, **7**, has been reported to undergo catalytic reduction to the pyrrolidinone, **8**.[5] Therefore, overnight acetylation of **6** in acetic anhydride and pyridine was attempted. The product obtained was not the expected enol acetate, **9**, but rather a compound analyzing for a diacetate. The nmr spectrum revealed signals for two singlet methyl groups in addition to that of the N-methyl group. The only structure consistent with the above data is the pentasubstituted pyrrole, **10**, which presumably was formed by acetylation of the desired enol acetate. When the acetylation period was limited to 20 min, **9** was isolated in high yield and could be successfully reduced to one of the two possible isomeric esters, **11**. The nmr signals for the methyl and methylene protons of the ester function occurred at unusually high fields, 0.90 ppm and 3.68 ppm, respectively, indicating the *cis* configuration, **11b**, for the reduction product since, according to molecular models, these protons should be shielded by the aromatic cloud. As predicted also from molecular models, the corresponding signals of the *trans* ester, **11a**, prepared from **4a**, occurred at normal fields, 1.28 ppm for the methyl triplet and 4.22 ppm for the methylene quartet. Saponification of the ester isolated from the above reduction yielded an acid identical in all respects with the *cis* acid, **4b**, obtained from the succinic anhydride–benzylidinemethylamine condensation.

A review of the literature revealed that the condensation of succinic anhydride with benzylidineaniline (**12**) is reported to yield N-phenylsuccinamic acid (**13**).[6] However, when subjected to the reaction conditions employed in our study, a mixture of the isomeric pyrrolidinones, **14**, was obtained from which the *trans* isomer, **14a**, was isolated in pure form. The structure of **14a** followed directly from its nmr spectrum which showed a doublet at 4.58 ppm characteristic of the C_5 methine proton.

These different experimental results can be rationalized by assuming a common intermediate, the charged species **15**, which would be stabilized by cyclization to the lactone, **16**. Such an intermediate might survive



mild conditions and subsequently undergo hydrolysis to the succinamic acid and benzaldehyde. However, when subjected to the prolonged heating used in our studies, this same intermediate could undergo rearrangement to form the pyrrolidinones. In support of this proposal is the report that benzylidineaniline (**12**) and acetic anhydride form the acetoxy derivative, **17**, which is analogous to the proposed cyclic intermediate, **16**.[7] Additionally, charged structures similar to **15** have been proposed for reaction products if imines and maleic anhydride.[8] Such a reaction pathway differs markedly from the mechanism commonly accepted for the Perkin condensation.[9] Further studies on this reaction are currently in progress.

Experimental Section[10]

***trans*- and *cis*-1-Methyl-4-carboxy-5-phenyl-2-pyrrolidinones (4a and 4b).**—Benzylidinemethylamine[11] (11.9 g, 100 mmol), bp 102° (30 mm), nmr δ 3.45 ppm d (J = 1.5 Hz, NCH_3), 8.37 q (J = 1.5, $NCHC_6H_5$), and succinic anhydride (11.0 g, 100 mmol) were heated at reflux in 200 ml of anhydrous benzene for 36 hr. The slightly yellow reaction mixture was extracted with aqueous bicarbonate; the combined extracts were washed with benzene and hexane and then filtered. Upon acidification with phosphoric acid to pH 2 an oil separated which crystallized slowly on standing at 5° to give 16.3 g (71.2%) of crude product melting at 108–185°. Concentration of the aqueous layer to $^1/_2$ its original volume yielded an additional 2.4 g. The over-all yield of the mixture of acids was 18.7 g (82.5%).

Crystallization of the crude acid (10.0 g) from acetone gave 1.6 g of the *cis* acid, **4b**, which after recrystallization from acetone was analytically pure: mp 244–245°; ir (Nujol) 3300–2500 cm^{-1} (OH), 1740 (carboxyl C=O), 1660 (lactam C=O); nmr (deuteriopyridine) δ 2.72 ppm q (J = 9 Hz, C_3H), 2.72 s (NCH_3), 3.43 q (J = 9, C_3H), 3.85 q (J = 9, H_b), 4.97 d (J = 9, H_a), 7.30 m (C_6H_5).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.98; N, 6.39; NE, 219. Found: C, 65.64; H, 5.90; N, 6.45; NE, 217.

The above mother liquors were concentrated to dryness and the residue crystallized twice from water to yield 5.2 g *trans* acid, **4a**: mp 127–128°; ir (Nujol) 3300–2500 cm^{-1} (OH), 1750 (carboxyl C=O), 1680 (lactam C=O); nmr (deuteriopyridine) δ 2.67 ppm s (NCH_3), 3.35 m (CH_2 + H_b), 5.09 d (J = 5, H_a), 7.38 m (C_6H_5).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.93; N, 6.39; NE, 219. Found: C, 65.51; H, 5.93; N, 6.31; NE, 218.

***trans*-1-Methyl-4-ethoxycarbonyl-5-phenyl-2-pyrrolidinone (11a).**—The *trans* acid (1.0 g, 4.56 mmol), absolute ethanol (50 ml), concentrated sulfuric acid (1.0 g), and molecular sieves (2.5 g) were stirred overnight at room temperature. The filtered reaction mixture in chloroform was washed with saturated aqueous bicarbonate and water; the chloroform was dried ($MgSO_4$) and concentrated. The residue was distilled to yield 0.9 g (80%) *trans* ester, **11a**, as a colorless oil: bp 120° (1.5 mm, short path); ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 1.28 ppm t (J = 7 Hz, CH_2CH_3), 2.70 s (NCH_3), 2.93 m (CH_2 + H_b), 4.22 q (J = 7, OCH_2CH_3), 4.81 d (J = 5, H_a), 7.39 m (C_6H_5).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.99; H, 6.82; N, 5.67.

5-Phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrrolin-2-one (6).—A mixture of benzaldehyde (10.6 g, 100 mmol), 40% aqueous methylamine (7.75 g, 100 mmol), and the sodium salt of diethyl

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(6) A. Ludwig and R. I. Georgescu, *Bul. Chim. Soc. Romane Chim.*, **39**, 41 (1937–1938).

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(8) J. van Alphen, *Rec. Trav. Chim. Pays-Bas*, **61**, 895 (1942).

(9) Y. Ogata and M. Tsuchida, *J. Org. Chem.*, **24**, 78 (1959).

(10) All reactions were performed under a nitrogen atmosphere and solvents were concentrated on a rotary evaporator under vacuum. Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Except where noted, infrared spectra were measured in chloroform solution with a Perkin-Elmer Model 337 spectrophotometer and ultraviolet spectra in 95% ethanol with a Cary Model 11 spectrophotometer. Nmr spectra were recorded in the Model A-60A Varian Associates spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard (TMS = 0.0 ppm). Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

(11) C. K. Ingold and C. W. Shoppe, *J. Chem. Soc.* 1199 (1929).

oxalacetate (21.0 g, 100 mmol) in 100 ml of ethanol was heated at reflux with stirring until solution was complete (about 30 min). The reaction mixture was then added to 1l. of water and the pH adjusted to 2 with dilute phosphoric acid to precipitate 20.0 g (76.7%) of crude product melting at 162–165°. Two recrystallizations from ethanol provided the pure pyrroline, **6**: mp 164–165°; ir 3430 cm^{-1} (OH), 1710 (lactam C=O), 1680 (ester C=O); uv 272 mμ shoulder (ε 10,900), 242 (ε 25,100); (10^{-3} *N* ethanolic NaOH) 307 mμ (ε 23,900), 229 (ε 20,900); nmr δ 1.11 ppm t (*J* = 7 Hz, CH_2CH_3), 2.82 s (NCH_3), 4.17 q (*J* = 7, OCH_2CH_3), 5.06 s ($NCHC_6H_5$), 7.32 m (C_6H_5), 8.50 b (OH, exchanges with D_2O).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.53; H, 5.64; N, 5.59.

1-Methyl-2,3-diacetoxy-4-ethoxycarbonyl-5-phenylpyrrole (10).—The hydroxypyrrolinone, **6** (13.1 g, 50 mmol), was stirred overnight at room temperature in 40 ml of acetic anhydride containing anhydrous pyridine (4.0 g, 50 mmol). The reaction mixture was concentrated and the residue dissolved in chloroform which was then washed twice with water. After drying ($MgSO_4$) and removing the solvent, a solid was obtained which was crystallized from benzene to give 12.0 g (70%) of the pyrrole, **10**: mp 122–124°; ir 1780 cm^{-1} (acetoxy C=O), 1710 (ester C=O), uv 273 mμ (ε 7000), 220 mμ shoulder (ε 16,400); nmr δ 1.00 ppm t (*J* = 6 Hz, CH_2CH_3), 2.40 s and 2.42 s ($COCH_3$), 3.97 q (*J* = 7, OCH_2CH_3), 7.30 s (C_6H_5).

Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found C, 61.84, 62.89; H, 5.56, 5.91; N, 4.12.

1-Methyl-3-acetoxy-4-ethoxycarbonyl-5-phenyl-3-pyrrolin-2-one (9).—Following the above procedure, only limiting the acetylation period to 20 min, the hydroxypyrrolinone, **6** (13.1 g, 50 mmol), was monoacetylated. The solid obtained after removing the chloroform was washed with ether to yield 14.7 g (97.5%) of crude enol acetate, **9**. Sublimation at 90° (0.05 mm) provided an analytical sample: mp 101–102°; ir 1790 cm^{-1} (acetoxy C=O), 1710 (ester C=O), 1670 (lactam C=O); uv, end absorption; nmr δ 1.10 ppm t (*J* = 7 Hz, CH_2CH_3), 2.32 s ($COCH_3$), 2.73 s (NCH_3), 4.08 m (OCH_2CH_3), 5.13 s ($NCHC_6H_5$), 7.30 m (C_6H_5).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.15; H, 5.99; N, 4.87.

***cis*-1-Methyl-4-ethoxycarbonyl-5-phenyl-2-pyrrolidone (11b).**—Enol acetate **9** (7.5 g, 25 mmol) in 50 ml of glacial acetic acid was hydrogenated at atmospheric pressure over 50 mg of PtO_2 for 15 hr. An additional 50 mg of catalyst was added and hydrogenation continued for 10 hr. The total hydrogen uptake was 40 mmol. Filtration and removal of the solvent gave, after washing with ether, 4.0 g (65%) of crude ester **11b**. Sublimation at 80° (0.05 mm) provided the analytical sample: mp 80–81°; ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 0.90 ppm t (*J* = 7 Hz, CH_2CH_3), 2.52 q (*J* = 9, C_3H), 3.11 q (*J* = 9, C_3H), 3.68 m (H_b + OCH_2CH_3), 4.81 d (*J* = 9, H_a), 7.20 m (C_6H_5).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.78; N, 5.64.

The above ester (2.0 g, 8.1 mmol) was heated at reflux in 25 ml of 5 *N* HCl containing 10 ml of dioxane. Removal of the solvent and crystallization of the residue from acetone gave 1.6 g (90%) of a solid identical in all respects with the *cis* acid **4b**.

***trans*-1,5-Diphenyl-4-carboxy-2-pyrrolidinone (14a).**—Following the procedure describing the preparation of **4**, benzylideneaniline (18.1 g, 100 mmol) and succinic anhydride (11.0 g, 100 mmol) were heated at reflux in 200 ml of benzene for 36 hr. Cooling and scratching induced crystallization and yielded 20.0 g (71.5%) of crude product melting at 120–158°. Three crystallizations from acetone gave the pure *trans* acid **14a**: mp 179–180° with softening at 166°; ir (Nujol) 2800–2500 cm^{-1} (OH), 1740 (carboxyl C=O), 1670 (lactam C=O); nmr δ 3.07 ppm m (CH_2 + H_b), 5.55 d (*J* = 4 Hz, H_a), 7.25 m (2 C_6H_5).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.63; H, 5.02; N, 4.91.

Registry No.—Succinic anhydride, 108-30-5; **2**, 622-29-7; **4a**, 20-178-20-5; **4b**, 20-178-21-6; **6**, 20-178-22-7; **9**, 20-178-23-8; **10**, 20-178-24-9; **11a**, 20-178-25-0; **11b**, 20-178-26-1; **14a**, 20-178-27-2.

N-Acylenamines from Oxazolines. A New Route to 2-Acetamidoglycals

WILMAR L. SALO[1] AND HEWITT G. FLETCHER, JR.

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare, Bethesda, Maryland 20014

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When acetylated with isopropenyl acetate in the presence of a trace of *p*-toluenesulfonic acid, the two epimeric aldoses, 2-acetamido-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-mannose, show sharply divergent behavior. The former gives a mixture of the anomeric 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-D-glucopyranoses, together with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose.[2] The latter, on the other hand, gives at least five products[3,4] and among these is 3,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-1,2-dideoxy-D-*crabino*-hex-1-enopyranose, obtained in 14% yield; partial deacetylation of this di-*N*-acylenamine gives 2-acetamido-D-glucal (**4**, 2-acetamido-1,2-dideoxy-D-*arabino*-hex-1-enopyranose), the first amino sugar related glycal to be encountered. It was unfortunate that a substance of such potential interest should be available in such low yield from a comparatively expensive aldose, and we now wish to report an alternative and novel synthesis of **4** which makes this unsaturated amino sugar much more readily accessible.

Ozazolines that are derived from 2-acylamino-2-deoxyaldoses, and in which C-1 and C-2 of the sugar moiety are part of the oxazoline ring, have been made by a variety of methods[5–9] and an investigation in this laboratory has recently shown that acetylated oxazolines (such as **1** and **3**) may be prepared quite conveniently by treatment of 2-acylamino-2-deoxyaldoses with a mixture of acetic anhydride and anhydrous zinc chloride.[10] We have now found that the acetylated oxazoline, **1**,[9,11] from 2-acetamido-2-deoxy-D-glucose, readily isomerizes when heated at 100° in tetramethylurea solution containing a trace of *p*-toluenesulfonic acid. Thin layer chromatography of the amorphous product revealed a compound which was unsaturated; on de-*O*-acetylation with sodium methoxide, it gave a crystalline product which proved to be 2-acetamido-D-glucal (**4**). That the immediate product of the isomerization, **2**, had not crystallized was not surprising, since an earlier attempt[3] to obtain this substance in crystalline form had failed. (See Scheme I.)

The acetylated oxazoline derived from 2-acetamido-2-deoxy-D-mannose (**3**)[9,10] also gave **2** and, after de-*O*-

(1) Staff Fellow, National Institutes of Health, 1967–1969.
(2) T. D. Inch and H. G. Fletcher, Jr., *J. Org. Chem.*, **31**, 1815 (1966).
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(4) N. Pravdić and H. G. Fletcher, Jr., *ibid.*, **32**, 1811 (1967).
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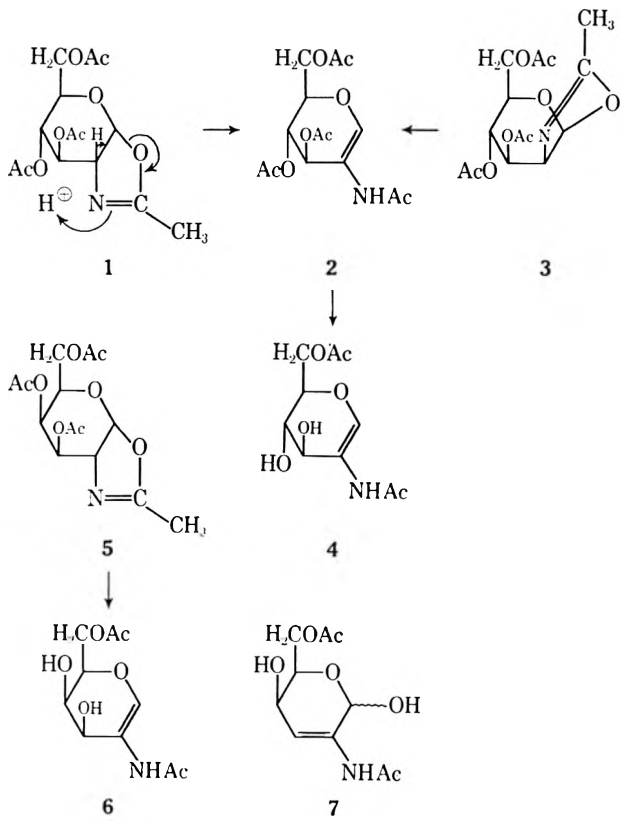
SCHEME I



acetylation, **4**.[12] The facile rearrangement of these two oxazolines in which a proton is lost from the 4 position of the heterocycle and the C-5–oxygen bond cleaves to give an *N*-acylenamine is, as far as we are aware, unique. However, owing to the special character of C-5 (which is also C-1 of an aldose) in oxazolines such as **1** and **3**, these heterocycles may be expected to differ considerably in their properties from those oxazolines in which C-5 of the heterocycle is attached to only one oxygen atom. It may be relevant to note that the proton at the 4 position of an aldofuranose-derived 2-phenyloxazoline has been found to be labile under alkaline conditions, the oxazoline undergoing an elimination to give an oxazole.[13] Mechanistic considerations aside, the rearrangement described here affords a practicable synthetic pathway for the preparation of 2-acetamido-D-glucal (**4**) from the relatively accessible 2-acetamido-2-deoxy-D-glucose. In addition, if the process is a general one, it should serve to make available isomeric 2-acetamidoglycals. To explore this possibility, we have heated 2-methyl(3′,4′,6′-tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyrano)[2′,1′:4,5]-2-oxazoline[10] (**5**) in tetramethylurea solution containing *p*-toluenesulfonic acid. De-*O*-acetylation of the initial product from the reaction gave a crystalline substance which proved to be identical with an unsaturated compound prepared earlier in this laboratory[14] through de-*O*-acetylation of one of the products from the action of isopropenyl acetate–*p*-toluenesulfonic acid on 2-acetamido-2-deoxy-D-galactose. Evidence obtained in the course of the earlier investigation was interpreted as indicating that this compound was 2-acetamido-2,3-dideoxy-D-*threo*-hex-2-enose (**7**). However, formation of the material from the oxazoline, **5**, strongly suggests that it is not **7** but the analog of **4**, namely, 2-acetamido-D-galactal (**6**). Independent evidence confirming this suggestion will be presented in a separate communication.[15]

(12) A transient brick-red color is formed when 2-acetamidoglycal derivatives on thin layer silica gel or paper are sprayed with 10% sulfuric acid. Dr. G. G. Ashwell of this institute informs us that thin layer chromatography of the crude product obtained through the action of acetic anhydride and zinc chloride on 2-acetamido-2-deoxy-D-mannose, followed by sulfuric acid spray, reveals a component which gives this red color. It is likely, therefore, that a derivative of **2** is formed as a by-product in the preparation of **3** by the method of ref 10.

(13) R. Gigg and C. D. Warren, *J. Chem. Soc., C*, 1903 (1968).

(14) N. Pravdić and H. G. Fletcher, Jr., *Croat. Chem. Acta*, **39**, 71 (1967).

Experimental Section[16]

2-Acetamido-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (4, 2-Acetamido-D-glucal). A. From 2-Methyl(3′,4′,6′-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2′,1′:4,5]-2-oxazoline (1).—The oxazoline (**1**) was prepared in 65% yield from 2-acetamido-2-deoxy-D-glucose by a modification[17] of the procedure described earlier:[10] $[\alpha]^{20}D$ 7.0° (*c* 0.99, chloroform), 0.45° (*c* 1.79, acetone); Khorlin and his coworkers[9] recorded $[\alpha]^{20}D$ 10° (chloroform). Although the material was syrupy, it was homogeneous when chromatographed on a thin layer of silica gel G_{254} (E. Merck, Darmstadt) using benzene–ether–methanol (14:14:1). One gram of **1** was dissolved in tetramethylurea (5 ml) which had been dried over molecular sieve, type 4-A (Fisher Scientific Co.), and the solution was passed through a column (3 × 5 cm) of molecular sieve, type 4-A, and directly into a dry flask containing a saturated solution of anhydrous *p*-toluenesulfonic acid in benzene (67 μl). The column was washed with an additional 28 ml of dry tetramethylurea which was allowed to run into the reaction mixture. The solution was heated at 100° (oil bath) and samples were removed periodically for examination. Each sample was freed of tetramethylurea *in vacuo* and then subjected to tlc on silica gel G_{254} using benzene–ether–methanol (14:14:1). The acetylated glycal was detected by fluorescein–bromine[3] or by spraying with 10% sulfuric acid, the latter reagent reacting with **2** to give a brick-red color. After 21 hr, virtually all of the **1** had disappeared and the reaction mixture then consisted of **2** and of another component whose chromatographic behavior suggested that it might be 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose, the normal hydrolytic product of **1**. The reaction mixture was cooled and then concentrated *in vacuo* (*ca.* 1-mm pressure) at 35° (bath) to give an amber-colored oil which was chromatographed on a column of silica gel (2.9 × 25 cm, no. 7734 of E. Merck) using benzene–ether–methanol (14:14:1) to yield **2**: 521 mg, 52% yield. A portion of the syrupy **2** was de-*O*-acetylated in conventional fashion with sodium methoxide to yield crystalline **4**, mp 124–125°; a mixture melting point with material prepared earlier from 2-acetamido-2-deoxy-D-mannose[3] was undepressed.

B. From 2-Methyl(3′,4′,6′-tri-*O*-acetyl-1,2-dideoxy-β-D-mannopyrano)[2,′1′:4,5]-2-oxazoline (3).—Crystalline **3** (470 mg), prepared in 11% yield from 2-acetamido-2-deoxy-D-mannose by a modification[17] of the method described earlier,[10] was treated exactly as described above for its D-*gluco* analog. After 6 hr, only a trace of **3** remained; removal of solvent and chromatography of the crude product gave **2**: 286 mg, 61%. De-*O*-acetylation afforded **4**, mp and mmp 124.5–125°.

2-Acetamido-1,2-dideoxy-D-*lyxo*-hex-1-enopyranose (6, 2-Acetamido-D-galactal) from 2-Methyl(3′,4′,6′-tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyrano)[2′,1′:4,5]-2-oxazoline (5).—The oxazoline, **5** (1 g), prepared as described by Pravdić, Inch, and Fletcher,[10] was treated exactly as described for the other two oxazolines (**1** and **3**) to yield a chromatographically homogeneous syrup (330 mg) which gave a red color when sprayed (tlc) with 10% sulfuric acid[12] and also gave a positive fluorescein–bromine test for unsaturation. De-*O*-acetylation of a sample of the syrup with sodium methoxide yielded, from 2-propanol, a crystalline compound of mp 152–153.5° and $[\alpha]^{20}D$ 83.2° (c 0.53, water). The nmr spectrum of this product was identical with that of a substance previously designated as 2-acetamido-2,3-dideoxy-D-*threo*-hex-2-enose (**7**)[14] and reported as having mp 152–153° and

(15) N. Pravdić and H. G. Fletcher, Jr., *ibid.*, in press.

(16) Melting points correspond to corrected values.

(17) E. Bach and H. G. Fletcher, Jr., unpublished results.

$[\alpha]^{20}D$ 76.1° (c 1.0, water); a mixture melting point was undepressed.

Registry No.—4, 10293-59-1; 7, 17327-17-2.

2-Cyclopropylpyridine

R. P. MARIELLA AND K. H. BROWN

Department of Chemistry, Loyola University, Chicago, Illinois 60626

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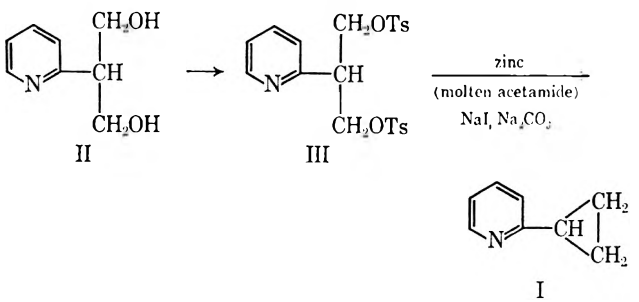
The synthesis of 2-cyclopropylpyridine (I) has previously been reported by one of us.[1] It had been prepared in small quantity in a six-step synthesis. The ultraviolet spectrum had been reported [λ_{max} 2690 Å (log ϵ 3.58)] in absolute alcohol. Although derivatives had been prepared, no analysis had been reported on I itself.[2]

In a recent publication,[3] Gray and Kraus cast doubt as to whether I had been obtained. Although they[3] did not actually prepare I, they did prepare 4-cyclopropylpyridine. Other data[4,5] seem to confirm the earlier report of Gray and Kraus.

It was felt that the unequivocal synthesis of I itself would be necessary to solve the dilemma. A new synthesis of I was achieved and is reported here. Commercially available II[6] was converted into III by standard procedures. Using a modification of the method of Dolbier,[7] III was readily converted into I in 80% yield of crude material. The product, I, was purified by preparative gc and was free from all detectable contamination.



Pure I had a λ_{max} of 2685 Å (log ϵ 3.60) in absolute alcohol. The ir spectrum (neat) and nmr spectrum were consistent with the structure assigned to I; the methinyl proton of the cyclopropyl ring appeared as the expected triplet of triplets at τ 7.8–8.3. A comparison of the spectra of I and cyclopropylbenzene[8] shows the close relation of the two compounds.

From the properties of this product, I, it is clear that the product reported previously was indeed impure. It is not possible to say what percentage of I was in the original product,[1] if indeed there was any, but the uv spectrum of I is essentially identical with that previously reported.

Attempts to prepare I from 2-vinylpyridine and methylene *via* the Simmons–Smith reaction[9] were uniformly unsuccessful.

Experimental Section

All melting points are corrected and were determined on a Fisher-Johns apparatus. Ir spectra were taken on a Beckman IR-4 spectrophotometer. Nmr spectra were taken on a Varian A-60-A instrument. Uv spectra were taken on a Cary 14 spectrophotometer. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Preparation of the Ditosylate of 2-(2-Pyridyl)-1,3-Propanediol (III).—2-(2-Pyridyl)-1,3-propanediol,[6] II (7.65 g, 0.05 mol), was dissolved in dry pyridine (125 ml) and cooled to 0–5°. *p*-Toluenesulfonyl chloride (38 g, 0.02 mol) was slowly added. The mixture was placed in a refrigerator overnight and then poured onto ice–water (700 ml) with stirring. The solid which came out of solution was crystallized from methyl alcohol, giving 15.0 g (65%) of white crystals: mp 106–107°; ir (KBr) 1175 cm^{-1} (tosylate);[10] nmr ($CDCl_3$) τ 1.50–2.67 (m, 12), 5.60 (d, 4), 7.00 (quintet, 1), 7.53 (s, 6).

Anal. Calcd for $C_{22}H_{23}NO_6S_2$: C, 57.23; H, 5.02; N, 3.04. Found: C, 57.22; H, 5.02; N, 3.09.

2-Cyclopropylpyridine (I).—A mixture of dry acetamide (40 g), sodium iodide (1 g), and sodium carbonate (3 g) was heated to 150° in a three-neck flask fitted with magnetic stirrer, thermometer, solid addition device,[11] and a Liebig condenser connected by tubing to a solution of calcium hydroxide. Powdered zinc (AR grade) (8 g, 0.06 mol) was added and the temperature was maintained at 150°. The ditosylate II (9.24 g, 0.02 mol) was slowly added (10 min) through the solid addition flask. Carbon dioxide, as expected, was evolved and formed calcium carbonate in the calcium hydroxide trap.[12] After 10 min, the condenser was removed and the apparatus was set up for distillation. The pot temperature was raised to 220° and a liquid began to distil at a head temperature of 150–180°. No cold water was used in the distilling condenser since acetamide (bp 222°, mp 82°) was distilling over with the product. The distillation was continued for 40 min. Water (50 ml) was added to the distillate, followed by ether (50 ml). The layers were separated and the ether layer was washed with water (three 25-ml portions), dried ($MgSO_4$), concentrated, and distilled, giving 2.0 g (83%) of crude 2-cyclopropylpyridine. The crude liquid was then purified by preparative gc on a dinonylphthalate column. The preparative gc gave a clear, colorless liquid (characteristic alkyl pyridine odor) free from all detectable contamination: bp 184–185° (758 mm), 31° (0.25 mm); $n^{25}D$ 1.5380; uv λ_{max} (100% ethanol) 268.5 mμ (log ϵ 3.60); ir (neat) 1030 and 1040 cm^{-1}; nmr (CCl_4) τ 2.70 (m, 4), 7.80–8.30 (3 triplets, 1), and 9.15 (m, 4).

Anal. Calcd for C_8H_9N: C, 80.67; H, 7.74; N, 11.76. Found: C, 80.75; H, 7.59; N, 11.69.

The picrate had mp 133–134°.

Anal. Calcd for $C_{14}H_{12}N_4O_7$: C, 48.28; H, 3.47. Found: C, 48.18; H, 3.50).

Registry No.—I, 20797-87-9; I (picrate), 20797-88-0; III, 20797-89-1.

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(6) Aldrich Chemicals, Milwaukee, Wis.

(7) W. R. Dolbier, Jr., *Tetrahedron Lett.*, No. 4, 393 (1968).

(8) See Varian Spectra Catalogue, Vol. 2, No. 528, 1963.

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(11) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath & Co., Boston, Mass., 1957, p 265.

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The Amine Addition Products of Pseudoascaridole

ALFONSE RUNQUIST, GARY PIERSON, AND OLAF RUNQUIST

Department of Chemistry, Hamline University, St. Paul, Minnesota 55101

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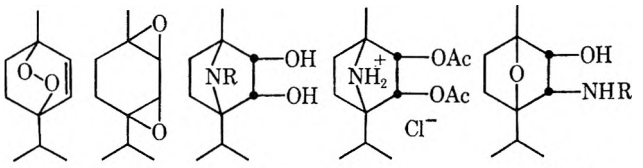
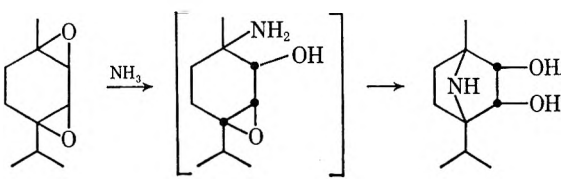
Ascaridole (**1**), the main constituent of chenopodium oil, undergoes thermal rearrangement to yield pseudoascaridole, an isomeric *cis*-diepoxide (**2**).[1] Thoms and Dobke[2] treated pseudoascaridole with aqueous ammonia and methylamine and assigned structures **5a** and **5b**, respectively, to the resulting products. This paper presents data indicating that the correct structures for these amino alcohols are represented by **3a** and **3b**. The



1 **2** **3a**, R = H; **b**, R = CH_3 **4** **5a**, R = H; **b**, R = CH_3

product resulting from the reaction of aqueous ammonia and pseudoascaridole (**3a**) was recovered unchanged after 5-hr reflux with 5% HCl. The infrared spectrum of **3a** showed the presence of two hydroxyl groups (two resolved strong peaks at 3230 and 3350 cm^{-1}) while the nmr spectrum showed two one-proton doublets at τ 6.30 and 6.45 with coupling constants of 9 ± 1 Hz. The position of these doublets is indicative of the CH(OH)-CH(OH) structure and the large J value confirms the *cis* configuration of the hydroxyls at C-2 and C-3. Treatment of **3a** with acetyl chloride gave the diacetate hydrochloride **4**. The infrared spectrum of the latter compound showed no absorption in the 3100–3700 cm^{-1} region but had a strong carbonyl band at 1730 cm^{-1}. The product resulting from the reaction of methylamine and pseudoascaridole, **3b**, had a strong peak in the infrared at 3400 cm^{-1} and two one-proton doublets at τ 6.17 and 6.51 with coupling constants of 8 ± 1 Hz.

The structures of the amine addition products can be rationalized by the following reactions which involve an initial attack of the amine at C-1 (or C-4) followed by an internal attack of nitrogen at C-4 (or C-1). While



the initial attack of nitrogen at a tertiary carbon seems unlikely on steric grounds, it is consistent with the observation that basic hydrolysis of **2** yields the all-*trans* *p*-menthane-1,2,3,4-tetrol (**6**).[1a]

Experimental Section[3]

Pseudoascaridole (**2**).—Ascaridole was isomerized according to the procedure described by Nelson.[4] The pseudoascaridole was purified by distillation; bp 70–73° (0.5 mm).

1,4-Imino-*p*-menthane-2,3-diol (**3a**).—Pseudoascaridole and 25% NH_4OH were heated at 125° in a sealed tube for 5 hr. The reaction mixture was extracted with ether. The ethereal solution was dried and concentrated to yield 1,4-imino-*p*-menthane-2,3-diol, mp 141°; nmr (8% $CDCl_3$) τ 6.30 (d, 1, J = 9 Hz), 6.45 (d, 1, J = 9 Hz), 7.9–8.3 (m, 5), 8.75 (s, 3), 9.0 (d, 3, J = 7 Hz), 9.1 (d, 3, J = 7 Hz), and a three-proton peak whose position was concentration dependent; ir (Nujol) 3230 and 3350 cm^{-1} (COH).

1,4-Imino-*p*-menthane-2,3-diacetoxy hydrochloride (**4**) was prepared by adding acetyl chloride to compound **3a**. Recrystallization of the crude product from chloroform–petroleum ether C afforded the hydrochloride, mp 237–238°; ir (Nujol) 1730 cm^{-1} (O=C—O), no absorption between 3700 and 3100 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_4NCl$: C, 54.98; H, 7.91. Found: C, 54.58; H, 7.84.

N-Methyl-1,4-imino-*p*-menthane-2,3-diol (**3b**).—A mixture of 16 g of pseudoascaridole and 13 g of absolute alcohol containing 4 g of methylamine was heated in a sealed tube at 125–130° for 12 hr.

The ethanol was removed by evaporation and the residue was recrystallized from petroleum ether C–chloroform to yield a white solid, mp 156.5–157.0°; nmr (8% $CDCl_3$) τ 6.17 (d, 1, J = 8 Hz), 6.51 (d, 1, J = 8 Hz), 7.5–8.7 (m, 5), 8.8 (s, 3), 9.00 (d, 3, J = 7 Hz) 9.02 (d, 3, J = 7 Hz), and a two-proton peak whose position was concentration dependent; ir (Nujol) 3400 cm^{-1} (COH).

Registry No.—**3a** 20797-85-7; **3b**, 20817-02-1; **4**, 20797-86-8.

Acknowledgment.—The support of this work by a research grant (E-3095) from the National Institute of Allergy and Infectious Diseases, Public Health Service, and a grant from the Louis W. and Maud Hill Family Foundation is gratefully acknowledged.

(1) (a) O. A. Runquist, Ph.D. Thesis, University of Minnesota, July 1956, pp 20–46; *Dissertation Abstr.*, **16**, 2313 (1956). (b) J. Boche and O. Runquist, *J. Org. Chem.*, **33**, 4285 (1968).

(2) H. Thoms and W. Dobke, *Arch. Pharm.*, **268**, 128 (1930).

(3) Melting points are uncorrected.

(4) E. K. Nelson, *J. Amer. Chem. Soc.*, **33**, 1404 (1911).

Knoevenagel Condensation in the Homophthalic Acid Series. A Synthesis of Zearalenone

N. N. GIROTRA AND N. L. WENDLER

Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Rahway, New Jersey 07065

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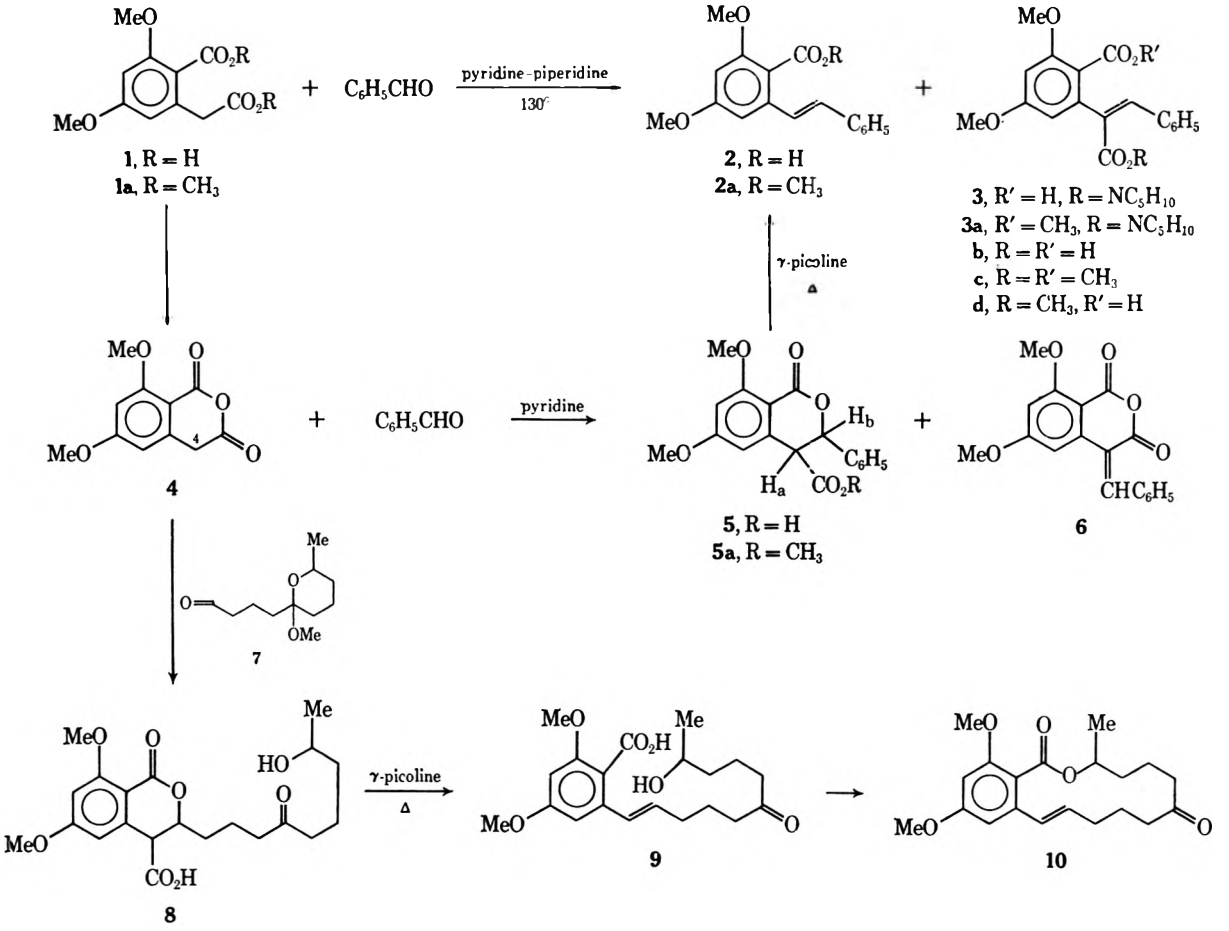
The homophthalic acid system is formally an aromatic analog of malonic acid and might consequently be expected to function in some measure in a Knoevenagel condensation with resultant loss of carbon dioxide and water.[1]

(1) For a recent review of the Knoevenagel reaction, see G. Jones, *Org. Reactions*, **15**, 204 (1967).



Benzaldehyde was observed to condense with 3,5-dimethoxyhomophthalic acid (**1**) in refluxing pyridine containing piperidine to yield the Knoevenagel product **2** as the major component together with a minor amount of aldolization product as its amide derivative **3**. In the absence of piperidine, the minor component formed appeared as the free diacid **3b**. Under the above conditions, the diester **1a** underwent little or no condensation.

By employing the anhydride **4** as the donor component together with benzaldehyde, condensation in pyridine occurred rapidly at room temperature. The inordinate lability of the C_4 protons of **4** was demonstrated by their rapid exchange with deuterium in pyridine–D_2O solution. The product from the condensation of **4** with benzaldehyde was largely a diastereoisomeric mixture of lactonic acids **5**. The latter could be decarboxylated in hot γ-picoline to produce the Knoevenagel product obtained from the diacid condensation, namely, **2**. Alternatively, esterification of **5** with diazomethane followed by hydrolysis with 1 equiv of alkali provided the half-ester **3d** related to the minor product in the diacid series.

Condensation of the anhydride **4** with γ-(2-methoxy-6-methyltetrahydropyran-2-yl)butyraldehyde (**7**) produced, in analogy with the benzaldehyde case, a crude mixture of lactonic acids[2] formulated as **8**. The latter, in hot γ-picoline, was converted to the known seco acid **9** derived from zearalenone, which in turn was converted to *dl*-zearalenone dimethyl ether **10** by trifluoroacetic anhydride in benzene.[3]

(2) For a preliminary account of this work, see N. N. Girotra and N. L. Wendler, *Chem. Ind.* (London), 1493 (1967).

Experimental Section

Reaction of 3,5-Dimethoxyhomophthalic Acid with Benzaldehyde. A. In Pyridine with Piperidine Catalysis.—A mixture of 0.841 g (0.0035 mol) of 3,5-dimethoxyhomophthalic acid[4] and 0.743 g (0.007 mol) of benzaldehyde in 1.4 ml of dry pyridine containing three drops of piperidine was heated at 80–90° for 1 hr and then at 125–130° for 17 hr in a nitrogen atmosphere. The cooled reaction mixture was made acidic with dilute hydrochloric acid and extracted with chloroform. The organic layer was extracted several times with 5% sodium bicarbonate, and the alkaline layers were combined, made acidic, and extracted with chloroform. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 0.851 g of gummy material. The latter, on standing in an acetone–ether mixture, deposited 0.202 g of crystalline **3**, recrystallized from methanol to mp 212–216°; ir (Nujol) 3.0–4.0, 5.84, 6.14 μ; λ_{max}^{MeOH} 277.5 mμ (ε 18,600).

Anal. Calcd for $C_{23}H_{25}O_5N$: N, 3.54. Found: N, 3.40.

Methyl Ester 3a was obtained by treatment of **3** with diazomethane; mp 147–149° (ether–petroleum ether, bp 30–60°); ir ($CHCl_3$) 5.84 and 6.15 μ; λ_{max}^{MeOH} 280 mμ (ε 20,200); nmr ($CDCl_3$) δ 1.01–1.75 (m, 6 H), 3.72, 3.78, 3.82 (each s, 3 OCH_3), 6.31, 6.48 (each br d, 2 H), 7.22 (s, 5 H), and 7.81 (s, 1 H). The signal due to the two methylenes adjacent to nitrogen of the piperidine moiety was partially obscured by the signals due to the methoxyl hydrogens.

Anal. Calcd for $C_{24}H_{27}O_5N$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.01; H, 6.58; N, 3.41.

A sample (0.607 g) of the noncrystalline residue from the isolation of **3** was chromatographed (dry column technique) on 50 g of silica gel H and eluted with chloroform–ethyl acetate–acetic

(3) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968).

(4) H. L. Slates, S. Weber, and N. L. Wendler, *Chimia*, 468 (1967).

acid (50:40:5). Initial fractions afforded a small amount of benzoic acid; succeeding fractions[5] on crystallization from ether–petroleum ether afforded 0.300 g of **2**, mp 121–123°; ir ($CHCl_3$) 2.8–4.1, 5.81, 5.91 (the two carbonyl bands due to monomeric and dimeric forms), 6.12, and 10.38 μ; λ_{max}^{MeOH} 300 (ε 27,900), 242.5 (ε 14,300), 232.5 (ε 16,400), and 225 (ε 18,000); nmr ($CDCl_3$) δ 3.88 (s, 2 OCH_3), 6.45, 6.81 (each d, J = *ca.* 2.5 cps, 2 H), 7.45 (br m, 7 H), and 10.85 (s, 1 H, exchanges with D_2O).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.01; H, 5.65.

Methyl ester 2a was obtained by treatment of the acid **2** with diazomethane; mp 74–76° (ether–petroleum ether); ir ($CHCl_3$) 5.81, 6.10, and 10.38 μ; uv λ_{max}^{MeOH} 299 (ε 27,900), 242.5 (ε 14,700), 232.5 (ε 16,300), and 218 mμ (ε 18,800); nmr ($CDCl_3$) δ 3.81, 3.85, 3.91 (each s, 3 OCH_3), 6.41, 6.78 (each d, J = 2 cps, 2 H), 7.08 (s, 2 H), and 7.38 (m, 5 H).

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.70; H, 5.81.

B. In Pyridine.—Treatment of 0.841 g of 3,5-dimethoxyhomophthalic acid with 0.743 g of benzaldehyde in 1.4 ml of dry pyridine under the conditions described above gave 0.794 g of sodium bicarbonate soluble material. Dry column chromatography of the latter on 75 g of silica gel H and elution with chloroform–ethyl acetate–acetic acid (55:50:5), followed by crystallization of pertinent fractions, gave (1) 0.360 g (ether–petroleum ether) of **2**, mp 121–123°, identical with material obtained by procedure A; and (2) 0.050 g of **3b**, mp 184–188° (acetone–hexane); ir (Nujol) 3.0–4.0, 5.86, 5.98, and 6.24 μ.

Dimethyl ester **3c** was obtained by treatment of **3b** with diazomethane; mp 136–137° (acetone–hexane); ir ($CHCl_3$) 5.82, 5.84, and 6.14 μ; uv λ_{max}^{MeOH} 280 mμ (ε 20,200); nmr ($CDCl_3$) δ 3.70, 3.72, 3.78, 3.89 (each s, 4 OCH_3), 6.28, 6.54 (each br d, J = *ca.* 2.5 cps, 2 H), 7.19 (br s, 5 H), and 7.81 (s, 1 H).

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.19; H, 5.53.

Reaction of 3,5-Dimethoxyhomophthalic Anhydride with Benzaldehyde.—To a mixture of 0.889 g of 3,5-dimethoxyhomophthalic anhydride[4] and 0.849 g of benzaldehyde was added 1.8 ml of dry pyridine. After stirring for 5 hr at room temperature, the reaction mixture was diluted with water and extracted with chloroform. The chloroform layer was in turn washed with dilute hydrochloric acid, saturated sodium bisulfite, and finally 5% sodium bicarbonate to give, after evaporation of the solvent, 0.108 g of neutral material. From the bicarbonate extract was obtained 1.034 g of acidic material. The neutral material, on three crystallizations from acetone–hexane, gave yellow **6**, mp 162–166°; ir ($CHCl_3$) 5.63 and 5.76 μ.

Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.47; H, 4.41.

Treatment of **6** with dilute sodium hydroxide furnished **3b**. Since the acidic material resisted purification either by crystallization or by dry column chromatography, a sample (0.325 g) recovered from chromatography was treated with excess diazomethane. The dry column chromatography of the resulting gummy material on 25 g of silica gel H and elution with chloroform–ethyl acetate (90:35) led to the isolation of 0.164 g of single-spot material which was a mixture of *trans* and *cis* isomers of **5a** in the ratio of *ca.* 65:35, respectively, as indicated by nmr. The signals due to hydrogens of methoxyl groups in the two isomers appeared very close to one another at δ 3.83, 3.86, 3.92, and 3.93. However, carbomethoxyl hydrogens in the *cis* and *trans* isomers gave well-separated signals at δ 3.45 and 3.67 in the ratio of 35:65, the former peak appearing at higher field due to the shielding effect of the *cis*-oriented monosubstituted phenyl group. Methine H_a exhibited a signal comprised of two doublets of unequal intensities at δ 4.04 (J = *ca.* 3.5 cps) and 4.22 (J = *ca.* 8.0 cps); the former was less intense and was ascribed to the *cis* isomer on the basis of small coupling constants, as expected from the dihedral angle between *cis* H_a and H_b. Further confirmation of the structures **5** and **5a** was obtained by the following two experiments.

Treatment of 5a with Aqueous Sodium Hydroxide.—A solution of 0.158 g of **5a** in 4.65 ml of 0.1 *N* sodium hydroxide and 10 ml of methanol was allowed to stand at room temperature, heated on a steam bath for 0.5 hr, and evaporated to remove methanol. The solution was extracted with ethyl acetate, made acidic with dilute hydrochloric acid, and extracted with chloroform to give 0.152 g of pratially crystalline acidic material which on crystallization twice from acetone–ether furnished 0.115 g of **3d**, mp 138–141°; ir ($CHCl_3$) 2.80–4.0 (br), 3.10, 5.80, 5.86, and 6.15 μ; λ_{max}^{MeOH} 279 mμ (ε 20,300); nmr ($CDCl_3$) δ 3.69, 3.73, 4.04 (each s, 3 OCH_3), 6.32, 6.58 (each br d, 2 H), 7.13 (m, 5 H), 7.78 (s, 1 H), and 9.97 (br, 1 H exchange with D_2O).

Anal. Calcd for $C_{17}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.37; H, 5.37.

Treatment of a small amount of **3d** in methanol with ethereal diazomethane furnished **3c**.

Treatment of 5 with γ-Picoline.—A solution of 0.150 g of crude **5** in 1 ml of γ-picoline was heated at *ca.* 145° for 8 hr under an atmosphere of nitrogen. After dilution with water, the cooled reaction mixture was acidified with dilute hydrochloric acid and extracted with 5% sodium bicarbonate to give, on acidification of the bicarbonate extract, 0.036 g of **2** (single spot), mp 121–123° (ether–petroleum ether).

γ-(2-Methoxy-5-methyltetrahydropyran-2-yl)butyraldehyde (7).—A slow stream of 3% ozone was passed through a solution of 3.966 g of 2-(pent-4-enyl)-2-methoxy-6-methyltetrahydropyran[3] in 50 ml of ethyl acetate at *ca.* −60° until the reaction mixture was saturated with ozone. The excess ozone was removed by a stream of nitrogen and the solution was added at room temperature to 0.792 g of 10% Pd–C and 0.792 g of 5% Pd–$CaCO_3$, presaturated with hydrogen, in 50 ml of ethyl acetate. The addition was accompanied by evolution of heat. The reaction mixture was cooled to room temperature and stirred in a hydrogen atmosphere for 1.5 hr. At the end of this time, a negative test for peroxide was registered. After removal of the catalyst by filtration, the filtrate was evaporated at room temperature; the residue was dissolved in petroleum ether, washed with 5% sodium bicarbonate, dried (Na_2SO_4), and evaporated to give 3.85 g of **7** as an oil, ir (film) 3.73 and 5.80 μ; nmr (CCl_4) δ 1.08 (d, J = 6.5 cps, CH_3–CH–), 3.13 (s, OCH_3), and 9.75 (t, HC=O). The nmr spectrum underwent a change within a short time, thus indicating the labile nature of the aldehyde, which, therefore, was used in the following experiment without further purification.

(±)-Zearalenone Dimethyl Ether (10).—A solution of 0.556 g of 3,5-dimethoxyhomophthalic anhydride (**4**) and 0.751 g of **7** in 5 ml of pyridine was stirred at room temperature for 4 hr. At the end of this period the reaction mixture was diluted with water, made acidic with dilute hydrochloric acid, and extracted with chloroform. The organic layer was extracted several times with 5% sodium bicarbonate. The alkaine extracts were made acidic and on extraction with chloroform furnished 0.474 g of crude amorphous material, ir ($CHCl_3$) 2.80–4.10, 5.84, and 6.23 μ; nmr ($CDCl_3$) δ 1.15, 1.22 (each d, J = *ca.* 6.5 cps, CH_3–CH–) (multiplicity of the signal changed to a doublet centered at δ 1.15 on addition of D_2O, possibly a consequence of the two forms of **8** as hydroxy ketone and hemiacetal forms), 3.87, 3.91 (each br s, 2 OCH_3), and 6.59 (aromatic H).

A solution of 0.200 g of crude **8** in 0.8 ml of γ-picoline was heated at 145–150° for 6 hr in an atmosphere of nitrogen. The cooled reaction mixture was diluted with water, made acidic with dilute hydrochloric acid, and extracted with chloroform. The chloroform layer was extracted with 5% sodium bicarbonate and the alkaline extract was acidified with dilute hydrochloric acid followed by extraction with chloroform to give 0.073 g of crude **9**. Tlc analysis of crude **9** showed a major spot corresponding to authentic **9**,[3] ir ($CHCl_3$) 2.80–4.30, 5.80, 5.88, and 10.31 μ.

To a stirred solution of 0.069 g of crude **9** in 20 ml of dry benzene at 10° was added 0.058 g of trifluoroacetic anhydride in 1 ml of dry benzene. After 2.5 hr, 5% sodium hydroxide was added until the reaction mixture was basic. The layers were separated, the alkaline layer was extracted with benzene, and the combined benzene layers were washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 0.031 g of gummy product. Preparative thin layer chromatography on silica gel ($CHCl_3$–acetone 95:5) followed by crystallization from ether–petroleum ether furnished 0.005 g of (±) **10**, mp 124–126°, undepressed on admixture with authentic (±) **10**.[3] The ir spectra of the product and of authentic ±**10** were identical.

Registry No.—**2**, 20797-93-7; **2a**, 20797-94-8; **3**, 20797-95-9; **3a**, 20797-96-0; **3b**, 20797-97-1; **3c**, 20797-98-2; **3d**, 20797-99-3; *cis* **5a**, 20798-00-9; *trans* **5a**, 20798-01-0; **6**, 20798-02-1; (±) **10**, 20798-09-8.

(5) Thin layer chromatography of some fractions indicated a spot of low intensity close to that of **2** which might be due to the *cis* isomer. However, no attempts were made to isolate it.

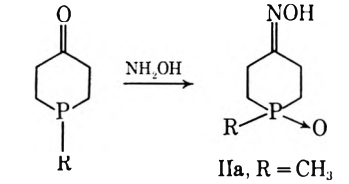
Oxidation of Tertiary Phosphines by Hydroxylamine[1]

MICHAEL D. MARTZ AND LOUIS D. QUIN[2]

Department of Chemistry, Duke University, Durham, North Carolina 27706

Received February 24, 1969

The oximes of phosphorinanones **1a** and **1b** were required as intermediates in the synthesis of the corresponding 4-aminophosphorinanes. However, the usual procedure[3] of treating ketone **1b** with hydroxylamine hydrochloride in aqueous sodium hydroxide or ethanol–pyridine (under nitrogen) failed to give the expected water-insoluble product. Since Ib had readily formed a thiosemicarbazone, no difficulty in oxime formation had been anticipated. The water-soluble, hygroscopic residue from evaporation of the ethanol–pyridine reaction medium was therefore further examined and found to be crystallizable from acetonitrile. The product proved to be the oxime of 1-ethyl-4-phosphorinanone-1-oxide (IIb), obtained in 65% yield. Its structure was evident from its elemental analysis as well as its spectral properties. Of particular significance was the ^{31}P nmr spectrum; this consisted of a broad singlet at −54 ppm (85% H_3PO_4 standard). This chemical shift is in the range characteristic of tertiary phosphine oxides;[4] the phosphines have positive values. Similar results were obtained with ketone Ia; only the oxime (IIa) of its 1-oxide could be isolated (25% yield).



Ia, R = CH_3
b, R = C_2H_5

IIa, R = CH_3
b, R = C_2H_5

Since considerable care had been exercised to prevent air oxidation of the phosphines, it appeared that hydroxylamine had been acting as the oxidizing agent, although to our knowledge it has not been previously used for this purpose. This possibility was explored by examining the behavior of two nonketonic tertiary phosphines toward hydroxylamine. Tri-*n*-butylphosphine was converted to its oxide in 66% yield after 2-hr reflux in ethanol, using conditions similar to those employed for oxime formation. Triphenylphosphine was less reactive, but after 16 hr of reflux in pyridine, a 75% yield of its oxide resulted. Presumably, the hydroxylamine is reduced to ammonia, although no effort was made to detect this product.

Many reagents are known to oxidize tertiary phosphines,[5] and the use of hydroxylamine for this purpose would appear to offer no special advantage. However, the occurrence of this reaction is worthy of note for two reasons. As in our experience, it can be a complication where trivalent phosphorous is present in a molecule undergoing reaction with hydroxylamine. Also, the transfer of oxygen from a system of general structure N–O–R to trivalent phosphorus is not common; one other example (conversion of a cyclic hydroxamide to a lactam) has very recently been reported.[6]

Experimental Section[7]

1-Ethyl-4-phosphorinanone Thiosemicarbazone.—To a mixture of 3.0 g (0.033 mol) of thiosemicarbazide and 3.0 g (0.021 mol) of 1-ethyl-4-phosphorinanone[8] (Ib) was added a solution of 6.0 g of sodium acetate in 30 ml of distilled water. The mixture was heated at 64–68° for 1.75 hr. After several hours, the crystalline material was filtered, washed three times with distilled water, and dried in a vacuum desiccator over solid potassium hydroxide and phosphorus pentoxide. The yield was 4.97 g (69.1%) of crude 1-ethyl-4-phosphorinanone thiosemicarbazone, mp 145–153° dec. After three recrystallizations, a sample had mp 153.5–154.5° dec.

Anal. Calcd for $C_8H_{16}N_3PS$: C, 44.22; H, 7.42; P, 14.50; S, 14.76. Found: C, 44.32; H, 7.56; P, 14.26; S, 15.02.

1-Ethyl-4-phosphorinanone 1-Oxide Oxime (IIb).—A mixture of 10.0 g (0.070 mol) of 1-ethyl-4-phosphorinanone (Ib), 10.0 g (0.14 mol) of hydroxylamine hydrochloride, 27 ml of pyridine, and 33 ml of absolute ethanol was refluxed under nitrogen for 1.75 hr. Most of the solvent was then removed on a rotary evaporator. The residue was extracted (under nitrogen) with 130 ml of boiling acetonitrile. The extract was concentrated to *ca.* 30 ml. Allowing the concentrate to stand at 7° for 1 day, and −10° for 1 day, yielded a crop of 6.06 g of oxime IIb, mp 180–182°. A second crop (1.86 g, mp 182–187°) was obtained from the mother liquor. The total yield was 7.92 g (65%). The oxime had ir bands (Nujol) at 3.15 (strong) and 3.25 μ (strong) for OH, 6.05 μ (weak) for C=N, 8.35 (medium) and 8.6 μ (strong, probably for free and hydrogen-bonded P→O). The ^1H nmr spectrum ($CDCl_3$) had a singlet (1 H) at δ 9.0 ppm, which exchanged with D_2O, and an envelope (13 H) at δ 0.96–3.3. The ^{31}P nmr (2 *M* D_2O) signal was located at −54 ppm. Two recrystallizations of a portion of IIb from acetonitrile gave an analytical sample, mp 190–193°.

Anal. Calcd for $C_7H_{14}NO_2P$: C, 48.00; H, 8.06; N, 7.99; P, 17.68. Found: C, 48.03; H, 8.03; N, 8.05; P, 17.70.

1-Methyl-4-phosphorinanone 1-Oxide Oxime (IIa).—A mixture of 5.00 g (0.038 mol) of 1-methyl-4-phosphorinanone[9] (Ia), 6.00 g (0.084 mol) of hydroxylamine hydrochloride, 14 ml of pyridine, and 14 ml of absolute ethanol was refluxed under nitrogen for 1.7 hr. Most of the solvent mixture was evaporated on a rotary evaporator. The residue was extracted with four 35-ml portions of boiling acetonitrile and two 25-ml portions of boiling 2-propanol. The filtered extracts were combined and the solvents were removed. The oily white residue was dried *in vacuo* over phosphorus pentoxide. This was dissolved in 95% ethanol; on addition of ethyl acetate a small amount of an oily solid precipitated and was discarded. The solvents of the filtrate were evaporated and the residue was dried in a vacuum oven at 70° to give 2.87 g of a brown solid. Recrystallization from acetonitrile yielded 1.54 g (25%) of 1-methyl-4-phosphorinanone 1-oxide oxime (IIa), mp 145–160°. Its ir spectrum (nujol) had peaks at

(1) This work performed under Contract DA-49-193-N10-2984, U. S. Army Medical Research and Development Command.

(2) To whom inquiries may be addressed.

(3) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1964, p 289.

(4) V. Mark, C. H. Dungan, M. M. Crutchfield, and J. R. Van Wazer in "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, p 284.

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(6) D. Döpp, *Chem. Commun*, 1284 (1968).

(7) All reactions were performed in a nitrogen atmosphere. Solvents were degassed with nitrogen before use. Melting points were taken with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer. Proton nmr spectra were recorded with a Varian Associates Model A-60 spectrometer using TMS as an internal standard in $CDCl_3$, and as an external standard in D_2O. ^{31}P nmr spectra were obtained with a Varian Associates Model HR-60 spectrometer using 85% H_3PO_4 as an external standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(8) R. P. Welcher, G. A. Johnson, and V. P. Wystrach, *J. Amer. Chem. Soc.*, **82**, 4437 (1960).

(9) H. E. Shook, Jr., and L. D. Quin, *ibid.*, **89**, 1841 (1967).

6.05 μ (weak, C=N) and 8.35 and 8.85 μ. Five recrystallizations from acetonitrile gave an analytical sample, mp 175–183°, whose ^{1}H nmr spectrum (D_2O) contained peaks at δ 2.3–3.6 (m, 8 H, CH_2) and 2.15 (d, 3 H, J_{PH} = 13 Hz, P-CH_3).

Anal. Calcd for $C_6H_{12}NO_2P$: C, 44.72; H, 7.60; N, 8.69; P, 19.22. Found: C, 44.56; H, 7.43; N, 8.52; P, 18.96.

Reaction of Tri-*n*-butylphosphine with Hydroxylamine.—A mixture of 10 ml of absolute ethanol, 1.0 g (0.014 mol) of hydroxylamine hydrochloride, and 1.3 ml (1.1 g, 0.0055 mol) of tri-*n*-butylphosphine was refluxed for 2 hr. The mixture was filtered under nitrogen and the filtrate was poured into saturated ammonium chloride solution. The mixture was extracted with two 25-ml portions of tetrahydrofuran. The combined extracts were washed with saturated sodium chloride solution and dried over sodium sulfate under nitrogen. The solvent was evaporated and the residue was dried *in vacuo* over phosphorus pentoxide to give 0.78 g (66%) of tri-*n*-butylphosphine oxide. The sample contained an ir peak (Nujol) at 8.65 μ for P→O; its ^{31}P nmr peak (5 *M* in tetrahydrofuran) was at −42.7 ppm (lit.[4] −43.2, −45.8 ppm).

This reaction was repeated using a 1:1 (*v*/*v*) pyridine–absolute ethanol solution. Work-up afforded a 50% yield, bp 126–130° (0.8 mm) [lit.[10] bp 300° (760 mm)].

Reaction of Triphenylphosphine with Hydroxylamine.—A mixture of 10.0 g (0.038 mol) of triphenylphosphine, 2.72 g (0.038 mol) of hydroxylamine hydrochloride, and 60 ml of pyridine was refluxed under nitrogen for 16 hr. The mixture was cooled and poured into 125 ml of saturated ammonium chloride solution. The two-phase mixture that formed was extracted with two 60-ml portions of benzene. The aqueous layer was filtered and extracted with a third 60-ml portion of benzene. The combined extracts were dried over sodium sulfate, and the solvent was removed to give 8.0 g (75%) of crude triphenylphosphine oxide, mp 151–159°, ^{31}P nmr signal (5.5 *M* in $CDCl_3$) at −27.6 ppm (lit.[4] −23.0 to −27.0 ppm). After recrystallization from benzene–cyclohexane, it melted at 158–161° (lit.[11] mp 156°).

Registry No.—Hydroxylamine, 7803-49-8; Ib thiosemicarbazone, 20817-03-2; IIa, 20797-90-4; IIb, 20797-91-5; tri-*n*-butylphosphine, 998-40-3; triphenylphosphine, 603-35-0.

Acknowledgment.—We are indebted to Stephen W. Dale for the ^{31}P nmr spectra.

(10) W. C. Davies and W. J. Jones, *J. Chem. Soc.*, 33 (1929).

(11) "Handbook of Chemistry and Physics," 45th ed, Chemical Rubber Co., Cleveland, Ohio, 1964, p C-473.

A Study of Some Substituted Cycloheptatrienecarboxylic Acids by Nuclear Magnetic Resonance Spectroscopy

STEPHEN HANESSIAN[1] AND GÜNTHER SCHÜTZE[2]

Department of Chemistry, University of Montreal, Montreal, Quebec, Canada, and Research Laboratories, Parke, Davis & Co., Ann Arbor, Michigan 48105

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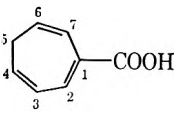
The thermal decomposition of ethyl diazoacetate in the presence of aromatic hydrocarbons, originally reported in 1885 by Buchner and Curtius,[3,4] constitutes one of the more direct preparative routes to cycloheptatriene derivatives. Since the pioneering work of Doering and his coworkers,[5,6] who were the first to recognize the existence of the cycloheptatrienyl (tropylium) cation in organic chemistry, there has been a sustained interest in this class of nonbenzenoid "aromatic" hydrocarbons. An added incentive has been the recognition that the thermal reaction of ethyl diazoacetate with aromatic hydrocarbons proceeds by a carbene mechanism.[7] Although the chemistry of cycloheptatriene has been adequately discussed in the literature,[4,8] the synthesis of substituted cycloheptatrienecarboxylic acids seems to have been confined to those members which are derived from methyl and methoxyl benzenes. Thus, in a series of papers following the initial discovery of the reaction, Buchner prepared alkylcycloheptatrienecarboxylic acids from the reaction of ethyl diazoacetate with toluene,[9] 1,3-dimethylbenzene,[10] and mesitylene.[11] In their extensive work, Johnson and coworkers described the preparation of alkoxycycloheptatrienecarboxylic acids resulting from the reaction of ethyl diazoacetate with anisole,[12] 1,3-dimethoxybenzene,[13,14] 1,4-dimethoxybenzene,[15] and 1,2,4-trimethoxybenzene.[14] Although the positions of the substituents in these products were established by chemical means, in few cases were the positions of the double bonds located. The lability[16] of the triene system under acidic conditions and also heat would preclude any definitive assignments based on chemical transformations.

We have recently had the occasion to prepare several of these known acids in connection with another problem,[17] and it became desirable to reinvestigate the structural assignments by nmr spectroscopic techniques. The monocyclic seven-membered-ring structure of the simplest member, β-cycloheptatrienecarboxylic acid **1**,[18,19] had been unambiguously established in 1956 by the same technique.



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The acids were prepared by published procedures with some minor modifications in some cases. Their melting points and nmr parameters are listed in Table I. Nearly all of the compounds gave first-order spectra with some long-range coupling being observed in certain cases. Their interpretation was based on the observations made on β-cycloheptatrienecarboxylic acid as well

(1) To whom all correspondence should be addressed at the University of Montreal.

(2) Geigy Research Laboratories, Switzerland.

(3) E. Buchner and T. Curtius, *Ber.*, **18**, 2377 (1885), and subsequent papers.

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(6) W. von E. Doering and L. H. Knox, *ibid.*, **76**, 3203 (1954).

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(8) For a review, see S. J. Rhoads in "Molecular Rearrangements," P. de Mayo, Ed., Part 1, Interscience, New York, N. Y. 1963, pp 700–703.

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(13) R. B. Johns, A. W. Johnson, and M. Tisler, *ibid.*, 4605 (1954).

(14) R. B. Johns, A. W. Johnson, and J. Murray, *ibid.*, 198 (1954).

(15) R. B. Johns, A. W. Johnson, A. Langemann, and J. Murray, *ibid.*, 309 (1955).

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TABLE I
NMR DATA OF CYCLOHEPTATRIENE CARBOXYLIC ACIDS

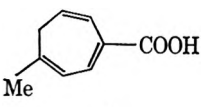
Acid	Mp, °C	Chemical shift[a,b] C-2	C-3	C-4	C-5	C-6	C-7	OMe	Me
1	143–144	474 d ($J_{2,3}$ = 6.0)	387[c] ($J_{3,2}$ = 6.0; $J_{3,4}$ = 9.4)	344[d] ($J_{4,3}$ = 9.4; $J_{4,5}$ = 6.5)	140 t (J = 7.0)	330[d] ($J_{6,7}$ = 9.4; $J_{6,5}$ = 6.5)	410 d ($J_{7,6}$ = 9.4)		
2	99–100	462 d ($J_{2,3}$ = 6.5)	372 d ($J_{3,2}$ = 6.5)		142 d (J = 6.5)	327 m ($J_{6,7}$ = 9.0; $J_{6,5}$ = 7.0)	404 d ($J_{7,6}$ = 9.0)		124 s
3	143–144	468 d ($J_{2,3}$ = 7.5)	338 d ($J_{3,2}$ = 7.5)		155 d (J = 7.0)	328 m ($J_{6,7}$ = 9.6; $J_{6,5}$ = 7.0)	410 d ($J_{7,6}$ = 9.5)	221 s	
4	149–150	457 d ($J_{2,3}$ = 6.5)	368 d* ($J_{3,2}$ = 6.5)		139 s		391 s		122 s
5	189	455 d ($J_{2,3}$ = 7.0)	334 d ($J_{3,2}$ = 7.0)		164 s*		361 s*	223 s	
6	141–142		358 s		136 s		388 s		140 s 120 s (2Me)
7	116–117	455 d ($J_{2,3}$ = 6.3)	370 d ($J_{3,2}$ = 6.3)		136 q (J = 7.0)		395 s		122 s, 63 d (J = 7.0)

[a] Chemical shifts and coupling constants are expressed in hertz. Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet. J values are within ±0.3 Hz. [b] An asterisk indicates the existence of long-range coupling. [c] Center of a quartet. [d] Center of two triplets; J values were obtained by decoupling.

as on the expected effects of methyl and methoxyl groups on the chemical shifts of the neighboring ring protons.

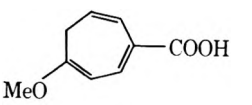
The spectrum of **1** was recorded at 100 MHz and the peaks corresponding to individual ring protons were assigned by means of spin-decoupling techniques. Irradiation of the C-2 proton doublet ($J_{2,3}$ = 6 Hz) caused the C-3 proton quartet to collapse to a doublet ($J_{3,4}$ = 9 Hz). Irradiation of the methylene triplet simplified the pattern of the multiplet given by the C-4 and C-6 protons from four triplets to a pair of doublets of approximately equal coupling (J = 9.4 Hz). Definitive assignment of the origin of the high field and low field portions of the complex multiplet was achieved by irradiating the C-7 proton. Thus the two triplets in the high field portion were simplified to a triplet ($J_{6,5}$ = 6.5 Hz), while the low field portion of the multiplet remained essentially unchanged. This indicates that the C-6 proton signal is in the high field portion of the multiplet. In this manner all of the peaks in the nmr spectrum of **1** were attributed to the respective ring protons.

The low field doublet in the nmr spectrum of 4-methyl-1,3,6-cycloheptatrienecarboxylic acid (**2**) is



2

assigned to the C-2 proton. Signals appearing at progressively higher fields are due to the C-7, C-3, C-6, and C-5 protons, respectively. The C-4 methyl group causes some shielding[20,21] of the C-3 proton, while the adjacent C-5 protons remain unaffected compared with those of **1**. The spectrum of the monomethoxycycloheptatrienecarboxylic acid[12] **3** can be interpreted



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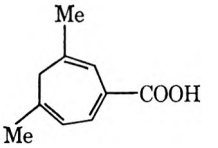
in much the same terms. While the chemical shifts and coupling constants of the C-2 and C-7 protons remain relatively unchanged compared with those of **1**, the C-3 proton is shielded considerably (49 Hz) owing to the delocalization effect[22,23] exerted by the C-4 methoxyl group.

The C-5 methylene protons centered at 155 Hz are somewhat deshielded compared with the doublet in **1**, owing to the inductive effect of the C-4 methoxyl group. Johnson and coworkers[12] had postulated a 1,3,5-triene structure for this compound, based on the mode of formation of anisic acid by degradation. The present nmr data indicate that the actual structure is that of 4-methoxy-1,3,6-cycloheptatrienecarboxylic acid (**3**).

Two 4,6-dimethylcycloheptatrienecarboxylic acids have been obtained by Buchner and coworkers[10] from the reaction of ethyl diazoacetate with 1,3-dimethylbenzene, and subsequent hydrolysis of the derived ester and amide derivatives, respectively. The acid obtained by hydrolysis of the ester can be designated as 4,6-dimethyl-1,3,6-cycloheptatrienecarboxylic acid (**4**), based on nmr spectral considerations. It is of



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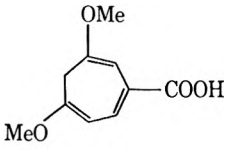
(20) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, p 723.

(21) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **83**, 237 (1961).

(22) See ref 20, p 721.

(23) J. Feeny, A. Ledwith, and L. H. Sutcliffe, *J. Chem. Soc.*, 2021 (1961).

interest to note that the same structure was proposed some 60 years ago, based on purely chemical methods. Inserting a second methyl group at C-6 causes little change in the chemical shifts of the ring protons compared with those of 2, except for some additional shielding of the C-3 and C-7 protons. The dimethoxy analog of 4, which is prepared by the reaction of 1,3-dimethoxybenzene and ethyl diazoacetate, exhibits strong shielding effects in its nmr spectrum. Thus the C-3 and C-7 protons are shielded to the extent of 53 Hz and 49 Hz, respectively, relative to 1. The C-5 methylene protons which are flanked by the two methoxyl groups are now more deshielded compared with those of 3. The data are consistent with structure 5.



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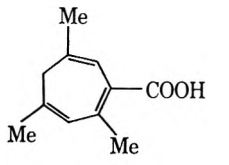
Of the seven isomeric 2,4,6-trimethylcycloheptatrienecarboxylic acids that could result from the reaction of ethyl diazoacetate with 1,3,5-trimethylbenzene, Buchner and Schottenhammer[11] had selected the 1,3,6- and 1,4,6-triene structures as the most compatible with the observed chemical properties. Consideration of the nmr data also leads to these two possible structures, namely 2,4,6-trimethyl-1,3,6-cycloheptatrienecarboxylic acid (6) and the isomeric 1,4,6-triene structure (not shown). A peak in the region expected of the C-3 proton appears at higher field than in the spectrum of the monomethyl derivative 2, presumably because of the presence of a second α-methyl group. Two of the three methyl groups seem to be equivalent. Unfortunately the available data at 60 MHz cannot distinguish between the two isomeric triene structures. The thermal reaction between ethyl diazoacetate and 1,2,3-trimethylbenzene led, after hydrolysis of the resulting ester, to a crystalline acid which is designated as 4,5,6-trimethyl-1,3,6-cycloheptatrienecarboxylic acid (7). The slight shielding of the C-3 and C-7 protons is consistent with the presence of methyl groups on C-4 and C-6, respectively (compare 2 and 6). The presence of a high field quartet and a three-proton doublet due to the C-5 proton and methyl group, respectively, is also consistent with the structural assignment.



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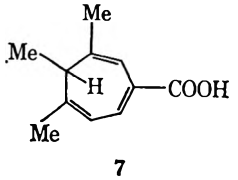

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Experimental Section

Melting points are uncorrected. Nmr spectra were obtained on 60-MHz[24] and 100-MHz[25] instruments in deuteriochloroform, using tetramethylsilane as internal reference. Compounds 1, 3, and 5 were prepared by published procedures.

4-Methyl-1,3,6-cycloheptatrienecarboxylic Acid (2).—A mixture of ethyl diazoacetate[26] (40 g) and toluene (1 l.) was gradually heated to 150° in an atmosphere of nitrogen at 25 atm. The pressure was then raised to 40 atm and the mixture was maintained at 150° for 4 hr. Cooling and evaporation of the solvent afforded a dark oil which was fractionated by distillation. A fraction boiling at 60° (0.17 mm) was collected (42.6 g) and was found to be a mixture of at least five components by vpc analysis. A portion of this mixture was dissolved in 60 ml of 10% aqueous methanol containing 10% potassium hydroxide and the solution was stirred overnight at room temperature. Acidification with 3 *N* hydrochloric acid, followed by extraction with ether and processing in the usual way, gave a pale yellow syrup which crystallized partially after standing at 0° for 2 weeks. The product was recrystallized from a mixture of ether and petroleum ether: yield 0.5 g; mp 99–100° (lit.[9] mp 107–108°); λ_{max} 290 mμ (MeOH, aqueous HCl), 283 (MeOH, aqueous NaOH).

Anal. Calcd for $C_9H_{10}O_2$: C, 71.95; H, 6.72. Found: C, 71.88; H, 6.69.

4,6-Dimethyl-1,3,6-cycloheptarienecarboxylic Acid (4).—Ethyl diazoacetate (40 g) was added dropwise to 500 ml of *m*-xylene while the solution was gradually heated. After the addition was complete, the solution was refluxed for 16 hr, the solvent was removed, and the residual dark oil was fractionated by distillation. A fraction boiling at 69–76° (0.17 mm) was collected (40 g) and showed at least five peaks in a vpc analysis. A portion (10 g) of this oil was dissolved in 60 ml of 10% aqueous methanol containing 10% potassium hydroxide, and the solution was heated at 70° for 2 hr. After cooling, acidification, extraction with ether, and processing, a crystalline solid was obtained which was filtered from petroleum ether (bp 30–60°). Recrystallization from a mixture of chloroform and petroleum ether gave the product (3 g): mp 149–150° (lit.[10] mp 148°); λ_{max} 273 mμ (MeOH, aqueous HCl), 267 (MeOH, aqueous NaOH).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.11; H, 7.38. Found: C, 72.96; H, 7.43.

4,5,6-Trimethyl-1,3,6-cycloheptatrienecarboxylic Acid (7).—Ethyl diazoacetate (40 g) was gradually added to 1,2,3-trimethylbenzene (400 ml) while the solution was slowly heated to 145°. The solution was stirred at this temperature for 6 hr after the addition was complete, and then it was cooled. The solution was evaporated and the residual yellow oil was fractionated by distillation. The fraction boiling at 85–90° (0.16 mm) (36 g) was collected and a portion (20 g) was hydrolyzed with aqueous methanolic potassium hydroxide at room temperature. Acidification and processing as described above, gave a light yellow oil which was fractionally crystallized from petroleum ether. A crop (1.7 g) had mp 108–111° and proved to be 2,3-dimethylphenylpropionic acid. A second and third crop of crystals obtained from the mother liquors corresponded to the desired product: yield 4 g; mp 114–115° (recrystallization from chloroform–petroleum ether afforded material with mp 116–117°); λ_{max} 290 mμ (MeOH, aqueous HCl), 284 (MeOH, aqueous NaOH).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.15; H, 7.92. Found: C, 74.17; H, 7.91.

2,4,6-Trimethyl-1,3,6-cycloheptatrienecarboxylic Acid (6).—Ethyl diazoacetate (40 g) was added dropwise to mesitylene (450 ml) with stirring and gradual heating to 150° during 3 hr. The mixture was stirred at the same temperature for an additional 6 hr, cooled, and evaporated. The dark oily residue was fractioned by distillation to give a fraction boiling at 60–82° (0.2 mm): yield 37 g. A portion (10 g) of this mixture was dissolved in aqueous methanolic potassium hydroxide and the solution was heated at 70° for 2 hr. Careful acidification of the chilled solution afforded a precipitate which was filtered and washed with petroleum ether: yield 4 g; mp 141–142° (lit.[11] mp 142°)

(24) We thank Mr. R. B. Scott of Parke, Davis & Co. for recording the 60-MHz spectra.

(25) We are grateful to Mr. D. F. Williams, Department of Chemistry, University of Montreal, for recording the 100-MHz spectra and for decoupling experiments, and to Dr. M. St-Jacques of the same department for helpful discussions.

(26) A product of Aldrich Chemical Co., Milwaukee, Wis.

(recrystallization from aqueous methanol did not change the melting point); λ_{max} 279 mμ (MeOH, aqueous HCl), 273 (MeOH, aqueous NaOH).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.15; H, 7.92. Found: C, 74.06; H, 8.06.

Registry No.—**1**, 21297-55-2; **2**, 21297-56-3; **3**, 21297-57-4; **4**, 21297-58-5; **5**, 21297-59-6; **6**, 21297-60-9; **7**, 21297-61-0.

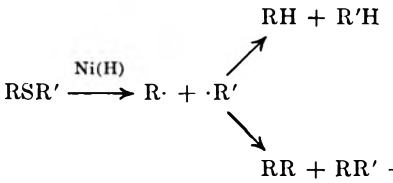
Raney Nickel Desulfurization of Cyclooctyl Mercaptan and Cyclooctyl Sulfide

ARTHUR C. COPE[1] AND JOHN E. ENGELHART[2]

Massachusetts Institute of Technology, Cambridge, Massachusetts

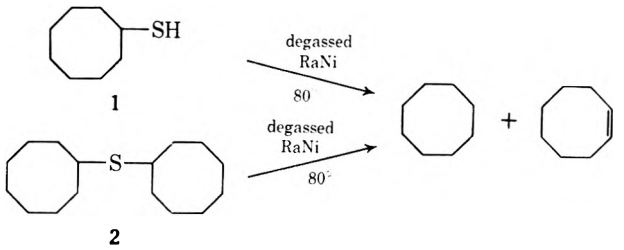
Received January 9, 1969

It has been suggested that the Raney nickel desulfurization of an organic mercaptan or sulfide proceeds through a free-radical intermediate which is subsequently hydrogenated or recombines to form a coupled product.[3-7] The following equation illustrates the process by which such reactions are believed to take place.[3]



In view of our interest in the free-radical reactions of medium sized ring compounds,[9] we undertook a brief study of the desulfurization of cyclooctyl mercaptan and cyclooctyl sulfide. If a cycloalkyl mercaptan or sulfide of this type is desulfurized with degassed Raney nickel with the subsequent formation of cycloalkyl radicals, one would expect these radicals to undergo characteristic disproportionation and coupling reactions rather than being hydrogenolyzed to a hydrocarbon.

For this study, cyclooctyl mercaptan (**1**) was prepared in 43% yield by the reaction of cyclooctyl bromide with thiourea followed by basic hydrolysis of the intermediate isothiouronium salt. Cyclooctyl sulfide (**2**) was prepared in 41% yield by the reaction of sodium sulfide nonahydrate with cyclooctyl bromide. The desulfurization reactions were carried out by refluxing a benzene solution of mercaptan or sulfide with a tenfold excess of degassed Raney nickel for time intervals up to 48 hr. The desulfurization of cyclooctyl mercaptan gave a 80–85% yield of a product mixture containing only cyclooctane and *cis*-cyclooctene. The relative amounts of these products varied over a wide range depending on the length of time the Raney nickel was degassed. Generally, the product mixture contained about 80% cyclooctane and 20% *cis*-cyclooctene. However, if the Raney nickel was vigorously degassed for periods of 24 hr or more, the yield of *cis*-cyclooctene approached 80% whereas the yield of cyclooctane dropped to 20%. The desulfurization of cyclooctyl sulfide proceeded very slowly and always gave back on the order of 70% unchanged starting material. From the sulfide which did decompose there was obtained a 71% hydrocarbon yield which consisted principally of *cis*-cyclooctene. No bicyclooctyl could be isolated from desulfurization of either **1** or **2**, lending some doubt as to whether these particular desulfurizations proceed



through a conventional free-radical intermediate under the experimental conditions employed. In addition, the relative amounts of cyclooctane and *cis*-cyclooctene which are formed in these desulfurizations indicate that disproportionation of cyclooctyl radicals is not an important reaction pathway. The cyclooctane formed in these desulfurizations does not arise by hydrogenation of *cis*-cyclooctene since a sample of *cis*-cyclooctene was unaffected when refluxed with degassed Raney nickel in benzene. Cyclooctane is apparently formed by partial hydrogenolysis of the mercaptan or sulfide and is dependent on the amount of hydrogen bound to the surface of the degassed Raney nickel. The formation of *cis*-cyclooctene, however, is presumably due to elimination of the elements of hydrogen sulfide from cyclooctyl mercaptan or elimination of a mercaptan moiety from cyclooctyl sulfide.

Because of the highly complex nature of metallic surfaces, it is difficult to postulate an exact mechanism for these elimination reactions. In the case of a Raney nickel catalyst, a further complicating factor is the presence of substantial amounts of basic oxides.[10] One possible explanation would involve coordination of the sulfur with a metal surface followed by a homolytic weakening of the carbon–sulfur bond. Hydrogenolysis of the carbon–sulfur bond would yield cyclooctane as expected. Abstraction of a hydrogen atom on the 2 position of the ring at the metal surface, together with complete homolytic cleavage of the carbon–sulfur bond, would yield *cis*-cyclooctene. Further work on the desulfurization of alkyl mercaptans and sulfides would be useful to better understand the nature of this reaction.

Experimental Section

Boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses. Gas chromatography was carried out with 1.90 × 0.8 cm Pyrex columns containing 25–30% by weight liquid stationary phase on 60–80 or 80–100 mesh Johns-Manville Chromosorb. Samples were eluted with helium gas at 15 psi and detected by use of a thermal conductivity cell.

(1) Deceased, June 4, 1966.

(2) (a) National Science Foundation Cooperative Predoctoral Fellow 1959–1960. (b) To whom inquiries should be addressed: Esso Agricultural Products Laboratory, Linden, N. J.

(3) H. Hauptmann and B. Wladislaw, *J. Amer. Chem. Soc.*, **72**, 707, 710 (1950); H. Hauptmann, *et al.*, *Ann.*, **576**, 45 (1952).

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(5) G. W. Kenner, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 957 (1948).

(6) W. Baker, A. S. El-Nawawy, and W. D. Ollis, *ibid.*, 3163 (1952).

(7) G. M. Badger and W. H. F. Sasse, *ibid.*, 3862 (1957).

(8) G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, 359 (1962).

(9) A. C. Cope and J. E. Engelhart, *J. Amer. Chem. Soc.*, **90**, 7092 (1968).

(10) R. J. Kokes and P. H. Emmett, *ibid.*, **83**, 29 (1961).

Cyclooctyl Mercaptan (1).—The general procedure of Urquhart, Gates, and Connor[11] was used to prepare this compound. To a solution of 15.2 g of thiourea in 150 ml of absolute ethanol was added 38.2 g of cyclooctyl bromide and the resulting solution was refluxed for 48 hr. To the cooled solution was then added 120 ml of 10% sodium hydroxide solution and the mixture was refluxed for an additional 2 hr. The mercaptan layer was separated and the neutralized aqueous layer extracted with three 100-ml portions of benzene and the benzene extracts were dried over sodium sulfate. The benzene was removed by distillation through a Vigreux column under reduced pressure and the product was distilled through a semimicro column yielding 12.44 g (43%) of crude mercaptan, bp 31–34° (0.35 mm), n^{24}D 1.4822–1.5034. A portion of this product was chromatographed on Merck activity II acid-washed alumina and eluted with petroleum ether (bp 35–60°) to yield pure cyclooctyl mercaptan. Further elution with petroleum ether yielded a fraction shown to be cyclooctyl ethyl ether by comparison of its infrared spectrum with that of an authentic spectrum. This ether usually contaminated the crude reaction product to the extent of about 10%. The pure mercaptan had bp 98–99° (20 mm), n^{25}D 1.5076–1.5078. Its infrared spectrum had the characteristic mercaptan absorption[12] at 2540 cm^{-1}.

Anal. Calcd for $C_8H_{16}S$: C, 66.63; H, 11.18; S, 22.19. Found: C, 66.86; H, 11.17; S, 21.66.

Cyclooctyl Sulfide (2).—The method of Bost and Conn[13] was used in the preparation of this compound. To a solution of 6 g of sodium sulfide nonahydrate in 50 ml of absolute ethanol was added 9.6 g of cyclooctyl bromide and the resulting solution was refluxed for 20 hr. The solution was then cooled and 50 ml of water was added. The sulfide layer was separated, the aqueous layer was extracted with five 20-ml portions of petroleum ether, and the combined extracts were dried over sodium sulfate. After removal of the petroleum ether under reduced pressure with a rotary concentrator, the crude product was distilled through a semimicro column. A total of 2.6 g (41%) of product, bp 126–127° (0.25 mm), n^{25}D 1.5250–1.5286, was obtained. An analytical sample of cyclooctyl sulfide had bp 126–127° (0.25 mm), n^{25}D 1.5255.

Anal. Calcd for $C_{16}H_{30}S$: C, 75.53; H, 11.89; S, 12.58. Found: C, 75.22; H, 11.90; S, 12.58.

Preparation of Degassed Raney Nickel.—The procedure used was adapted from a similar one used by Hauptmann.[4] Commercial W-2 Raney nickel (Raney Catalyst Co., Chattanooga, Tenn.) was thoroughly washed with large portions of distilled water, ethanol, and finally reagent benzene. The wet Raney nickel was transferred to a Carius tube and the excess benzene was removed under reduced pressure. A 1500-G permanent magnet surrounding the outside of the Carius tube held the powdered nickel in place. The system was then evacuated to 1–2-mm pressure and heated to 150°. Heating was continued for at least 8 hr, after which the system was cooled and the vacuum was slowly released under nitrogen pressure. The degassed nickel was then poured into an empty reaction flask under nitrogen and a benzene solution of mercaptan or sulfide was added.

Desulfurization of Cyclooctyl Mercaptan.—A 1.10-g sample of cyclooctyl mercaptan dissolved in 35 ml of dry benzene was refluxed for 49 hr with about 10 g of degassed Raney nickel. The benzene solution was then decanted from the nickel and the nickel was carefully transferred to a Soxhlet extraction apparatus and continuously extracted with pentane for 96 hr. The pentane extracts and benzene solution were then combined and the benzene and pentane were removed by distillation. Distillation of the product mixture at 25–40° (10 mm.) yielded 698 mg (82%) of a mixture consisting of approximately 80% cyclooctane and 20% *cis*-cyclooctene. The small amount of residue contained no bicyclooctyl as determined by gc analysis on a silicon grease column heated to 230°.

Desulfurization of Cyclooctyl Sulfide.—A 1.10-g sample of cyclooctyl sulfide dissolved in 35 ml of dry benzene was refluxed with about 10 g of degassed Raney nickel for 48 hr. Separation of the reaction products was accomplished using the procedure described in the desulfurization of cyclooctyl mercaptan. Distillation of the product mixture at 25–40° (10 mm) yielded 200 mg (71% based on recovered sulfide) of a mixture of 7% cyclooctane and 93% *cis*-cyclooctene as determined by gc using an NMPN column at 30°. Chromatography of the high boiling residue on 20 g of Merck activity II acid-washed alumina and elution with pentane yielded 388 mg of a colorless oil. This material was shown to be unreacted cyclooctyl sulfide by the use of infrared and gas chromatographic techniques (silicon gum rubber at 300°). No other product could be isolated from the column chromatogram.

Registry No.—1, 20628-54-0; 2, 20628-55-1.

(11) G. G. Urquhart, J. W. Gates, Jr., and R. Connor, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 363.

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Second ed, John Wiley & Sons, Inc., New York, N. Y., 1958.

(13) R. W. Bost and M. W. Conn, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 547.

The Reaction of N-Sulfinylamines and N-Sulfinylsulfonamides with Carbonyl Chloride. A New Synthesis of Isocyanates

HENRI ULRICH, B. TUCKER, AND A. A. R. SAYIGH

The Upjohn Company,
Donald S. Gilmore Research Laboratories,
North Haven, Connecticut 06473

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The direct phosgenation of amine salts to isocyanates is well known; however, long reaction times are required because of the poor solubility of amine salts in organic solvents.[1] The facile reaction of amines and sulfonamides with thionyl chloride[2] provides a method of protection of the amino group, and the generated N-sulfinyl derivatives are easily soluble in organic solvents. Subsequent phosgenation could produce the corresponding isocyanate with regeneration of thionyl chloride. The over-all reaction is shown below (eq 1, 2).

$$RNH_2 + SOCl_2 \longrightarrow RN{=}S{=}O + 2\ HCl \quad (1)$$

$$RN{=}S{=}O + COCl_2 \longrightarrow RN{=}C{=}O + SOCl_2 \quad (2)$$

When carbonyl chloride is added to N-sulfinylaniline (N-thionylaniline) in *o*-dichlorobenzene at 180°, no reaction occurs. In contrast, facile conversion could be achieved in refluxing benzene (80°), provided that a catalytic amount of pyridine or N,N-dimethylformamide is added to the reaction mixture. The reaction is general, and aliphatic and aromatic amines as well as aromatic sulfonamides can be converted to the corresponding isocyanates (see Table I).

TABLE I[a]

CONVERSION OF N-SULFINYLAMINES AND N-SULFINYLSULFONAMIDES TO ISOCYANATES

$RN{=}S{=}O + COCl_2 \longrightarrow RN{=}C{=}O + SOCl_2$

Registry no.	R	Scale, mol	Time,[b] min	Yield,[c] %	Bp, °C (mm)
103-71-9	C_6H_5	0.03	85	60	55–57 (16)
4083-64-1	4-$CH_3C_6H_4SO_2$	0.03	90	62	90–92 (0.5)
622-58-2	4-$CH_3C_6H_4$	0.03	120	67	88 (17)
104-12-1	4-ClC_6H_4	0.03	45	75	87 (8.5)
5416-93-3	4-$CH_3OC_6H_4$	0.03	300	73	102 (6.5)
3173-53-3	C_6H_{11}	0.035	630	61	76 (17)

[a] An amount of 5% (by weight) of pyridine was used as the catalyst. [b] The flow rate of carbonyl chloride was approximately 145 ml/min. [c] The yields are not optimal. Losses in distillation were encountered because of the small-scale experiments.

(1) W. Siefken, *Ann.*, **562**, 75 (1949).

(2) G. Kresze and W. Wucherpfennig in "Newer Methods of Preparative Organic Chemistry," Vol. V, Academic Press, New York, N. Y., 1968, p 113–115.

The catalytic effect of N,N-dimethylformamide in phosgenation reactions can be attributed to the rapid formation of chlorodimethylformiminium chloride ($Me_2\overset{+}{N}{=}CHCl]Cl^-$), which in fact is the catalyst.[3] Chlorodimethylformiminium chloride is an exceedingly reactive electrophile, and its reaction with N-sulfinyl derivatives to form 1:1 adducts has been reported recently [4] In the case of pyridine, the 1:1 complex with carboryl chloride (1) is believed to be the species which attacks the N=S=O bond to form compound 2, which collapses to the reaction products (eq 3).

$$RN{=}S{=}O + \underset{\mathbf{1}}{C_5H_5\overset{+}{N}COCl]Cl^-} \longrightarrow \underset{\mathbf{2}}{RN(COCl){-}SOCl} + C_5H_5N$$

$$RN(COCl){-}SOCl \longrightarrow RN{=}C{=}O + SOCl_2 \qquad (3)$$

Experimental Section

The starting N-sulfinyl derivatives were prepared according to the literature procedures.[2]

Isocyanates. General Procedure.—The preparation of 4-chlorophenyl isocyanate demonstrates the general procedure followed in the synthesis of the isocyanates listed in Table I. To a refluxing solution of 5.2 g (0.03 mol) of N-sulfinyl-4-chloroaniline and 0.26 g of pyridine in 60 ml of benzene, carbonyl chloride was added over a period of 45 min, the progress of reaction being followed by infrared spectroscopy. The solvent was evaporated and vacuum distillation of the residue yielded 3.45 g (75.2%) of 4-chlorophenyl isocyanate, bp 87° (8.5 mm).

Instead of the pyridine, a 10% (by weight) amount of N,N-dimethylformamide can be used as catalyst, and the results are similar.

Registry No.—Carbonyl chloride, 75-44-5.

(3) E. Ulrich, "The Chemistry of Imidoyl Halides," Plenum Press, New York, N. Y., 1968, p 82–83.

(4) Y. Ito, S. Katsuragawa, M. Okano, and R. Oda, *Tetrahedron*, **23**, 2159 (1967).

Reactions of Bis(trifluoromethyl)diazomethane with Perfluorothiocarbonyl Compounds

WILLIAM J. MIDDLETON

Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

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Several investigators have reported that diazo compounds react with thio ketones by loss of nitrogen to give episulfides.[1] It has been assumed that an unstable thiadiazoline is first formed as an intermediate,[1a] but there appears to be no report of the isolation or confirmation of such an intermediate.

We have found that bis(trifluoromethyl)diazomethane (1)[2] reacts readily with certain perfluorothiocarbonyl compounds to yield thiadiazolines, which can be isolated and characterized because of their stabilization by fluorine. Thus, 1 reacts with hexafluorothioacetone[3] to give the thiadiazoline 2, which can be distilled at reduced pressure and is relatively stable at room temperature.

$$(CF_3)_2C{=}S + (CF_3)_2CN_2 \longrightarrow \underset{\mathbf{2}}{(CF_3)_2C(N{=}N)C(CF_3)_2S} \longrightarrow \underset{\mathbf{3}}{(CF_3)_2C{-}C(CF_3)_2S}$$

(1)

The ^{19}F nmr spectrum of 2 shows only a single absorption peak, indicating the symmetrical 1,3,4-thiadiazoline instead of the unsymmetrical 1,2,3-thiadiazoline. The thiadiazoline 2 is thermally unstable and can be decomposed with loss of nitrogen to give the known episulfide 3[4] by simply refluxing it at its atmospheric boiling point for a few hours.

Bis(trifluoromethyl)thioketene[5] also reacts with 1 to give an adduct which is the thiadiazoline 4. This

$$(CF_3)_2C{=}C{=}S + 1 \longrightarrow \underset{\mathbf{4}}{(CF_3)_2C{=}C(N{=}N)C(CF_3)_2S} \longrightarrow \underset{\mathbf{5}}{(CF_3)_2C{=}C{-}C(CF_3)_2S}$$

thiadiazoline is somewhat more stable than 2, possibly because the N=N double bond is stabilized by conjugation with the C=C double bond. However, it can also be decomposed with loss of nitrogen to give the episulfide 5 by heating it to reflux for several hours at atmospheric pressure. We believe that 5 is the first example of an allene episulfide. The infrared double-bond absorption of compound 5 at 5.75 μ is appreciably shorter than that of compound 4 at 6.17 μ, apparently because of introduction of strain by the three-membered ring and loss of conjugation.

Experimental Section[6]

2,2,5,5-Tetrakis(trifluoromethyl)-1,3,4-thiadiazoline (2).—An 18.2-g sample (0.1 mol) of hexafluorothioacetone[3] was cooled to −30°, and 17.8 g (0.1 mol) of bis(trifluoromethyl)diazomethane[2] was added slowly with stirring. The blue color faded to yellow. The reation mixture was distilled at reduced pressure to give 33.0 g (92%) of 2 as a colorless liquid: bp 37° (50 mm); $n^{25}D$ 1.3202; ir (liquid) 6.24 μ (N=N?); ^{19}F nmr (neat) δ 68.5 ppm (s).

Anal. Calcd for $C_6F_{12}N_2S$: C, 20.01; F, 63.31; N, 7.78; S, 8.89. Found: C, 20.22; F, 63.16; N, 7.97; S, 8.51.

Tetrakis(trifluoromethyl)thiirane (3).—A 20.0-g sample of 2 was heated at reflux for 4 hr and the distilled to give 17.5 g (95%) of 3 as a colorless liquid: bp 91°; $n^{25}D$ 1.3164; ^{19}F nmr (neat) δ 59.9 ppm (s).

Anal. Calcd for $C_6F_{12}S$: C, 21.70; F, 68.65; S, 9.65. Found: C, 21.75; F, 68.68; S, 9.69.

2,2-Bis(trifluoromethyl)-5-bis(trifluoromethyl)methylene-1,3,4-thiadiazoline (4).—A 1.94-g sample (0.01 mol) of bis(trifluoromethyl)thioketene[5] and 1.78 g (0.01 mol) of bis(trifluoromethyl)-

(1) (a) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833 (1920); (b) A. Schonberg and S. Nickel, *Chem. Ber.*, **64**, 2323 (1931); (c) W. J. Middleton and W. H. Sharkey, *J. Org. Chem.*, **30**, 1384 (1965).

(2) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 3617 (1966).

(3) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Org. Chem.* **30**, 1375 (1965).

(4) W. J. Middleton, U.S. Patent 3,136,781 (1964).

(5) M. S. Raasch, *Chem. Commun.*, 577 (1966).

(6) Fluorine nmr spectra were obtained with a Varian A56-60 spectrometer. Peak center positions for fluorine are reported in parts per million upfield from $CFCl_3$ used as an internal reference.

diazomethane were mixed at −78° and allowed to warm slowly to room temperature. Distillation gave 3.57 g (96%) of **4** as a colorless liquid: bp 44–45° (20 mm); $n^{25}D$ 1.3622; ^{19}F nmr (neat) δ 57.3 ppm (q, J = 8 Hz, 3 F), 63.2 (q, J = 8 Hz, 3 F), 70.7 (s, 6 F); ir (liquid) 6.17 and 6.48 μ (C=C and N=N); Raman, 1630 and 1552 cm^{-1}; uv (isooctane) λ_{max} 327 mμ (ϵ 4200).

Anal. Calcd for $C_7F_{12}N_2S$: C, 22.59; F, 61.27; N, 7.53; S, 8.61. Found: C, 22.89; F, 61.67; N, 7.67; S, 8.67.

2,2-Bis(trifluoromethyl)-3-bis(trifluoromethyl)methylenethiirane (5).—A 2.0-g sample of **4** was heated at reflux for 24 hr and then distilled to give **5** as a colorless liquid: bp 93°; $n^{25}D$ 1.3279; ir (liquid) 5.75 μ (C=C); uv (ethanol) λ_{max} 239 mμ (ϵ 11,400), ^{19}F nmr (neat) δ 61.0 ppm (m, 3 F), 63.0 (q, J = 6 Hz, 3 F), 67.4 (q, J = 4 Hz, 6 F).

Anal. Calcd for $C_7F_{12}S$: C, 24.43; F, 66.25; S, 9.32. Found: C, 24.55; F, 66.32; S, 9.23.

Registry No.—**1**, 684-23-1; **2**, 20728-38-5; **3**, 2375-87-3; **4**, 20708-15-0; **5**, 20728-39-6.

1,2 and 1,4 Addition of Ethylene to Butadiene

RICHARD K. LYON

Corporate Research Laboratories, Esso Research and Engineering Company, Linden, New Jersey 07036

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In a recent paper[1] Bartlett and Schueller report that at 175° the addition product of ethylene to butadiene consisted of 99.98% cyclohexene (CH) and 0.02% of a second product. Since this second product had the same retention time on two gas chromatographic columns as authentic vinylcyclobutane (VCB), they identify it as VCB. The conditions of the experiment were such that the product ratio, CH/VCB, is equal to the ratio of rate constants $k_{1,4}/k_{1,2}$ where $k_{1,4}$ and $k_{1,2}$ are the rate constants for formation from ethylene and butadiene of CH and VCB, respectively. The authors discuss the implications of this new reaction to the mechanism of the Diels–Alder reaction. It is the purpose of this paper to point out that there exist data in the literature from which the value of $k_{1,4}/k_{1,2}$ can be independently calculated.

The author feels the calculation is of interest both because it confirms Bartlett and Schueller product identification and because it provides new information, the temperature dependence of $k_{1,4}/k_{1,2}$.

It can easily be shown that $k_{1,4}/k_{1,2} = (k_{-1,4}/k_{-1,2})\,K_3$ where $k_{-1,4}$ and $k_{-1,2}$ are the rate constants for decomposition to ethylene and butadiene of CH and VCB, respectively, and K_3 is the equilibrium constant for the isomerization of VCB to CH. Using the tables given by Benson,[2] one calculates, *via* the group additivity method, that $\log K_3 = -1.604 + (25500/4.57\ T)$.

Uchizama, Tomioka, and Amano[3] report that $\log k_{-1,4} = 15.16 - (66200/4.575\ T)$. $k_{-1,2}$ has not been measured directly but it should be very nearly equal to the rate at which isopropenylcyclobutane[4] decomposes to ethylene and isoprene; *i.e.*, $\log k_{-1,2} = 14.64 - (51030/4.575\ T)$. This assumes that introducing a methyl group in a next nearest neighbor position does not change the rate of cyclobutane ring rupture. This assumption may be justified by comparing the rate constants of decomposition of methyl cyclobutane[5] and ethyl cyclobutane.[6] At 450° they are 7.6×10^{-4} sec^{-1} and 6.6×10^{-4} sec^{-1}, respectively. Thus one calculates that $\log k_{1,4}/k_{1,2} = 1.08 + (10350/4.575\ T) = 3.97$ at 175°, in good agreement with Bartlett and Schueller's value of 3.7.

Registry No.—Ethylene, 74-85-1; butadiene, 106-99-0.

(1) P. D. Bartlett and K. E. Schueller, *J. Amer. Chem. Soc.*, **90**, 6071 (1968).

(2) S. W. Benson, "Thermochemical Kinetics," John Wiley & Sons, Inc., New York, N. Y., 1968.

(3) M. Uchizama, T. Tomioka, and A. Amano, *J. Phys. Chem.*, **68**, 1878 (1964).

(4) R. J. Ellis and H. M. Frey, *Trans. Faraday Soc.*, **59**, 2076 (1963).

(5) M. N. Das and W. D. Walters, *Z. Physik. Chem.* (Frankfurt), **16**, 22 (1958).

(6) R. E. Wellman and W. D. Walters, *J. Amer. Chem. Soc.*, **79**, 1542 (1957).

Thiabenzenes. VI. Steric Factors Influencing the Stability of 2-Phenyl-2-thianaphthalenes

CHARLES C. PRICE AND DOUGLAS H. FOLLWEILER[1]

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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The first thiabenzene prepared, the 1,2,4,6-tetraphenyl compound,[2a] was relatively unstable compared to others prepared later.[2b,c] While it failed to protonate readily like the phosphorabenzenes,[3] it rearranged to the isomeric thiopyran and reacted readily with oxygen. These differences in stability, as well as a difference in color, the unstable analog being purple while all the stable compounds were red-brown, was rationalized on the basis of a hypothesis that there was very little, if any, barrier to out-of-plane bending at phenyl–sulfur bond in these molecules due to relatively equal energy p^3 and sp^2 bonding geometry at the sulfur atom in thiabenzenes.[2b,c,3] This low barrier to bending was also offered as an explanation for the amorphous nature of these compounds as well as their remarkably broad absorbance of visible and ultraviolet radiation.

In order to test these theories further, we have now prepared two hindered analogs of the stable thiabenzene, 2-phenyl-2-thianaphthalene, by the following synthetic route, taking advantage of the fact that, while phenyllithium generally couples on the sulfur of thiopyrylium salts,[2] the Grignard reagent couples on carbon.

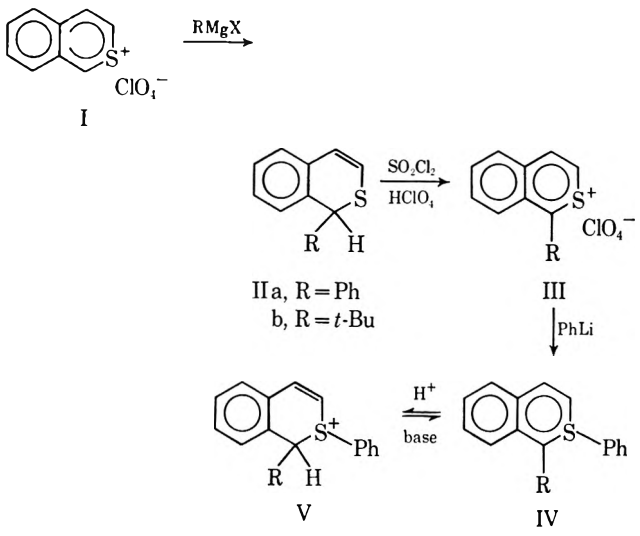
For the case of R = *t*-Bu, it was not possible to isolate the thianaphthalene IVb. Reaction mixtures for its preparation were deep wine red or purple (although the color faded in a day or so), but quenching with aqueous ammonium chloride gave the protonated form, Vb, as colorless crystals. This salt could be deprotonated only by base as strong as potassium ethoxide in DMSO, indicating a pK_a in the range of 20–25.

(1) Supported in part by a grant from the National Science Foundation, NSF GP-5269.

(2) (a) G. Suld and C. C. Price, *J. Amer. Chem. Soc.*, **83**, 1770 (1961); **84**, 2094 (1962). (b) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *ibid.*, **85**, 2278 (1963). (c) C. C. Price, M. Polk, and M. Siskin, *ibid.*, in press.

(3) G. Markl, *Angew. Chem.*, **75**, 168, 669, 1121 (1963).

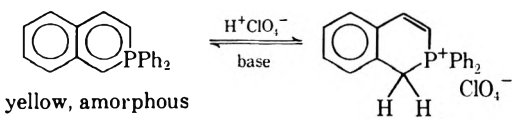
For the case of R = Ph, it was possible to isolate IVa as a purple amorphous solid. It was readily interconvertible to Va, and pH titration indicated a pK_a of 2.9.



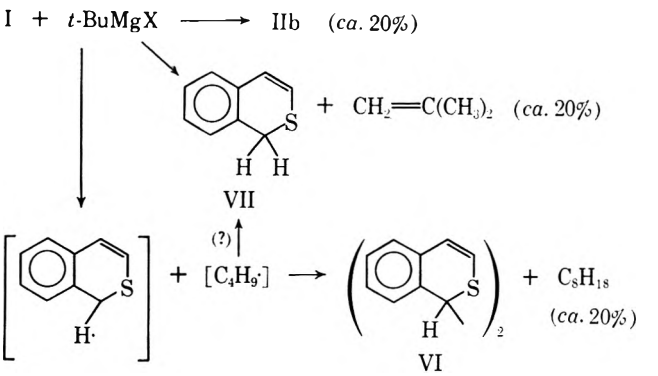
While the color of solutions of IVb faded in a day or so, even under nitrogen, the color of solutions of IVa faded only slowly in a month under nitrogen, although oxygen discharged the color rapidly. This latter property is similar to that of 1,2,4,6-tetraphenylthiabenzene. In fact, the analytical sample of IVa evidently picked up oxygen before it was analyzed.

Since unsubstituted 2-phenyl-2-thianaphthalene is stable to oxygen and to aqueous acids, it seems clear that steric hindrance in the form of a 1-phenyl or 1-*t*-butyl group has a major influence on the stability of this ring system. Since the bulkier *t*-butyl group has the larger influence, it does seem that a steric factor is a reasonable explanation. The great steric influence of a single substituent *ortho* to the S-phenyl group in this system may be due to the buttressing effect of the *peri* hydrogen.

The destabilization caused by the *ortho* hindrance we ascribe to a diminished contribution from the planar sp^2 geometry at sulfur, which permits participation of the 3p orbital on sulfur in the aromatic π bonding. In the sterically favored nonplanar p^3 geometry, only 3d orbitals on sulfur would be free to participate in the aromatic π bonding. It is significant to note that the phosphabenzenes,[3] which also must use 3d orbitals for aromatic π bonding, are also readily and reversibly protonated, even in the absence of *ortho* hindrance.



It is of interest to note that conversion of I to II was accomplished in good yield for R = Ph, but for R = *t*-Bu considerable *one-* and *two*-electron reduction accompanied coupling at position 1. The one-electron reduction produced octane and dimer VI, while two-electron reduction produced isobutylene and 2-thio-3-chromene (VII). The dimer VI was isolated in both the *meso* and the *dl* forms.



Experimental Section

1-Phenyl-2-thio-3-chromene (IIa).—Phenylmagnesium chloride (25 ml, 2.5 *M* in tetrahydrofuran) was added dropwise to a stirred suspension of 10 g of 2-thianaphthalenium perchlorate[4] in 200 ml of ether under nitrogen. After washing, the product distilled at 132–133° (0.15 mm), mp 37–38°.

Anal. Calcd for $C_{15}H_{12}S$: C, 80.31; H, 5.39; S, 14.29. Found: C, 80.22; H, 5.34; S, 14.27.

The uv spectrum in methanol showed λ_{max} (log ϵ) at 207 (4.55), 245 (4.07), and 322 mμ (3.70), while the nmr showed a phenyl multiplet at τ 2.50–3.20 (9 H), two vinyl doublets at 3.43 and 3.93 (J = 10 cps, 1 H each), and a singlet at 4.95 (1 H).

1-Phenyl-2-thianaphthalenium perchlorate (IIIa) was prepared from 3.1 g of IIa in 50 ml of ether by slow addition of 3 ml of sulfuryl chloride in 50 ml of ether at −78°. The orange precipitate was collected cold and resuspended in 100 ml of ether at −78°, and 50 ml of 70% perchloric acid at −30° was added with stirring. The bright yellow crystals were recrystallized from glacial acetic acid to yield 3.07 g (68%) of yellow needles, mp 184–185°.

Anal. Calcd for $C_{15}H_{11}SClO_4$: C, 55.82; H, 3.44; S, 9.93; Cl, 10.98. Found: C, 55.72; H, 3.39; S, 10.03; Cl, 10.83.

This salt showed uv absorbance (methanol) at λ_{max} (log ϵ) 235 (3.94), 242 (3.90), 267 (3.66), 293 (3.81), and 308 mμ (3.80), while the nmr (trifluoroacetic acid) showed a sharp singlet at τ 0.80 (2 H), a multiplet at 1.20–1.67 (4 H), and a singlet at 2.17 (5 H).

1,2-Diphenyl-2-thiochromenium perchlorate (Va) was prepared by adding 3 ml of 2.46 *M* phenylmagnesium chloride in THF dropwise to a slurry of 1 g of IIIa in 25 ml of ether under nitrogen. The purple solution was quenched with aqueous ammonium chloride, precipitating 0.52 g (42%) of Va, mp 160° dec. It recrystallized from glacial acetic acid as colorless plates.

Anal. Calcd for $C_{21}H_{17}SClO_4$: C, 62.92; H, 4.27; S, 8.00; O, 15.96; Cl, 8.84. Found: C, 62.74; H, 4.34; S, 7.97; O, 15.99; Cl, 8.67.

This compound showed uv absorbance at λ_{max} (log ϵ) 202 (4.67) and 285 (4.13), and nmr bands at τ 1.62 (doublet, J = 9 cps, 1 H),[5] 1.97–2.93 (multiplet, 14 H), 3.12 (singlet, 1 H), and 3.20 (doublet, J = 9 cps, 1 H).[5]

1,2-Diphenyl-2-thiabenzene (IVa) was isolated from reaction of 1 g of IIIA in 50 ml of ether with 5 ml of 0.91 *M* phenyllithium in ether at −78°. When this purple reaction mixture was quenched with aqueous ammonium chloride, the purple color was not destroyed, although 0.37 g of Va precipitated, mp 159–160° dec. Further washing and then evaporation of the ether left 0.39 g of IVa as a purple amorphous solid softening at 60–100°. Compound IVa showed only broad aromatic absorbance at τ 2.2–3.4 in the nmr spectrum. Analysis indicated that this material, like 1,2,4,6-tetraphenylthiabenzene,[2a] picked up oxygen.

Anal. Calcd for $C_{21}H_{16}SO$: C, 79.60; H, 5.08; S, 10.10. Found: C, 79.00; H, 4.86; S, 10.56.

The uv spectrum showed a continuous increase in absorbance from 350 to 220 mμ with a shoulder at 245 mμ.

It was also possible to convert Va to IVa by base. For example, 131 mg of Va in 50 ml of ethanol was titrated with 5.34 m*M* potassium hydroxide in ethanol[6] using a Beckman pH meter.

(4) A. Lüttringhaus and N. Engelhard, *Ber.*, **93**, 1525 (1960).

(5) M. Caserio, R. Pratt, and R. Holland, *J. Amer. Chem. Soc.*, **88**, 5747 (1966), report, for dimethyl β-styrylsulfonium fluoroborate, τ 2.17 for Hβ and τ 3.33 for Hα, with J = 9.5 cps.

(6) R. C. Bates "Determination of pH, Theory and Practice," John Wiley & Sons, Inc., New York, N. Y., 1960, p 227.

The pH at half-neutralization (pK_a) was 2.9, and the neutralization equivalent was 396 (calcd, 400.6). Purple solutions of Va prepared from IVa by base and kept under nitrogen slowly faded in a month at room temperature.

1-*t*-Butyl-2-thio-3-chromene (IIb) was prepared by treating 30 g of I in 500 ml of ether with 100 ml of 1.48 *M* *t*-butylmagnesium chloride.[7] When the ether layer was quenched with aqueous ammonium chloride, 2.1 g (12%) of white crystalline dimer of I, mp 230–231°, precipitated. The ethe layer was stripped of solvent by distillation; the distillate was found to have glpc peaks corresponding to isobutylene and 2,2,4-trimethylpentane. Addition of a small amount of acetone to the residue gave the isomeric dimer of I, mp 199–200°.[8] The acetone mother liquor was evaporated and vacuum distilled to give a main fraction, bp 120–133° (0.07 mm). Vacuum sublimation of this oil at 0.3 mm at room temperature gave 4.0 g (22%) of liquid 2-thio-3-chromene, and, when the sublimation temperature was raised to 40°, 5.5 g (22%) of IIb, mp 63–64°.

Anal. Calcd for $C_{13}H_{16}S$: C, 76.41; H, 7.89; S, 15.63. Found: C, 76.29; H, 7.75; S, 15.86.

1-*t*-Butylnaphthalenium perchlorate (IIIb) was prepared from IIb by treatment with sulfuryl chloride at −78° (as for IIa). Recrystallization from glacial acetic acid gave light yellow leaflets, mp 196–197°.

Anal. Calcd for $C_{13}H_{15}SClO_4$: C, 51.56; H, 4.99; S, 10.59; Cl, 11.71. Found: C, 51.82; H, 5.00; S, 10.37; Cl, 11.80.

The uv absorbance (methanol) showed λ_{max} (log ϵ) at 205 (4.41), 240 (3.90), 290 (3.57), 302 (3.67) and 320 mμ (3.72), and the nmr (trifluoroacetic acid) showed bands at τ 0.80 (3 H), 1.30–1.83 (3 H), and 7.87 (9 H).

1-*t*-Butyl-2-phenyl-2-thio-3-chromenium perchlorate (Vb) was prepared by treating a slurry of 1 g of IIIb in 50 ml of ether with 5 ml of 2.46 *M* phenylmagnesium bromide in THF. The purple solution was quenched with cold aqueous ammonium fluoride, precipitating 1.11 g (88%) of IVb. Recrystallization from glacial acetic acid gave 0.88 g (70%), mp 169–170°.

Anal. Calcd for $C_{19}H_{21}SClO_4$: C, 59.91; H, 5.56; S, 8.42; O, 16.80; Cl, 9.31. Found: C, 60.03; H, 5.41; S, 8.57; O, 16.84; Cl, 9.26.

The same compound was obtained in 36% yield with phenyllithium. The uv absorbance showed λ_{max} (log ϵ) at 232 (5.34), 275 (3.70), and 297 mμ (3.87), and nmr bands at τ 1.52 (doublet, 1 H, J = 10 cps), 1.90–2.53 (multiplet, 9 H), 2.78 (double doublet, 1 H, J = 10 and 2 cps), 4.93 (doublet, 1 H, J = 2 cps), and 8.73 (9 H).

Efforts to convert IVb to Vb were unsuccessful with potassium hydroxide in ethanol; the pH jumped from 6 to 12 on addition of less than 10% of 1 equiv of base. By reaction with potassium ethoxide or *t*-butoxide in DMSO, however, a port-wine color developed, perhaps due to Va. The color faded in a day or so, as did that of a phenyllithium reaction mixture.

Registry No.—IIa, 20707-97-5; IIb 20707-98-6; IIIa, 20728-45-4; IIIb, 20707-99-7; IVa, 20708-00-3; Vb, 20708-01-4; Va, 20708-02-5.

(7) "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p 524.

(8) Structure proof, properties, and other methods of preparation of these *meso*- and *dl*-1,1 dimers of I are described in theses by M. Siskin and C. K. Miao, Department of Chemistry, University of Pennsylvania.

Reactions of Alkyl Halides in Amides Containing Water or Ammonia

JOSEPH S. MATTHEWS AND JANE P. COOKSON

Gulf Research & Development Company, Pittsburgh, Pennsylvania 15230

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The reaction of alkyl halides with anhydrous acetamide has been reported by Erickson[1] to yield the substituted amide and by Joyce[2] to yield esters. Bredereck[3] and coworkers reported that the reactions of anhydrous formamide with alkyl halides yield formates or substituted formamides depending on the structure of the halide. In all of the above reactions, at least 2 mol equiv of anhydrous amide are required and only primary amides react.

Aqueous Amides.—We wish to report that, in the presence of water, all types of amides react with halides to yield a mixture of the corresponding ester and alcohol (Table I). In addition, only 1 mol of amide is consumed per mol of halide. All types of halides react (Table II) except fluorides, vinylic halides, and halogenated aromatics. The over-all reaction is as follows

$$RX + R'CONR_2'' + H_2O \longrightarrow R'CO_2R + NR_1''H_2X \quad (1)$$

$$R'CO_2R + H_2O \rightleftharpoons ROH + R'CO_2H \quad (2)$$

where R is alkyl or aralkyl, and R′ and R″ are organic or hydrogen.

By contrast, less than 2% ester–alcohol formed when anhydrous dimethylformamide was refluxed (152°) with *n*-octyl bromide for 3 hr.

For purposes of determining the stoichiometry of the reaction of octyl bromide with aqueous formamide, the distribution of alcohol in the product was determined by acetylation; excess (unreacted) water was determined by Karl Fischer titration; ammonium bromide was determined by titration with standard silver nitrate solution; and the excess formamide was determined by distilling and weighing. No determination of free formic acid, if any, was made. The recovery procedure for the material balance takes advantage of the fact that at room temperature, about 90% of the alcohol–ester product separates as a top layer. This may be

TABLE I

REACTION OF AQUEOUS AMIDES WITH *n*-OCTYL BROMIDE

Amide	Bromide conversion, %[a]	Products, %[b] Alcohol	Ester	Temp, °C	Time, hr	A/W/H[c]
$HCONH_2$	100	17.9	80.6	160	1	20:2:1
$HCON(CH_3)_2$	94.8	24.3	70.5	135	2	28:5:1
$CH_3CON(CH_3)_2$	74	49	25	130	3	9:6:1
$C_6H_5CONH_2$	99.4	18.0	79.4	170	3	20:3:1
$HCONHC_6H_5$[d]	99	19.4	79.6	160	2	20:3:1

[a] Based on unreacted bromide recovered. [b] The difference, if any, between % products and % conversion is due to formation of N-alkyl-substituted amides. [c] Molar ratios of amide/water/halide. [d] There was appreciable (5–10%) hydrolysis to aniline also.

TABLE II

REACTIONS OF VARIOUS HALIDES WITH AQUEOUS FORMAMIDE[a]

Halide	Halide conversion, %[b]	Temp, °C	Time, hr
$C_8H_{17}Cl$	63	140	3
$C_8H_{17}Br$	100	140	3
$C_8H_{17}I$	100	140	3
$C_6H_{13}CHBrCH_3$	97	140	3

[a] Molar ratio of amide/water/halide, 22:6:1. [b] Products are the corresponding formate–alcohol mixture.

(1) J. L. E. Erickson, *Chem. Ber.*, **59B**, 2665 (1926).

(2) R. M. Joyce (to Du Pont Co.), U. S. Patent 2,375,301 (1945).

(3) H. Bredereck, R. Gompe-, and G. Theilig, *Chem. Ber.*, **87**, 537 (1954).

due in part to the salting-out effect of the ammonium bromide in solution. After separating this layer, the rest of the product and unreacted formamide were separated by vacuum distillation. Due to its extreme solubility in formamide (0.5 g of NH_4Br/1 of g formamide at 100°), the ammonium bromide did not precipitate out until about 95% of the formamide had distilled [100° (9 mm)]. This was filtered off and distillation was continued until all the liquid had distilled.

Combination of the composition of various parts of the separation gave the material balance in Table III.

TABLE III
MATERIAL BALANCE

					Products	Moles
$C_8H_{17}Br$	+ H_2O +	$HCONH_2$	$\xrightarrow{135°,\ 3\ hr}$		$C_8H_{17}OH$	0.13
mol 0.5	1.0	10.0			$HCO_2C_8H_{17}$	0.33
					NH_4Br	0.5
					H_2O	0.41
					$C_8H_{17}Br$	0
					$HCONH_2$	9.4

The amount of formamide recovered was 99% of theory for the reaction of 1 mol per mol of bromide. The analyses for ammonium bromide (determined by molecular weight and bromide determination) and octyl bromide (by gas chromatography) show that all of the octyl bromide had reacted. However, the octyl products as such account for only 92% of theory. Later work showed that *n*-octyl formamide was formed, thus accounting for this discrepancy. There was no evidence for the formation of an olefin[4] from octyl bromide in this reaction. The amount of water consumed can be seen from the distribution of ester–alcohol obtained. The total molar amount of octyl products, 0.46 mol, plus the moles of alcohol formed due to hydrolysis, 0.13 mol, agree exactly with the water balance, 0.59 mol consumed, to show that the stoichiometry of the reaction is as written in eq 1 and 2.

Ammonia in Formamide.—When ammonia reacted with a mixture of the halide and formamide, either anhydrous or aqueous (5–10%), the major product is the N-alkyl-substituted amide in 90% yield.

$$RX + HCONH_2 + NH_3 \xrightarrow[1\ hr]{150°} HCONHR + NH_4X$$

There is about 5% dialkylformamide formed as well as 5% alcohol. In effect, the high selectivity of this reaction provides a new route to primary amines from primary alkyl halides.

Experimental Section

Gas chromatographic analyses of the reaction products were performed on an F & M Model 720 chromatograph using 10 ft × $^1/_8$ in. columns packed with 15% Carbowax on 60–80 mesh HMDS-treated Chromosorb W. The C_8 alcohol, ester, and bromide were analyzed at 140° and the substituted amides at 200°. Product peaks were identified by comparison of retention time with authentic samples and by combined mass-glpc and ir-glpc analyses of the individual peaks.

Aqueous Formamide.—A mixture of 96.5 g (0.5 mol) of *n*-octyl bromide, 450 g (10 mol) of formamide, and 18 g (1 mol) of water was heated at 135° for 3 hr in a 1-l., three-neck flask equipped with stirrer, condenser, and thermometer. After heating, the solution was cooled to room temperature, and it separated into two layers. The upper layer and the 60–90° cut from the bottom layer, obtained by vacuum distillation at 9 mm, contained all the *n*-octyl formate and *n*-octyl alcohol. These two fractions were combined and distilled to produce 52 g (0.33 mol) of *n*-octyl formate and 17 g (0.13 mol) of *n*-octyl alcohol for an over-all yield of ester–alcohol of 92%.

Formamide and Ammonia.—Anhydrous ammonia (0.47 mol) was dissolved in 2.5 mol of formamide and 0.125 mol of *n*-octyl bromide in a stirred autoclave and heated to 150°. At the end of 1.5 hr, the solution was cooled down and analyzed; 97.6% of the bromide had been converted. The products were 91% *n*-octylformamide, 2.7% N,N-dioctylformamide, and 6.3% *n*-octyl alcohol.

Registry No.—*n*-Octyl formate, 112-32-3; *n*-octyl alcohol, 111-87-5.

(4) N. Kornblum and R. K. Blackwood, *J. Amer. Chem. Soc.*, **78**, 4037 (1956).

Benzene Shifts in the Nuclear Magnetic Resonance Spectra of Alcohols

PAUL V. DEMARCO AND L. A. SPANGLE

Department of Molecular Structure Research, The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

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In previous studies, solvent shifts induced by benzene in a wide variety of solutes containing different functional groups were examined.[1] On the basis of these studies, widely differing models have been proposed for the geometry of benzene–solute collision complexes. Recently, in an attempt to generalize the phenomena of benzene–polar solute associations, Ledaal[2] has proposed that the geometry of such interactions can be rationalized in terms of one model,[3] common to solutes containing any polar functional group, and has demonstrated considerable success in applying this model to a wide variety of examples.

This communication has two purposes: first, to demonstrate that aromatic solvent induced shifts, ASIS ($\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$), in compounds containing the hydroxyl function cannot be adequately rationalized in terms of the model proposed by Ledaal for solute–solvent associations; second, to emphasize that in systems where the solute dipole is free to assume a number of preferred conformations, as in hydroxyl-containing solutes, the magnitude of resultant solvent shifts will be dependent upon the population of each conformational species in solution, a fact not pointed out in previous studies, although of intrinsic importance to the interpretation of ASIS.

In accordance with the Ledaal model,[2] two solute–solvent geometrical relationships are possible for benzene association to hydroxyl-containing solutes. These are illustrated in Figure 1a and 1b.

Because of the nature of the screening environment associated with aromatic systems,[4] both models, a and b, predict increased shielding for *all solute protons* in benzene relative to chloroform. Analysis of the results

(1) J. Ronayne and D. H. Williams, *J. Chem. Soc., B*, 540 (1967), and references cited therein.

(2) T. Ledaal, *Tetrahedran Lett.*, No. 14, 1683 (1968).

(3) According to this model, benzene association takes place from the positive end of the solute dipole and in such a manner as to allow the solute dipole axis to be located along the sixfold axis of symmetry of the associated benzene nucleus.

(4) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956); J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., 1959, pp 180–183.

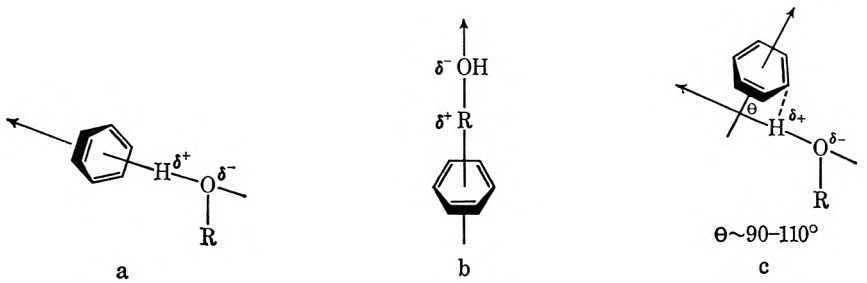

Figure 1.—Possible modes of benzene–hydroxyl function association.

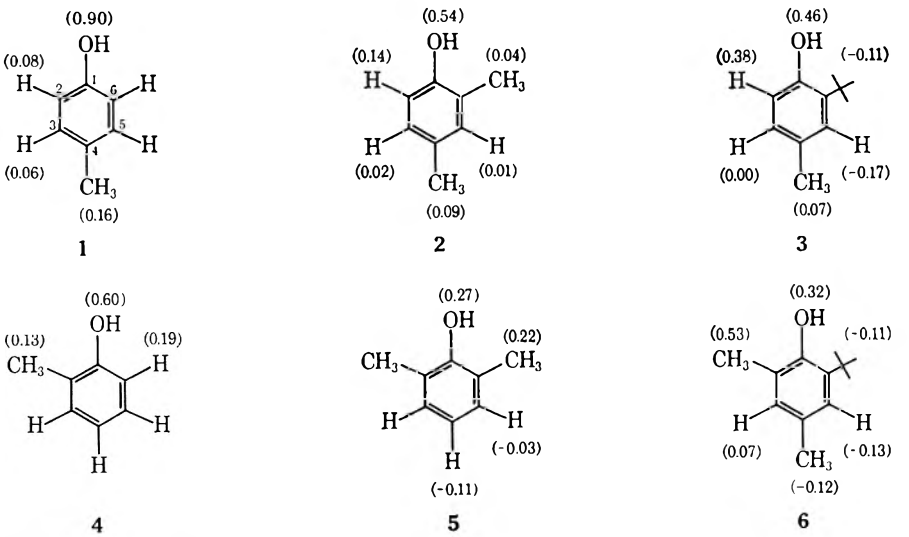

Figure 2.—Phenol Δ values (in parenthesis) beside corresponding protons (parts per million).

of solvent shift studies carried out on a number of phenol and androstanol derivatives, summarized in Figure 2 and Table I, indicate that both positive (increased shielding in benzene) and negative (decreased shielding in benzene) Δ values are recorded for the different solute protons in the systems under study. As a result, benzene–solute geometrical relationships a and b must be rejected on the grounds of incompatibility with the experiment data. We therefore propose an alternative model for benzene–alcohol association, depicted in Figure 1c, which is consistent with observed solvent shift results.

TABLE I

Δ VALUES[a] FOR H-18 AND H-19 PROTONS IN SOME HYDROXY STEROIDS

No.	Compd	Δ (H-19)	Δ (H-18)
7	5α-Androstan-1α-ol	0.10	
8	5α-Androstan-2α-ol	0.11	
9	5α-Androstan-2β-ol	−0.08	
10	5α-Androstan-3α-ol	0.08	
11	5α-Androstan-3β-ol	0.09	
12	5α-Androstan-4α-ol	0.10	
13	5α-Androstan-4β-ol	−0.11	
14	5α-Androstan-15α-ol		0.10
15	5α-Androstan-15β-ol		−0.11
16	5α-Androstan-16α-ol		0.08
17	5α-Androstan-16β-ol		−0.09
18	5α-Androstan-17α-ol		0.10
19	5α-Androstan-17β-ol		0.03

[a] $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$ ppm.

Because of considerable upfield shifts recorded for solute hydroxyl protons (see Figure 2) in benzene relative to chloroform, benzene–alcohol association is presumed to originate through the formation of weak hydrogen bonds between solute hydroxyl protons and the solvent π electrons,[5] the geometry of the association being such as to allow the sixfold axis of symmetry of the benzene nucleus and the axis of symmetry of the OH bond to lie mutually perpendicular or very nearly so (see Figure 1c). The validity of the proposed model becomes increasingly evident during the rationalization of observed ASIS.

Phenolic Systems.—In *ortho*-unsubstituted phenols (R = H), two conformers, a and b (Figure 3), are equally probable, with the result that their corresponding benzene-associated complexes will be equally populated in solution. Δ values for protons in **1** are thus net shift values resulting from the algebraic sum of screening contributions from solvent benzene molecules associated *syn* and *anti* to these protons.[8] Since solute protons *syn* are proximal to and in the shielding region of the associated benzene nucleus while solute protons *anti* are remote from and in the deshielding region, the shielding component experienced by a given solute proton is expected to be larger than the deshielding

(5) OH·····π hydrogen bonding has been amply demonstrated in previous infrared[6] and nmr[7] studies.

(6) P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Amer. Chem. Soc.*, **80**, 6691 (1958).

(7) M. Oki and H. Iwamura, *Bull. Chem. Soc. Jap.*, **35**, 1552 (1962); R. J. Ouellet, D. L. Mraks, and D. Miller, *J. Amer. Chem. Soc.*, **89**, 913 (1967); D. C. Kleinfelter, *ibid.*, **89**, 1734 (1967); L. W. Reeves and W. G. Schneider, *Can. J. Chem.*, **35**, 251 (1957).

(8) Solute protons are *syn* to associated benzene when they are on the same side of the solute as the direction of association (*e.g.*, H_2 and H_3 in a, Figure 3) and *anti* when they are on the opposite side (*e.g.*, R and H_5 in a, Figure 3).

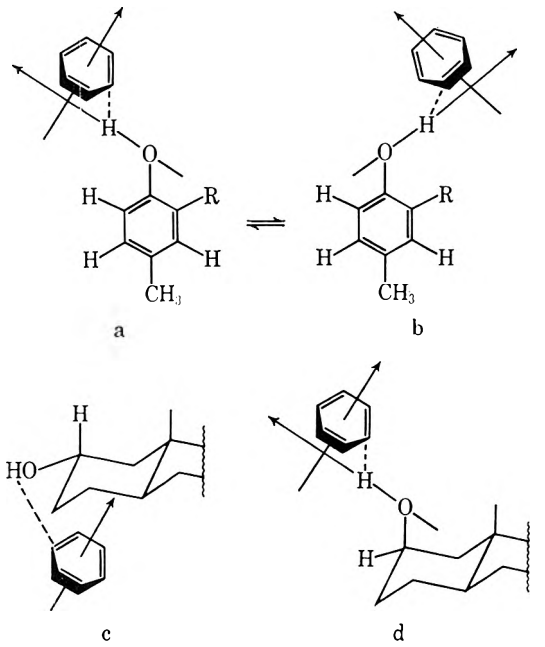

Figure 3.—Proposed model for stereochemical nature of benzene–alcohol association.

component. Thus, for compound **1** in benzene, the over-all net effect should be one of increased shielding for all solute protons. This is indeed observed to be the case, since $H_2(H_6)$, $H_3(H_5)$, and p-CH_3 illustrate increased shieldings of 0.08, 0.06, and 0.16 ppm, respectively.

Increase in the steric size of the *ortho* substituent in phenols will seriously disturb the population equilibrium between a and b such that, as R increases in size, the population of species b becomes smaller. Thus, progressive increases in the steric bulk of R from H, as in **1**, to $-CH_3$, as in **2**, to $-C(CH_3)_3$, as in **3**, should result in corresponding increases and decreases in the shielding of solute protons *syn* and *anti*, respectively, to the site of association. That this is observed to be the case is evidenced by the recorded Δ values for protons in **1**, **2**, and **3**. It is seen that H_2 becomes increasingly shielded [0.08 (**1**), 0.14 (**2**), and 0.38 (**3**)], while R [0.08 (**1**), 0.04 (**2**), and −0.11 (**3**)] and H_5 [0.06 (**1**), 0.01 (**2**) and −0.17 (**3**)] become increasingly deshielded. Parallel observations are observed for protons in **4**, **5**, and **6**, (see Figure 2) and add further support for the proposed model.

Hydroxy Steroids.—Small, but nevertheless significant, Δ values are recorded for the H-18 and H-19 protons in a number of monohydroxy steroids. Results, summarized in Table I, indicate that these protons experience increased shielding in benzene ($\Delta \cong 0.1$) except in those cases where hydroxyl and methyl groups are situated 1,3 diaxial (**9**, **13**, **15**, and **17**) to each other. In such cases, shifts to lower field are noted ($\Delta \cong -0.1$ ppm). The stereochemical nature of the benzene–solute complexes which rationalize these observations is shown in Figure 3c and 3d for solutes 5α-androstan-2α-ol, respectively, and demonstrate that in the former case benzene associates from the α face while in the latter case association takes place from the β face of the steroid molecule. The above findings indicate that, in addition to other solvent shift techniques,[9] benzene Δ values may be useful in establishing both the location and the stereochemical nature of protons situated in the vicinity of hydroxyl functions.

Although the model proposed above (Figure 1c) for benzene–hydroxyl function association is qualitatively in good agreement with observed solvent shift data, it is naive to presume that this model represents the total physical picture for such interactions. Indeed, it is possible that secondary association of benzene to solute phenol molecules, in a manner similar to that demonstrated for benzene association to toluene and *t*-butyl benzene,[2] could give rise to complexes of greater than 1:1 stoichiometry. Our interpretation of observed Δ values (Figure 2), however, if correct, suggests that the contribution to the total screening coefficient from such secondary associations is small.

(9) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

Experimental Section

Nmr spectra were recorded at 100 MHz at normal probe operating temperature (30 ± 1°) using TMS as internal lock and reference. Sample concentrations were maintained at less than 5% w/v. Peak positions were recorded by observing difference 1 on the frequency counter (*i.e.*, the difference between the manual and sweep oscillator frequencies) and phenolic proton resonance positions calculated from first-order analysis of their spectra.

Phenols 1–6 were commercially available compounds and were used without further purification. Hydroxy steroids (**7**–**19**), recorded in Table I, were synthetically prepared. Experimental details regarding their synthesis will be published elsewhere. These compounds display the requisite spectral properties and give correct elemental analyses.

Registry No.—**1**, 106-44-5; **2**, 105-67-9; **3**, 2409-55-4; **4**, 95-48-7; **5**, 576-26-1; **6**, 2311-05-9; **7**, 2287-84-5; **8**, 20707-85-1; **9**, 1225-47-4; **10**, 7657-50-3; **11**, 1224-92-6; **12**, 20707-77-1; **13**, 20707-78-2; **14**, 1090-01-3; **15**, 734-66-7; **16**, 1032-14-0; **17**, 1032-15-1; **18**, 19037-37-7; **19**, 1225-43-0.

Carbonium Ions. XXII. The Formation of Transient, Primary Carbonium Ions by Oxidation of Carboxylic Acids

N. C. DENO, W. E. BILLUPS, JOHN S. BINGMAN, ROBERT R. LASTOMIRSKY, AND ROBERT G. WHALEN

Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802

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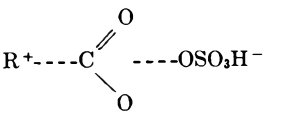
Solutions of $K_2S_2O_8$ in sulfuric acid or oleum oxidize carboxylic acids at 25°. The structures of the products are in accord with a mechanism involving formation of a mixed anhydride of the carboxylic acid and peroxymonosulfuric acid (Caro's acid) followed by exothermic decomposition of the mixed anhydride as shown.



I

The reaction possesses two points of interest. The intermediate R^+ forms $ROSO_3H$ in respectable yields. Since these alkyl hydrogen sulfates can be hydrolyzed in dilute acids to the alcohols, the reaction is a method for converting fatty acids into the alcohol with one less carbon. For example, butyric acid produces 1-propanol (eq 1).

$$CH_3CH_2CH_2COOH \longrightarrow CH_3CH_2CH_2OSO_3H \longrightarrow CH_3CH_2CH_2OH \quad (1)$$

The second point of interest is that the products are analogous to those formed in electrolytic oxidation of carboxylic acids, loss of N_2 from RN_2^+, loss of CO from ROC^+ in deoxidation, and loss of CO_2 from $ROCO^+$. This is most evident where R is branched and extensive rearrangements occur. The decomposition shown in I can thus be added to the above list[1] of methods for generating highly reactive, extensively rearranging carbonium ions. Such ions have been variously termed hot, encumbered, or free.[2]

The reactions are conducted by dissolving $K_2S_2O_8$ into 96% H_2SO_4 (or 25% oleum) in the ratio 1:3. The carboxylic acid is then cautiously added. The reaction is exothermic, so cooling is required and the CO_2 evolution can be vigorous. Reverse addition, *i.e.*, addition of $K_2S_2O_8$ to a stirred solution of the RCOOH in the acid, gives about the same results in the examples described below.

Acetic acid is notably more reluctant to react than its higher homologs. A fivefold excess of oxidant in 96% H_2SO_4 gave ultimately only 2% methyl hydrogen sulfate. However, in 25% oleum, a fivefold excess of oxidant gave 60% methyl hydrogen sulfate and more oxidant led ultimately to complete conversion. In the reaction in 96% H_2SO_4, an nmr band at δ 2.35 appeared and disappeared. This was interpreted as formation of a peracetic acid derivative, which decomposed back to acetic acid. The methyl hydrogen sulfate and acetic acid (protonated) were identified by adding methanol and acetic acid directly to the reaction mixture and establishing exact coincidence of nmr bands. This method of identification was used throughout.

Propionic acid was converted to 36% ethyl hydrogen sulfate with 51% unchanged propionic acid using 1 equiv of $K_2S_2O_8$ in 96% H_2SO_4. The yield based on reacted propionic acid is thus 72%. Accompanying the ethyl hydrogen sulfate was 4% acetic acid and 10% ethylene glycol, as its hydrogen sulfate. The glycol is believed to arise by some of the intermediate ethyl cation losing a proton to form ethylene, which epoxidizes. It was independently demonstrated that ethylene produces ethylene glycol under the reaction conditions and that ethyl hydrogen sulfate does not.

In 25% oleum, there was a far greater tendency to produce ethylene. Using equimolar $K_2S_2O_8$, the major product is ethionic acid ($HO_3SOCH_2CH_2SO_3H$, nmr triplets at δ 3.80 and 4.60, J = 5.2 cps), the known product of ethylene and oleum,[3] with lesser amounts of ethyl hydrogen sulfate and a trace of ethylene glycol hydrogen sulfate. Again the reaction uses the oxidant more efficiently in the oleum, but the greater preponderance of alkene derivatives is a disadvantage in designing RCOOH to ROH conversions.

Butyric acid with an equimolar quantity of $K_2S_2O_8$ in 96% H_2SO_4 gave 34% 1-propyl hydrogen sulfate, 29% unreacted butyric acid, 18% acetic acid, 9% 2-propyl hydrogen sulfate, 7% acetone, and 4% methyl hydrogen sulfate.

A number of larger fatty acids have been examined and all react, but conditions for optimum yields have not been determined.

A typical branched acid is 3-methylbutyric acid. Using a threefold excess of oxidant in 96% H_2SO_4, the products were 32% 2,3-butanediol hydrogen sulfate,[4] 26% ethyl hydrogen sulfate, 29% acetic acid, and 13% methyl hydrogen sulfate. The large preponderance of 2,3-butanediol and ethanol is remarkable, because these are formed from 2-butanol and $K_2S_2O_8$ in sulfuric acid, but are not formed from either isobutyl or *t*-butyl alcohols.[5]

It is concluded that the intermediate isobutyl cation largely rearranges by methyl shift to form the 2-butyl cation. This partly loses a proton to form 2-butene, which undergoes a normal epoxidation and opening to form 2,3-butanediol. The remainder oxidizes to 2-butanone, which undergoes a Baeyer–Villiger cleavage to ethanol and acetic acid. These interpretations were supported by demonstrating that *cis*- or *trans*-2-butene gave 2,3-butanediol (>90%) and that 2-butanone gave ethanol (>90%) and acetic acid when oxidized by solutions of $K_2S_2O_8$ in 96% H_2SO_4.

The preponderance of methyl shift (to form 2-butyl cation) relative to hydride shift (to form *t*-butyl cation) has been observed before as in the anodic oxidation of 3-methylbutyric acid,[6,7] deoxidation of isobutyl alcohol,[6] and aprotic deaminations of isobutylamine,[8] but never in as high a ratio as the 20:1 estimated from the above results.

The reactions described do not occur to any appreciable extent in 80% and more dilute sulfuric acids, and are only indirectly related to peroxymonosulfate[9] and persulfate[10] oxidations in aqueous media.[8]

Registry No.—Butyric acid, 107-92-6; acetic acid, 64-19-7; propionic acid, 79-09-4; 3-methylbutyric acid, 79-31-2.

Acknowledgment.—Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this work.

(1) P. Beak, R. J. Trancik, J. B. Mooberry, and P. Y. Johnson, *J. Amer. Chem. Soc.*, **88**, 4288 (1966); P. Beak and R. J. Trancik, *ibid.*, **90**, 2714 (1968).

(2) J. T. Keating and P. S. Skell in "Carbonium Ions," Vol. 2, G. A. Olah and P. von R. Schleyer Ed., Interscience Publishers, Inc., New York, N. Y., in press.

(3) A. Michael and N. Weiner, *J. Amer. Chem. Soc.*, **58**, 295 (1936).

(4) In all cases, primary and secondary alcohol groups are presumably present as the hydrogen sulfates, since it has been shown that such conversions are general in 96% sulfuric acid (N. Deno and M. S. Newman, *ibid.*, **72**, 3852 (1950).

(5) A later paper will describe the products from these alcohols.

(6) B. S. and M. S. Theses of R. J. Maxwell, Pennsylvania State University, 1962 and 1963, directed by P. S. Skell.

(7) W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **86**, 4686 (1964).

(8) J. H. Bayless, F. D. Mendicino, and L. Friedman, *ibid.*, **87**, 5790 (1965); J. H. Bayless, A. T. Jurewicz, and L. Friedman, *ibid.*, **90**, 4466 (1968).

(9) R. J. Kennedy and A. M. Stock, *J. Org. Chem.*, **25**, 1901 (1960).

(10) D. D. Tanner and S. A. A. Osman, *J. Amer. Chem Soc.*, **90**, 6572 (1969).

On the Question of Diequatorial Opening of Epoxides. 2,3-Dimethyl-2-octalin Oxide[1]

BRUCE RICKBORN[2] AND DAVID K. MURPHY

Department of Chemistry, University of California, Santa Barbara, Santa Barbara, California 93106

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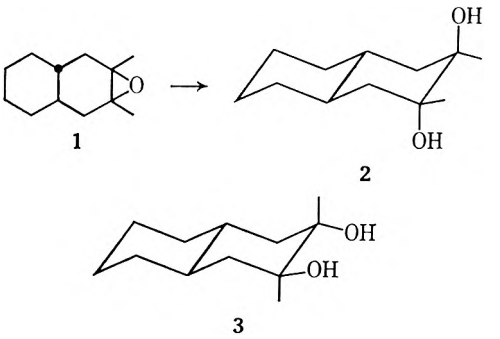
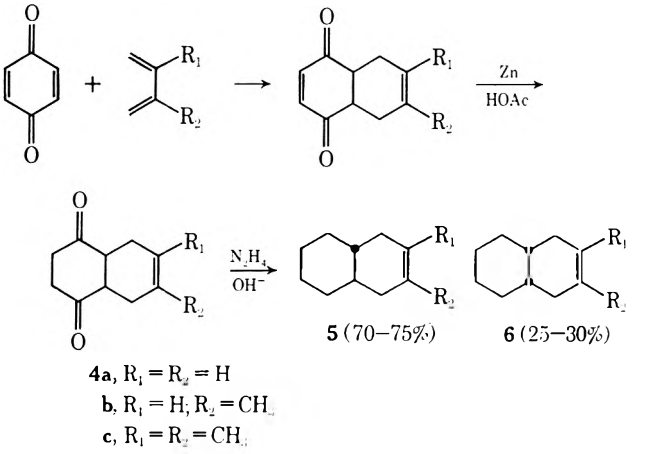
Henbest, Smith, and Thomas[3] have reported that the acid-catalyzed hydration of *trans*-2,3-dimethyl-2-octalin oxide **1** gives a mixture of *trans*-diaxial diol **2** (71%) and *trans*-diequatorial diol **3** (23%).



This work has been described without critical comment in at least one review,[4] even though it represents the *only reported example of "diequatorial" opening* of a normal epoxide.[5]

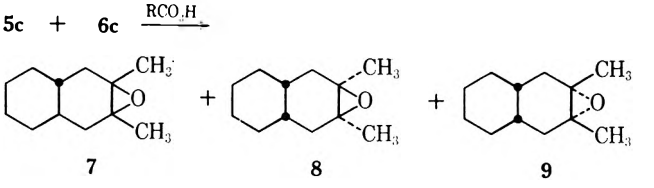
We wish to report that in fact Henbest's observation results from using a mixture of *cis* and *trans* ring-fused olefins (and hence epoxides). While working with 2-octalin[7] and 2-methyl-2-octalin,[6] we first noted the close similarity between the ratio of olefin products and the diol mixture obtained by Henbest. The route to the 2-octalins has been described previously.[3,8]

Henbest[3] subjected the *cis*-hexahydronapthoquinone **4c** to base-catalyzed equilibration and recrystallization to obtain *trans* ring-fused material. As Johnson[8] has pointed out in connection with the synthesis of **5a**, this procedure is unnecessary and fruitless in view of the expected equilibration under the strongly basic Wolff–Kishner reaction conditions. Essentially the same mixture of **5** (*ca.* 75%) and **6** (*ca.* 25%) is obtained by this sequence regardless of the stereochemistry of **4** or the degree of substitution of the double bond (**a**, **b**, or **c**).



4a, $R_1 = R_2 = H$
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = R_2 = CH_3$

Unlike the parent olefin (**5a** + **6a**),[7] the dimethyl derivative (**5c** + **6c**) could not be separated by fractional distillation using a Teflon spinning-band column.[9] Conversion of a mixture (*ca.* 70% **5c**, 30% **6c**; no vinyl proton absorption by nmr) to the epoxide gave a mixture which showed two peaks by vpc (73.6%, 26.4%). Three epoxides should be formed under these conditions, although **6c** should lead predominantly to **8** by analogy with the reaction of *cis*-4,5-dimethylcyclohexene.[10] The percentages indicate that **7** and **8** were separated under the vpc conditions used, with **9** appearing under



one or the other of these peaks. Attempted fractional distillation of this epoxide mixture was also unsuccessful, although some enrichment of the major peak component could be accomplished.

Hydration of the same epoxide mixture was carried out with aqueous sulfuric acid in acetone. Two diol products were formed in a ratio of 76.4 to 23.6%; samples were collected by preparative vpc and proved by melting point to be analogous to those obtained by Henbest.[3] It is clear, therefore, that the major diol is the diaxial product **2**, while the minor diol is derived from *cis*-epoxide(s) **8** (and **9**).

Experimental Section

The procedure of Henbest and coworkers[3] was used to prepare the olefin mixture (**5c**, **6c**) except that the dione **4** was not equilibrated and purified. *m*-Chloroperbenzoic acid was used to generate the epoxide mixture (**7**, **8**, **9**); it gave two peaks by vpc, 73.6 to 26.4%.

A sample (0.3 ml) of this mixture was treated with 5 ml of 1% sulfuric acid in 5 ml of acetone for 23 hr at 25°. The product was taken up in ether, washed with water, dried, and evaporated to give a syrup which was separated by vpc using a Carbowax 20M column. The major diol had mp 115–116° (lit.[3] mp 119–121°); the minor product had mp 80–83° (lit.[3] mp 81–85°).

Registry No.—**1**, 21298-07-7; **2**, 21298-08-8.

(1) Support by the National Science Foundation (9383) is gratefully acknowledged.

(2) Alfred P. Sloan Fellow, 1967–1969.

(3) H. B. Henbest, M. Smith, and A. Thomas, *J. Chem. Soc.*, 3293 (1958).

(4) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part One, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1964, p 284.

(5) Several examples of kinetically controlled equatorial product forming reactions of epoxides are known, but these invariably involve conformationally flexible systems with particular substituent effects. We have recently discussed this problem in connection with hydride reduction of substituted cyclohexene oxides.[6]

(6) D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Amer. Chem. Soc.*, **91**, 2649 (1969).

(7) R. Thummel, unpublished results.

(8) W. S. Johnson, V. J. Baker, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961).

(9) Henbest[3] reported only diaxial diol from his sample of **5a**, which apparently was substantially purified by distillation.

(10) B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965); this olefin gives 13% *cis*-epoxide, suggesting that only 3–4% **9** would be formed in the above reaction.

Some Observations on the Reactions of Cyclopropane with Hydrochloric Acid and of Bromocyclopropane with Hydrobromic Acid

C. C. LEE, BO-SUP HAHN, KWOK-MING WAN, AND D. J. WOODCOCK

Department of Chemistry and Chemical Engineering, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

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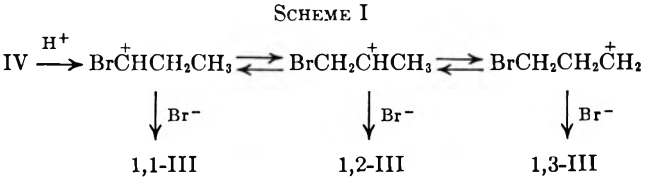
In a recent paper from this laboratory,[1] it was reported that the reaction between cyclopropane (I) and tritiated Lucas reagent ($ZnCl_2$–HCl-*t*) gave only 1-chloropropane (II-*t*) with no 2-chloropropane, and the *t* label was found in all three carbon positions of the 1-chloropropane. These results were interpreted as arising from equilibrating edge-protonated cyclopropane intermediates. In these experiments, II-*t* was swept out of the reaction mixture by an excess of I. This procedure also served to minimize the contact between II-*t* and the Lucas reagent, since Reutov and Shatkina[2] have reported that when 1-^{14}C-1-chloropropane (II-1-^{14}C) was treated with $ZnCl_2$–HCl, although no 2-chloropropane was formed, various extents of rearrangement to II-3-^{14}C were observed, depending on temperature and contact time; for example, at 50° for 100 hr, 7.5% rearrangement was noted. In an attempt to verify this reported 1,3-hydride shift, 1-*t*-1-chloropropane (II-1-*t*) and $ZnCl_2$–HCl were heated under reflux at 50 ±2° for 100 hr. The recovered II-1-*t* was uncontaminated by 2-chloropropane, as found by Reutov and Shatkina;[2] however, it also showed no rearrangement of the isotopic label. These results were confirmed when the treatment of II-1-*t* with $ZnCl_2$–HCl was carried out with shaking in a sealed tube at 50 ±2° for 100 hr. The present results, similar to those obtained in the earlier work on the deamination of 1-^{14}C-1-aminopropane,[3] again failed to confirm the 1,3-hydride shift reported by Reutov and Shatkina, and thus established that the isotope position rearrangements observed in the reaction between I and $ZnCl_2$–HCl-*t* did not involve complications arising from interactions between II-*t* and the Lucas reagent.

Since I has been protonated by H_2SO_4-*t* or D_2SO_4 of various concentrations without any catalyst,[4] it is of interest to ascertain if the $ZnCl_2$ is necessary in effecting the reaction between I and HCl. When I was passed through 12 *M* HCl-*t* and the material swept out by the excess I was studied as previously,[1] only II-*t*, uncontaminated by 2-chloropropane, was obtained. The yields of II-*t* and the distributions of the *t*-label are summarized in Table I. It is seen that there is no significant difference in the results obtained from the reactions of I with 12 *M* HCl, with or without the presence of $ZnCl_2$. When the reaction was effected in the presence of 5% $AlCl_3$, however, the product II-*t* was contaminated by 3–4% 2-chloropropane, and somewhat different *t*-distributions in the II-*t*, also shown in Table I, were observed. These differences are likely due, at least in part, to the effects of $AlCl_3$ on the initially formed II-*t*, since Karabatsos and coworkers[5] have reported that when D-labeled 1-bromopropane was treated with $AlBr_3$ both conversion to 2-bromopropane and scrambling of the D-label in the recovered 1-bromopropane were observed.

Deno and Lincoln[6] have reported that the bromination of I, catalyzed by a Lewis acid, resulted in the formation of 1,1-, 1,2- and 1,3-dibromopropanes (1,1-, 1,2-, and 1,3-III), as well as some 1,1,2-tribromopropane. The production of the three isomeric dibromopropanes was attributed to the involvement of protonated bromocyclopropane intermediates derived from reaction of Br^+ with I. In view of these findings of Deno and Lincoln, an investigation was made on the formation of dibromopropanes from the reaction between bromocyclopropane (IV) and HBr. The experiments were carried out by stirring IV with 68% HBr at room temperature for various lengths of time, and the products were analyzed by vpc. Two runs were also carried out in the presence of a catalytic amount of $AlCl_3$. The results are summarized in Table II. The vapor phase chromatograms also showed some additional small peaks, indicating the presence of small amounts of other products, the nature of which, however, was not investigated. The complexity of these unidentified materials was greater when the reaction was effected in the presence of $AlCl_3$, suggesting some interactions between $AlCl_3$ and IV and possibly also between $AlCl_3$ and the products 1,1-, 1,2-, and 1,3-III.

In contrast to the bromination of I, which gave 1,3-III as the main product,[6] the reaction between IV and HBr gave mostly 1,1- and 1,2-III, with 1,3-III only as a minor product.[7] These results can be explained either by reactions involving classical carbonium ions (Scheme I[8]) or *via* short-lived nonisomerizing protonated bromocyclopropanes (Scheme II). A similar conclusion was reached by Deno and coworkers,[4c] who explained the sole formation of $CH_3CHClCH_2CH_2D$

SCHEME I



(1) C. C. Lee, W.K.-Y. Chwang, and K.-M. Wan, *J. Amer. Chem. Soc.*, **90**, 3778 (1968).

(2) O. A. Reutov and T. N. Shatkina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 180 (1963); O. A. Reutov, *Pure Appl. Chem.*, **7**, 203 (1963).

(3) C. C. Lee and J. E. Kruger, *J. Amer. Chem. Soc.*, **87**, 3986 (1965).

(4) (a) R. L. Baird and A. A. Aboderin, *ibid.*, **86**, 252 (1964); (b) C. C. Lee and L. Gruber, *ibid.*, **90**, 3775 (1968); (c) N. C. Deno, D. La Vietes, J. Mockus, and P. C. Scholl, *ibid.*, **90**, 6457 (1968).

(5) G. J. Karabatsos, J. L. Fry, and S. Meyerson, *Tetrahedron Lett.*, 3735 (1965).

(6) N. C. Deno and D. N. Lincoln, *J. Amer. Chem. Soc.*, **88**, 5357 (1966).

(7) Professor N. C. Deno, acting as a referee, has stated that some of the 1,3-III reported in ref 6 may have arisen from light-catalyzed free-radical addition of Br_2 to I. By operating entirely in the dark at 15°, the introduction of I into Br_2 containing 1% Fe powder was found to give 38% 1,1-III, 6% 1,2-III, 50% 1,3-III, and 6% 1,1,2-tribromopropane. Some work on the reaction between IV and HBr has also been done by Deno and Lincoln. When IV was stirred at 25° with a solution of one part 48% aqueous HBr and three parts $ZnBr_2$, after 2 weeks there was 70% unreacted IV, 23% 1,1-III, and 7% 1,2-III. Taking into consideration the difference in reaction conditions, Professor Deno regards their results as in substantial agreement with those obtained in the present work.

(8) It may be pointed out that direct protonation of IV could also give rise to the primary cations $CH_3CHBrCH_2^+$ and $BrCH_2CH_2CH_2^+$, which could react with Br^- to give 1,2-III and 1,3-III, respectively. However, by analogy with the protonation of methylcyclopropane,[4c] only the direct formation of $BrCHCH_2CH_3^+$ is shown in Scheme I.

TABLE I

ACTIVITY DISTRIBUTIONS IN THE 1-CHLOROPROPANE FROM REACTION OF CYCLOPROPANE WITH HCl-*t*

	c-C_3H_6 + $ZnCl_2$ − HCl-*t*[a]				*c*-C_3H_6 + HCl-*t*				*c*-C_3H_6 + $AlCl_3$ − HCl-*t*			
		t-Distribution, %				*t*-Distribution, %				*t*-Distribution, %		
Run	Yield,[b] g	C-1	C-2	C-3	Yield,[b] g	C-1	C-2	C-3	Yield,[b] g	C-1	C-2	C-3
1	4.6	38.6	16.6	44.7	3.4[c]	37.7	18.2	44.1	3.5[c]	33.3	21.4	45.3
2	4.8	37.2	19.7	43.1	5.7	37.7	15.6	46.7	5.9	33.8	22.8	43.4
3	5.8	37.7	18.8	43.5	4.8	38.3	17.1	44.6				

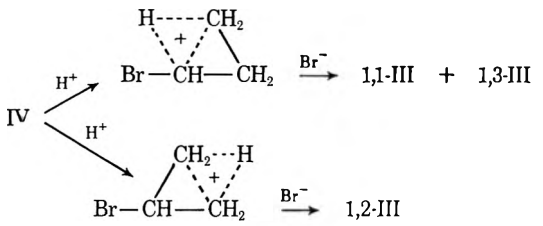
[a] From ref 1. [b] Estimated by isotope dilution calculations. [c] The *c*-C_3H_6 was bubbled through the reaction mixture for 16 hr; in the other experiments, the bubbling time was 24 hr.

TABLE II

DATA FROM REACTIONS BETWEEN BROMOCYCLOPROPANE (IV) AND HBr WITH OR WITHOUT THE PRESENCE OF $AlCl_3$

	Reaction time, hr	Recovered IV, %	Dibromopropane obtained, % 1,1-	1,2-	1,3-
No $AlCl_3$	1	95.8	0.8	1.1	...
	2	86.7	2.9	3.7	Trace
	6	71.6	9.0	10.4	3.5
	24	53.4	21.5	14.5	6.5
$AlCl_3$	2	69.6	6.6	8.1	Trace
	12	64.3	12.9	15.3	0.5

SCHEME II



from the addition of DCl to methylcyclopropane as the result of the addition of D^+ to methylcyclopropane to give the 2-butyl cation directly or *via* a short-lived nonisomerizing protonated methylcyclopropane.

Experimental Section

1-*t*-1-Chloropropane (II-1-*t*).—A mixture of 10.7 g (50 mmol) of 1-*t*-propyl tosylate and 11.0 g (100 mmol) of $CaCl_2$ in 75 ml of ethylene glycol was placed in a flask fitted for distillation. The flask was heated at 70–75° for 3 hr while a slow stream of nitrogen was passed over the reaction mixture to sweep out the product. The 1-*t*-1-chloropropane so obtained (in about 75% yield) was passed through anhydrous $CaCl_2$ and collected in a receiver cooled in Dry Ice–acetone.

Treatment of 1-*t*-1-Chloropropane (II-1-*t*) with $ZnCl_2$–HCl.—A mixture of 8.0 g (102 mmol) of II-1-*t*, 20.4 g (150 mmol) of $ZnCl_2$, and 12.5 ml (150 mmol) of 12 *M* HCl in a 50-ml flask was heated under reflux at 50 ± 2° for 100 hr. An efficient condenser was employed and the top of the condenser was loosely stoppered to minimize the loss of chloride. After the period of gentle refluxing was completed, about 2.0 g of II-1-*t* was recovered. Analysis by vpc showed the absence of 2-chloropropane. In a number of experiments starting with II-1-*t* of specific activities varying from about 200,000 to 1,200,000 cpm per mmol, the recovered II-1-*t* was converted to 1-*t*-1-propanol, which on oxidation gave inactive propanoic acid,[1] showing no rearrangement of the *t*-label to C-2 and C-3. The same results were obtained when the mixture of II-1-*t* and $ZnCl_2$–HCl in a sealed tube was placed in a hydrogenation bomb and then shaken and heated at 50 ±2° for 100 hr.

Reaction between Cyclopropane (I) and HCl.—I was bubbled through 25 ml of 12 *M* HCl-*t* at room temperature for 24 hr, and the product obtained was worked up and degraded as described previously.[1] Vpc analysis of the 1-chloropropane so obtained showed the absence of any 2-chloropropane. When the reaction was carried out in the presence of $AlCl_3$, 5.0 g of anhydrous $AlCl_3$ per 100 g of 12 *M* HCl was employed. Since the solubility of $AlCl_3$ in 12 *M* HCl was low, the suspension was stirred by a magnetic stirrer during the passage of I through the mixture. Vpc analysis of the product by an 8 ft × 0.25 in. stainless steel column packed with 25% FFAP on 60–80 mesh Chromosorb W showed that the 1-chloropropane contained about 3–4% 2-chloropropane.

Reaction between Bromocyclopropane (IV) and HBr.—The HBr solution was prepared by bubbling gaseous HBr into distilled water cooled at about 0° until a saturated solution was obtained. Titration showed the HBr concentration as 68%. The same batch of HBr solution was used in all the experiments.

A mixture of 2.42 g (20 mmol) of IV and 10 ml of 68% HBr, without or with the presence of 1.5 mmol of $AlCl_3$, was placed in a 50-ml flask fitted with a reflux condenser and was stirred at room tmperature for the desired length of time. Water was then added and the resulting material was extracted with ether. The extract was washed with water uutil free of acid, dried over anhydrous $MgSO_4$, and analyzed by vpc for IV, 1,1-III, 1,2-III, and 1,3-III by the FFAP column described above. All identifications and calibrations were based on chromatographically pure samples of IV, 1,1-III, 1,2-III, and 1,3-III. 1,1-III was prepared by the method of Stevens and coworkers,[9] while the other authentic samples were purchased commercially.

Registry No.—I, 75-19-4; hydrochloric acid, 7647-01-0; IV, 4333-56-6; hydrobromic acid, 10035-10-6.

Acknowledgment.—The financial support given by the National Research Council of Canada is gratefully acknowledged.

(9) C. L. Stevens, T. K. Mukerjee, and V. J. Traynelis, *J. Amer. Chem. Soc.*, **78**, 2264 (1956).

Alkylation of Naphthalene with Alkenes

H. M. FRIEDMAN AND A. L. NELSON[1]

Emkay Chemical Company, Elizabeth, New Jersey, and University College, Rutgers, The State University of New Jersey, New Brunswick, New Jersey

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Whitmore and James[2] reported the formation of 2-*t*-butylnaphthalene plus uncharacterized higher alkylation products in the aluminum chloride catalyzed reaction of naphthalene with isobutylene. Other reports of the alkylation of naphthalene with olefins, alcohols, or alkyl halides also indicate preferential formation of the 2 isomer.[3,4] This preference for the 2 isomer has been argued on steric grounds in the case of bulky olefin–catalyst complexes and on the basis of rearrangement of the kinetically favored 1 isomer.

This communication reports work undertaken to investigate the alkylation of naphthalene with olefins under nonisomerizing conditions and thereby to deter-

(1) To whom correspondence should be addressed at Wright Laboratory, Rutgers, The State University, New Brunswick, N. J. 08903.

(2) F. C. Whitmore and W. H. James, *J. Amer. Chem. Soc.*, **65**, 2088 (1943).

(3) "Friedel-Crafts and Related Reactions," Vol. II, G. Olah, Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, Chapter XIV.

(4) H. E. Nursten and A. T. Peters, *J. Chem. Soc.*, 729 (1950).

mine the kinetically controlled isomer distribution. For this purpose, BF_3–H_3PO_4 was chosen as the catalyst system, work by Topchiev and his coworkers[5,6] having shown alkylation to occur in high yields with lack of side reactions. The alkylation of benzene with propylene and the absence of transalkylation have been reported using this catalyst system.[3] The data obtained for six olefins are shown in Table I.

TABLE I
MONOALKYLATION OF NAPHTHALENE[a]

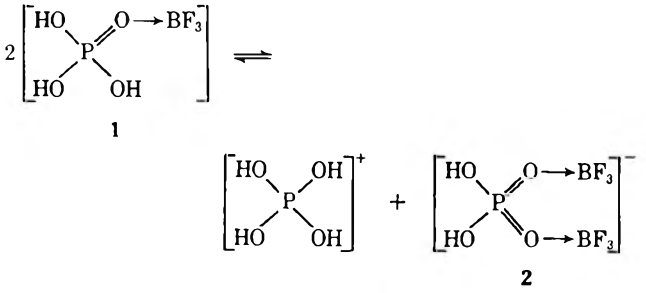
Alkene	Mono,[b] %	R	1, %	2, %
Propylene	69	—CHMe$_2$	70	30
1-Butene	76	—CHEt (Me)	74	26
cis-2-Butene	81	—CHEt (Me)	72	28
trans-2-Butene	83	—CHEt	70	30
Isobutylene	76	—CMe$_3$	0	100
Diisobutylene	81	—CMe$_3$	0	100

[a] Temperature 5–10°, catalyst BF_3–H_3PO_4, reaction time 6 hr. [b] Mole per cent of monoalkylate in a mixture of mono- and dialkylate. The mixture accounts for 75–90% of the weight of crude alkylate.

The mono-, di-, and polyalkylation products were separated by fractional distillation and the 1 and 2 isomer by vapor phase chromatography. The products were characterized by a combination of infrared and nuclear magnetic resonance spectroscopy.

It was shown that, under the conditions of the reaction, none of the 1 isomers rearranged. The 1-*t*-butylnaphthalene required for this purpose was prepared by the method of Illingworth and Peters.[7]

Topchiev and coauthors[6] review coordination compounds of the type formed between equimolar amounts of boron trifluoride and phosphoric acid. Greenwood and Thompson[8] postulate an equilibrium between the complex **1** of boron trifluoride and phosphoric acid and its ionic form **2**.



The electrophile in this Friedel–Crafts alkylation might be expected to be of form **3** resembling the 1:1:1 complex reported by Olah and coworkers[9] for α olefins, boron trifluoride, and hydrogen fluoride.

$$RCH{=}CH_2 + H_3PO_4 + BF_3 \rightleftharpoons RC^+HCH_3(H_2PO_4BF_3)^-$$
3

An attractive mechanism for the Friedel–Crafts alkylation of aromatics by olefins postulates an attack by the aromatic ring on the olefin–catalyst complex.[10] If such a mechanism were operative in the alkylation of naphthalene with olefin–catalyst complexes, one would anticipate substantial dependence upon steric factors and the degree of ionic character in the olefin–catalyst complex.

The similarity of product distribution for the three butenes suggests the intermediacy of the common ionic species, the *sec*-butyl cation. Also, the equivalence for propylene is not surprising in view of the correspondence in steric requirements between isopropyl and *sec*-butyl groups, reported by Brown.[11] The preferential alkylation at the 1 position is explicable on the basis of the low temperature of the reaction and the lower transition-state energy for the formation of the corresponding naphthalenonium ion complex in a kinetically controlled mechanism. Dewar, Mole, and Warford[12] found partial rate factors of 470 and 50, respectively, for the 1 and 2 positions in the nitration of naphthalene.

The formation of no detectable 1-*t*-butylnaphthalene in the reactions of the isobutylenes suggests that in these cases, for steric reasons, the 2 isomer becomes the exclusive kinetic product. For olefins of size intermediate between isobutylene and 1-butene, it should be possible to approach kinetic equivalence between the 1 and 2 positions in naphthalene. Work in this direction is in progress.

In the reactions of isobutylene and diisobutylene, in addition to predominant 2-*t*-butylnaphthalene, the same variety of minor products was obtained, as shown in Table II.

TABLE II
"BUTYLATION" OF NAPHTHALENE[a]

Naphthalene derivative	With isobutylene, %	With diisobutylene, %
2-*t*-Butyl	70.0	73.4
2-(1,1-Dimethylpropyl)	2.0	4.4
2-(1,1-Dimethylbutyl)	0.6	0.7
2-(1,1,2-Trimethylpropyl)	1.1	0.9
2-(1,1,3-Trimethylbutyl)	1.2	1.0
2,6-Di-*t*-butyl	15.6	11.6
2,7-Di-*t*-butyl	8.8	8.0

[a] Temperature 5–10°, catalyst BF_3–H_3PO_4, reaction time 6 hr.

The structures of these products were determined spectroscopically, and it is believed that they arise through a polymerization–depolymerization mechanism similar to that reported by Hofmann and Schriesheim.[13]

In summary, it has been shown that even with relatively large olefin–catalyst complexes the 1 isomer is the kinetically favored product in the Friedel–Crafts alkylation of naphthalene.

(5) A. V. Topchiev, S. V. Zavgorodnii, and Ya. M. Paushkin, "Boron Fluoride and Its Compounds as Catalysts in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, Chapter III.

(6) A. V. Topchiev, S. V. Zavgorodnii, and V. G. Kryuchkova, "Alkylation with Olefins," Elsevier Publishing Co., 1964, Chapter II.

(7) E. Illingworth and A. T. Peters, *J. Chem. Soc.*, 1602 (1951).

(8) N. N. Greenwood and A. Thompson, *ibid.*, 3493 (1959).

(9) G. A. Olah, H. W. Quinn, and S. J. Kuhn, *J. Amer. Chem. Soc.*, **82**, 426 (1960).

(10) G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuck, *ibid.*, **86**, 1046 (1964).

(11) H. C. Brown, *J. Chem. Ed.*, **36**, 424 (1959).

(12) M. J. S. Dewar, T. Mole, and E. W. T. Warford, *J. Chem. Soc.*, 3581 (1956).

(13) J. E. Hofmann and A. Schriesheim, *J. Amer. Chem. Soc.*, **84**, 953, 957 (1962).

Experimental Section

General.—Diisobutylene (Atlantic Richfield Co.), boron trifluoride (Allied Chemical Co.), and naphthalene (Fisher Scientific Co.) were used without purification. All other chemicals were of the highest purity available from the Matheson Chemical Co.

Boiling points are uncorrected. Infrared spectra were measured as neat films or in carbon tetrachloride solutions on a Beckman IR-10 instrument.

The vpc analyses were done on a Varian-Aerograph Model 1520 instrument under the following conditions.

Nuclear magnetic resonance spectra were obtained on Varian A-60 and HA-100 instruments. Microanalyses were performed by Micro-Analyses, Inc., Wilmington, Del.

Boron Trifluoride–Phosphoric Acid Complex.—In a dry 1000-ml three-neck flask, equipped with a thermometer, a gas dispersion tube, and a calcium chloride tube, 300 g (2.60 mol) of 85% phosphoric acid was saturated with boron trifluoride. The product, 585 g, sp gr 1.84 (30°), corresponded to an equimolar mixture.

Alkylation of Naphthalene. Standard Procedure.—Over a period of 60 min, 0.60 mol of the olefin was added at a constant rate to a slurry of 51 g of the catalyst and 64 g (0.50 mol) of naphthalene in a 500-ml three-neck flask equipped with a thermometer, reflux condenser, stirrer, gas inlet tube, and cooling bath. The reaction temperature was held at 5–10°. This procedure was repeated three more times by sequential additions of these quantities of the reactants.[14] Finally, the reaction mixture was held at 5–10° for 2 additional hr. The organic layer was separated from the lower catalyst layer, washed with water, 5% sodium hydroxide, and again with water, and dried over anhydrous sodium sulfate to yield a crude mixture, A, of naphthalene and mono- and dialkylnaphthalenes. Vpc (column A, 1 μl) gave the distribution of these three components. For isolation of the monoalkylnaphthalenes, it was found expedient to remove the naphthalene and dialkylnaphthalenes prior to preparative vpc analysis by vacuum distillation (1–10 mm) of A using a 12-in. Vigreux column followed by a redistillation through a Nester and Faust 24-in. Teflon spinning-band column to give purified mixture B. The 1- and 2-monoalkylnaphthalenes were separated by vpc through larger columns (Table III).

TABLE III

Column	Length, ft	Diameter, in.	Type	Helium rate, ml/min	Temp, °C: Injection	Temp, °C: Column
A	20	1/4	Apiezon L (20%)	100	290	230–300
B	20	3/8	EG-SP-Z (20%)	150	290	188
C	30	1/4	SE-52 (10%)	150	300	254
D	50	3/8	Apiezon L (20%)	170	290	232

Table IV gives a summary of the results of using this procedure with the six alkenes.

TABLE IV

COMPOSITION OF CRUDE ALKYLATE

Alkene	Wt of A, g	Vpc analysis,[a] mol %: Naphthalene	Dialkyl	Monoalkyl
Propylene	357	23.5	25.6	62.9
1-Butene	347	6.7	17.7	75.6
cis-2-Butene	338	9.7	14.0	76.3
trans-2-Butene	336	12.1	12.1	75.6
Isobutylene	388	34.5	12.9	52.6
Diisobutylene	368	39.4	9.4	51.2

[a] Column A (Table III), with results expressed as mole per cent.

In each case, the purified mixture B was separated by preparative vpc to give the data in Table V.

The new compounds reported in these series are as follows.

1-*sec*-Butylnaphthalene.—The ir region of 700–900 cm^{-1} was of particular value[15] in this identification, and the nmr spectra showed the patterns to be expected for *sec*-butyl groups: τ 9.15 (t, CH_3), 8.72 (d, CH_3), 8.0–8.5 (m, CH_2), 6.3–6.8 (m, CH), and 1.8–2.8 (naphthyl CH).

Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.11; H, 8.74.

(14) This procedure allowed satisfactory mixing of the reactants throughout the entire reaction cycle.

(15) American Petroleum Institute, Infrared Spectral Data, 763, 1980.

TABLE V

MONOALKYLATION PRODUCTS

Alkyl group	Column	Amount injected, μl	Retention time: 1-Alkyl	Retention time: 2-Alkyl
Isopropyl	C	15	81.1	73.2
sec-Butyl	D	40	65.1	68.6
t-Butyl	B	50	47.4[a]	41.3

[a] No 1-*t*-butylnaphthalene is formed in this alkylation. Retention time is for a sample prepared independently by the method of Illingworth and Peters.[7]

2-*sec*-Butylnaphthalene.—The 700–900-cm^{-1} region in the ir showed the expected substitution.[15] The nmr had τ 9.17 (t, CH_3), 8.71 (d, CH_3), 8.0–8.6 (m, CH_2), 7.0–7.6 (m, CH), and 2.1–2.8 (naphthyl CH).

Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.00; H, 8.91.

Four additional 2-alkylated naphthalenes were obtained in the reactions with both isobutylene and diisobutylene. Due to small quantities obtained (20–40 mg), identification was possible only by nmr, ir, and mass spectra, and is as indicated in Table VI.

TABLE VI

ADDITIONAL 2-ALKYLATED PRODUCTS FROM ISOBUTYLENES

Alkyl compd	Retention time[a]	Molecular formula[b]
1,1-Dimethylpropyl	21.0	$C_{13}H_{18}$
1,1-Dimethylbutyl	24.2	$C_{16}H_{20}$
1,1,2-Trimethylpropyl	26.3	$C_{16}H_{20}$
1,1,3-Trimethylbutyl	27.6	$C_{17}H_{22}$

[a] Column (SE-52), 30 ft × 0.25 in., 35-μl injection. [b] As determined from mass spectrum.

Attempted Isomerization of 1-Alkylnaphthalenes.—The heating of 100-mg samples of 1-*sec*-butyl-, *t*-butyl-, and isopropylnaphthalenes with the catalyst under reaction conditions gave no isomerization which could be detected by vpc.

Registry No.—Naphthalene, 91-20-3; 1-*sec*-butylnaphthalene, 1680-58-6; 2-*sec*-butylnaphthalene, 4614-03-3; 2-(1,1-dimethylpropyl)naphthalene, 20798-05-4; 2-(1,1-dimethylbutyl)naphthalene, 20798-06-5; 2-(1,1,2-trimethylpropyl)naphthalene, 20798-07-6; 2-(1,1,3-trimethylbutyl)naphthalene, 20798-08-7; propylene, 115-07-1; 1-butene, 106-98-9; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; isobutylene, 115-11-7.

Acknowledgment.—The invaluable assistance of John Jungnickel of Shell Development Company, for the recording and interpretation of a portion of the nmr and mass spectra, is greatly appreciated.

2,3-Dihydro-1H-imidazo[1,5-*b*]pyrazole-4,6(3aH,5H)-dione

JULIAN G. MICHELS AND GEORGE C. WRIGHT

Chemistry Division, The Norwich Pharmacal Company Research Laboratories, Norwich, New York 13815

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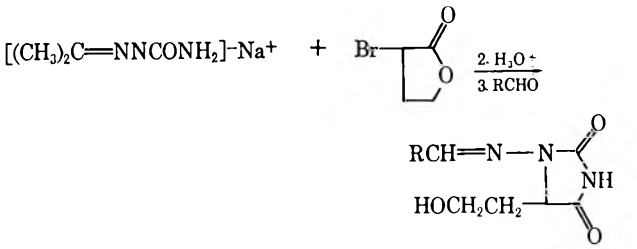
Our interest in nitrofurantoin[1] and its 3-substituted derivatives[2] has led us to prepare certain of its 5-substi-

(1) The generic name for 1-(5-nitrofurfurylidenamino)hydantoin, The Norwich Pharmacal Co.'s registered trademark of which is Furadantin®; K. J. Hayes, U. S. Patent 2,610,181 (1952).

(2) (a) J. G. Michels, U. S. Patents 3,075,972, 3,075,973, 3,075,974, and 3,097,202 (1963); (b) C. F. Spencer and J. G. Michels, *J. Org. Chem.*, **29**, 3416 (1964).

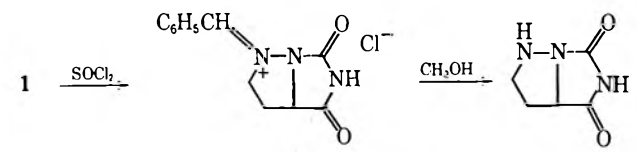
tuted derivatives. For the preparation of these compounds, advantage was taken of the method of Jack[3] for the synthesis of 1-aminohydantoin *via* acetone semicarbazone and ethyl chloroacetate.

When the sodium salt of acetone semicarbazone is allowed to react with α-bromo-γ-butyrolactone and the reaction mixture is then subjected to acid hydrolysis, 1-amino-5-(2-hydroxyethyl)hydantoin is formed. This product is most easily isolated as its benzaldehyde (**1**) or 5-nitro-2-furaldehyde (**2**) derivative.



1, R = phenyl
2, R = 5-nitro-2-furyl

With thionyl chloride, **2** was readily converted into the corresponding chloroethyl compound and thence to the pyridinium quaternary compound on treatment with pyridine. However, when an attempt was made to prepare the chloroethyl derivative of **1** by the same procedure, a compound (**3**) was obtained which contained ionic chlorine and liberated benzaldehyde in water. Solution of **3** in methanol followed by precipitation with dry ether converted it into another compound (**4**) which contained ionic chlorine but no longer liberated benzaldehyde in water. On recrystallization from 2-propanol, **4** lost hydrogen chloride and formed the free base **5**. The changes occurring in this sequence of reactions are interpreted as follows.



3

4, HCl salt
5, free base

Structure **3** is consistent with the easy hydrolysis, forming benzaldehyde, whereas the alternative benzylideneamino four-membered ring structure would not be expected to be so labile. The infrared spectrum of **3** shows a strong band at 6.03 μ which is also consistent with a highly polar C=N bond. This band is not present in **4**. von Euler and Hasselquist[4] suggested the imidazo[1,5-*b*]pyrazole ring system as one possibility for the compound which they obtained from the reaction of L-histidine with hydrogen peroxide in acetic acid, but an unequivocal synthesis has not previously been reported.

Experimental Section[5]

1-(Benzylidenamino)-5-(2-hydroxyethyl)hydantoin (1).—To a solution of 46 g (0.85 mol) of sodium methoxide in 150 ml of 2-propanol was added a suspension of 98 g (0.85 mol) of acetone semicarbazone in 50 ml of 2-propanol and the mixture was refluxed to effect solution. The cooled solution was added slowly, without heat, to a solution of 70 g (0.425 mol) of α-bromo-γ-butyrolacetone[6] in 75 ml of 2-propanol. The mixture was stirred for 15 min after the addition and was then cooled to about 15°. A mixture of 46 g (0.85 mol) of sodium methoxide and 50 ml of 2-propanol was added and the reaction was stirred at room temperature for 15 min. A second solution of 70 g (0.425 mol) of α-bromo-γ-butyrolactone in 50 ml of 2-propanol was then added during 15 min. The entire mixture was refluxed for 30 min, stirred for an additional hour, and then cooled in ice while 250 ml of 50% sulfuric acid was added. The mixture was refluxed and sufficient water was added to effect solution. After refluxing for about 15 min, the solution was cooled. To one-half of this solution was added with stirring 45 ml (0.43 mol) of benzaldehyde and the mixture was chilled thoroughly. The solid formed was filtered and washed with water. It was purified by dissolving in dilute ammonia, treating with charcoal, and reprecipitating with acid. After washing and air drying there was obtained 21 g (20%) of **1**, mp 180–183°. For analysis, a sample was recrystallized from water: uv max (H_2O) 288 mμ (*E* 21,100); nmr (DMSO-d_6 δ 2.15 (m, 2, CH_2CH_2CH), 3.53 (t, 2, $HOCH_2$), 4.50 (ex, 1, HO), 4.74 (t, 1, CH_2CH), 7.48 and 7.77 (m, 5, C_6H_5), 8.45 (s, 1, C_6H_5CH), 10.12 (ex, 1, NH).

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.21; H, 5.34; N, 17.01.

5-(2-Hydroxyethyl)-1-[(5-nitrofurfuryliden)amino]hydantoin (2).—The second half of the solution indicated above was treated with a solution of 60 g (0.43 mol) of 5-nitrofurfural in 200 ml of 2-propanol and then chilled in ice. The yellow product was filtered and washed with water. It was purified by dissolving in dilute ammonia, treating with charcoal, and reprecipitating with acid. After washing and air drying there was obtained 29 g (24%) of **2**, mp 217–218°. For analysis, a sample was recrystallized from water: the melting point did not change; uv max (H_2O) 365 mμ (*E* 17,150) and 265 (10,800); nmr (DMSO-d_6) δ 2.18 (m, 2, CH_2CH_2CH), 3.52 (t, 2, $HOCH_2$), 4.55 (ex, 1, HO), 4.76 (t, 1, CH_2CH), 7.21 (d, 1, furan-3), 7.78 (d, 1, furan-4), 8.38 (s, 1, CH=N), 11.33 (ex, 1, NH).

Anal. Calcd for $C_{10}H_{10}N_4O_6$: C, 42.56; H, 3.57; N, 19.85. Found: C, 42.53; H, 3.57; N, 19.79.

5-(2-Chloroethyl)-1-[(5-nitrofurfurylden)amino]hydantoin.—Compound **2** was smoothly converted into the chloro compound by refluxing for 2 hr with excess thionyl chloride. For analysis, it was recrystallized from 50% ethanol and from acetonitrile: mp 186–187°; uv max (H_2O) 368 mμ (*E* 17,400) and 265 (11,000); nmr (DMSO-d_6) δ 2.44 (m, 2, CH_2CH_2CH), 3.75 (t, 2, $ClCH_2$), 4.58 (t, 1, CH_2CH), 7.20 (d, 1, furan-3), 7.75 (d, 1, furan-4), 9.52 (s, 1, CH=N), 11.55 (ex, 1, NH).

Anal. Calcd for $C_{10}H_9ClN_4O_5$: C, 39.95; H, 3.02; Cl, 11.79; N, 18.64. Found: C, 39.83; H, 3.03; Cl, 11.70; N, 18.52.

1-{2-[1-(5-Nitrofurfurylidenamino)-2,4-dioxo-5-imidazolidinyl]-ethyl}pyridinium Chloride.—To a solution of 61 g (0.20 mol) of the above chloroethyl compound in 200 ml of freshly distilled dimethylformamide was added 30 ml (0.37 mol) of pyridine and the solution was refluxed for 30 min. After chilling overnight, the fine, yellow crystalline product was filtered and washed with cold acetone. The product (11.9 g, 15%) was recrystallized from 50% ethanol to give an analytical sample: mp 270–290° dec; uv max (H_2O) 365 mμ (*E* 16,700) and 250 (13,500); nmr (D_2O) δ 2.97 (m, 2, CH_2CH_2CH), 4.98 (m, 3, CH_2CH_2CH), 7.21 (d, 1, furan-3), 7.71 (d, 1, furan-4), 8.56 (s, 1, CH=N), 8.21, 8.63 and 9.05 (m, 5, pyridine).

Anal. Calcd for $C_{15}H_{14}ClN_5O_5$: C, 47.44; H, 3.72; Cl, 9.34. Found: C, 47.38; H, 3.95; Cl, 9.24.

1-Benzylidene-2,3,3a,4,5,6-hexahydro-4,6-dioxo-1H-imidazo-[1,5-*b*]pyrazolinium Chloride (3).—A mixture of 37.6 g (0.152 mol) of **1** and 100 ml of thionyl chloride was refluxed for 1 hr, then cooled, and filtered on a sintered-glass funnel. The product was washed with thionyl chloride and with anhydrous ether, with protection from atmospheric moisture, and stored in a vacuum desiccator over potassium hydroxide to remove hydrogen chloride. There was obtained 34.0 g (84%) of **3**. This material was too

(3) (a) D. Jack, *J. Pharm. Pharmacol.* **11**, 108T (1959); (b) D. Jack and G. Sutno, U. S. Patent 2,990,402 (1961).

(4) H. von Euler and H. Hasselquist, *Ark. Kemi*, **13**, 185 (1958); *Chem. Abstr.*, **53**, 11351*g* (1959).

(5) All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Nmr spectra were determined on a Varian Model A-60A nmr spectrometer in the deuterated solvents indicated using tetramethylsilane as an internal standard. We are indebted to Mrs. P. S. Curtis for the nmr spectra and to Mr. G. Gustin and Mr. M. Tefft for the microanalyses.

(6) Aldrich Chemical Co.

labile to be further purified. Its benzaldehyde content was determined by dissolving a weighed sample in 95% alcohol, treated with DNPH, and determining the benzaldehyde DNPH gravimetrically.

Anal. Calcd for $C_{12}H_{12}ClN_3O_2$: C_6H_5CH, 33.9; Cl, 13.55. Found: C_6H_5CH, 32.7; Cl, 13.7.

2,3-Dihydro-1H-imidazo[1,5-*b*]pyrazole-4,6(3a*H*,5*H*)-dione Hydrochloride (4).—Compound **3** (32.7 g, 0.123 mol) was dissolved in methanol, filtered, and mixed with excess ether. The precipitated product was filtered, washed with ether, and dried to give 19.0 g (87%) of **4**. An analytical sample was prepared by recrystallization from 2-propanol containing a little hydrochloric acid. The compound did not exhibit a sharp melting point but decomposed gradually at about 170°.

Anal. Calcd for $C_5H_8ClN_3O_2$: C, 33.81; H, 4.45; Cl, 19.97. Found: C, 33.93; H, 4.74; Cl, 19.96.

Recrystallization of **4** from 90% 2-propanol converted it into the free base **5**: mp 205–207°; no uv maximum above 220 mμ; nmr (DCl-D_2O) δ 2.61 (m, 2, CH_2CH_2CH), 3.72 (m, 2, CH_2-CH_2CH), 4.65 (m, 1, CH_2CH_2CH).

Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.54; H, 5.01; N, 29.77.

Registry No.—**1**, 20707-87-3; **2**, 20707-88-4; **3**, 20728-44-3; **4**, 20707-89-5; **5**, 20707-90-8; 5-(2-chloroethyl)-1-[(5-nitrofurfuryliden)amino]hydantoin, 20707-91-9; 1-{2-[1-(5-nitrofurfurylidenamino)-2,4-dioxo-5-imidazolidinyl]ethyl}pyridinium chloride, 20707-92-0.

A New Synthesis of Dicyclopropylcarbinoxymethanes—By-Products in the Simmons–Smith Reaction with Allyl Alcohols

ZDENKO MAJERSKI AND PAUL VON R. SCHLEYER

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

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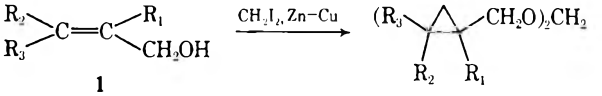
The effective and useful cyclopropanation reaction discovered by Simmons and Smith[1] can be applied with particular effectiveness to β,γ-unsaturated alcohols.[2] The neighboring hydroxyl group directs the stereochemical course and facilitates the reaction.[2] We were surprised when application of this synthesis to allyl alcohol (**1a** and **1b**) gave poor yields of cyclopropylcarbinol. Closer investigation of the reaction product showed that substantial amounts of the formal, dicyclopropylcarbinoxymethane, **2a** and **2b**, had formed. To our knowledge, observation of such a product in the Simmons–Smith reaction is unprecedented.[2,3]

In fact, it has been possible to develop this "side reaction" into a useful one-step synthesis of some dicyclopropylcarbinoxymethanes. Dialkoxymethanes (formals) are usually prepared by the treatment of formaldehyde with an alcohol (or, sometimes, an orthoformate ester) in the presence of an acid catalyst.[4] Occasionally, the reaction of alkoxides and a dihalomethane or α-halomethyl ether is employed.[4] Our synthesis may be advantageous in cases where the corresponding cyclopropylcarbinols are not readily available or where they are unstable toward acidic conditions.[5]



1

2a–2c, 40–45%
2d, 5–10%

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = D$; $R_3 = H$
c, $R_1 = H$; $R_2, R_3 = CH_3, H$
d, $R_1 = CH_3$; $R_2 = R_3 = H$

During the course of the Simmons–Smith reaction on allyl alcohol, the $(RO)_2CH_2/ROH$ (R = cyclopropylcarbinyl) ratio increases with time, demonstrating that an initially formed cyclopropylcarbinyl intermediate reacts subsequently with a methylene donor. If the allyl alcohol/CH_2I_2 ratio was kept constant, reduction in the amount of Zn–Cu couple used decreased the $(RO)_2$-CH_2/ROH product ratio. For this reason we believe that the bis(iodomethyl) zinc–zinc iodide complex[1] rather than methylene iodide is the species responsible for formal production. For example, it is conceivable that a species such as $(CH_2{=}CHCH_2OCH_2)_2Zn \cdot ZnI_2$, obtained by exchange,[2f] might decompose preferentially to the mixed formal, $C_3H_5CH_2OCH_2OCH_2CH{=}CH_2$, a precursor of **2a**. We have not investigated the mechanism of formal formation.

Methallyl alcohol (**1d**) gave significantly lower yields of formal than did the other allyl alcohols (**1a–1c**), evidently for steric reasons, known to be a factor in the Simmons–Smith reaction.[1,2] For this reason, formal by-products may not be significant when more highly substituted allyl alcohols are employed. The reported[2b] low yield (26%) of cyclopropylethanol obtained by the Simmons–Smith reaction on 1-buten-4-ol may be due to formal formation; if so, this procedure might be used for the synthesis of such compounds.

Unfortunately, it was difficult to prevent dialkoxylmethane formation in the cases of **1a–1c**. After a short reaction period, much starting allyl alcohol remained, while long reaction times favored formal production. The best conditions, we found, gave only 15–20% yields of cyclopropylcarbinol after the necessary purification by glpc. In addition, we were not successful in finding conditions for the hydrolysis of **2a**. Mild oxalic acid treatment produced no reaction, and more strenuous conditions are known to give rise to rearrangement of cyclopropylcarbinol.[5]

Experimental Section

General Procedure.—The following conditions are optimal for formal synthesis. Methylene iodide (0.2 mol) was added to a vigorously stirred mixture of 29.4 g of commercial Zn–Cu couple (Ventron/Alfa Inorganics), 0.2 g of iodine, and 125 ml of dry ether, maintained at 40°. After 0.5 hr, 0.1 mol of the appropriate allyl alcohol was added dropwise within 15 min (strongly exo-

(1) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959); H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964); E. P. Blanchard and H. E. Simmmons, *ibid.*, **86**, 1337 (1964).

(2) (a) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); (b) Y. Armand, R. Perraud, J.-L. Pierre, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 1893 (1965); (c) W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963); (d) E. J. Corey and R. L. Dawson, *ibid.*, **85**, 1782 (1963); (e) J. H.-H. Chan and B. Rickborn, *ibid.*, **90**, 6406 (1968); (f) G. Wittig and M. Jautelat, *Ann.*, **702**, 24 (1967).

(3) Confirmed by H. Simmons, private communication.

(4) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1953, p 261–267; "Rodd's Chemistry of Carbon Compounds," Vol. I, S. Coffey, Ed., Elsevier Publishing Co., New York, N. Y., 1965, Part C, p 28.

(5) M. C. Caserio, W. H. Graham, and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960).

thermic). After stirring for an additional 2.5 hr, 0.1 mol of methylene iodide was added. After another 5.0 hr of stirring, a further 0.05 mol of methylene iodide was added. The black reaction mixture was stirred overnight and then diluted with 150 ml of ether. An aqueous saturated NH_4Cl solution was added carefully dropwise until the ether layer discharged a black precipitate. The precipitate was extracted with ether; the combined etheral extracts were washed with saturated NH_4Cl solution, twice with saturated K_2CO_3 solution, and finally with a saturated NaCl solution. Sodium sulfate was used to dry the ether solution. The solvent was evaporated through a 50-cm column and the residue was distilled *in vacuo*. Bp: **2a**, 71–75° (12 mm); **2c**, 88–93° (12 mm); **2d**, 82–88° (12 mm). Yields: 40–45% (**2a–c**); 5–10% (**2d**) (+ 70% 1-methylcycloproylcarbinol). Purity (glpc): 95–98% (**2a–c**); 85–90% (**2d**).

Anal. Calcd for **2a**: C, 69.19; H, 10.33. Found for **2a**: C, 69.31; H, 10.32. Calcd for **2c,d**: C, 71.69; H, 10.94. Found for **2c**: C, 71.43; H, 11.01. Found for **2d**: C, 71.36; H, 11.08.

The nmr spectra of the formals show characteristic[6] sharp peaks at 4.6 (OCH_2O) and 3.3 ppm (carbinyl protons) in addition to the characteristic cyclopropane ring proton multiplets (**2a**, 0–1.4; **2c**, 0–1; **2d**, 0.2–0.5 ppm) and the methyl group absorptions (**2c**, 1.0; **2d**, 1.1 ppm). Mass spectra of **2a–d** display the characteristic pattern of dialkoxymethanes:[7] a weak $M^+ - 1$ signal (no parent peak), very strong signals corresponding to *m/e* for the "cyclopropylcarbinyl" cations (R^+), and moderately strong signals which correspond to *m/e* for RO^+ and $ROCH_2^+$. The ir spectra exhibit a stong doublet in the 1020–1120 cm^{-1} range which is known as characteristic of COCOC groups.[8]

Optimal Conditions for Cyclopropylcarbinol Formation.—A vigorously stirred mixture of 19.8 g of commercial Zn–Cu couple (Ventron/Alfa Inorganics), 0.2 g of iodine, 0.23 mol of methylene iodide, and 150 ml of dry ether was heated by an infrared heater until the reaction started and then stirred for 45 min more at 40°. Then allyl alcohol (0.1 mol in 25 ml of dry ether) was added dropwise (10 min), and the mixture was stirred for 75 min more at the same temperature. The work-up was as described above. The crude product was fractionated through a column and the fraction with bp 100–130° was purified by glc (25′ Carbowax 20M column at 112°).

Attempted Formal Hydrolysis.—Treatment of **2a** with 0.1 *N* oxalic acid for 45 min at 100° gave practically only the starting material. Stronger conditions were not attempted, due to the well-known[5] sensitivity of cyclopropylcarbinol toward acidic conditions.

Registry No.—**2a**, 20797-82-4; **2c**, 20797-83-5; **2d**, 20797-84-6.

Acknowledgment.—This research was supported by grants from the National Institutes of Health (AI-07766), the National Science Foundation, and the Petroleum Research Fund administered by the American Chemical Society.

(6) T. Sato, Y. Saito, M. Kainosho, and K. Hata, *Bull. Chem. Soc. Jap.*, **40**, 391 (1967).

(7) P. Brown, C. Djerassi, G. Schroll, H. J. Jakobsen, and S.-O. Lawesson, *J. Amer. Chem. Soc.*, **87**, 4559 (1965).

(8) K. Nukada, *Nippon Kagaku Zasshi*, **80**, 1112 (1959); *Chem. Abstr.*, **54**, 1071*b* (1960).

On the Mechanism of the Modified Hunsdiecker

P. W. JENNINGS AND T. D. ZIEBARTH

Department of Chemistry, Montana State University, Bozeman, Montana 59715

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The modified Hunsdiecker reaction discovered by Cristol and Firth[1] greatly facilitated the synthesis of organic halides *via* decarboxylation. We wish to report the preparation of one of the proposed intermediates, the proof of its validity as an intermediate, and the proof that mercuric halides do not participate in the reaction as catalysts. The proposed reaction sequence for the modified Hunsdiecker is shown below in eq 1–3.[2]

$$HgO + 2Br_2 \longrightarrow HgBr_2 + [Br_2O] \quad (1)$$

$$[Br_2O] + RCOOH \longrightarrow [RCOOBr] + HOBr \quad (2)$$

$$[RCOOBr] \longrightarrow RBr + CO_2 \quad (3)$$

Brackets are used to denote intermediates.

We have obtained Br_2O free of $HgBr_2$ and HgO by fractional sublimation in vacuum at Dry Ice–acetone temperatures. There is a 3% impurity of Br_2 as measured by ultraviolet spectroscopy. Ultraviolet absorption of Br_2O in carbon tetrachloride solutions shows two peaks at 3200 Å, and 6550 Å with ϵ of 240 and 12.3, respectively, which is in agreement with earlier work on Br_2O.[3] Further work is underway to ascertain the nature of bromine oxide from the HgO and Br_2 reactions as the data on Br_2O is tenuous. Dropwise addition of a CCl_4 solution of Br_2O to a solution of pentanoic acid in CCl_4 in the dark produced 30% yields of *n*-butyl bromide. Yields were based on the acid concentration. While these yields are modest compared to the normal modified Hunsdiecker, one must bear in mind that the Br_2O is not being generated *in situ* as is the case when one normally runs the modified Hunsdiecker. Furthermore, Br_2O decomposes slowly at temperatures above −50°, and, while the dropwise addition is occurring, some decomposition must occur. Also under the modified Hunsdiecker conditions, an excess of Br_2O and HgO is usually used.

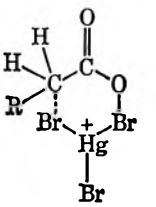
Table I shows the effect of $HgBr_2$ concentration versus per cent yield of alkyl halide. All of these reactions were run simultaneously under the same conditions of temperature and concentration. A CCl_4 solution of Br_2O was divided equally among the samples and added at the same rate. Obviously, there is no catalytic effect from the $HgBr_2$.

TABLE I

Sample no.	Mol of $HgBr_2 \times 10^{-5}$	Yield of alkyl halide, %
1	0.00	30.4
2	0.65	30.4
3	0.97	31.6
4	1.22	30.9
5	2.09	29.6
6	3.40	29.7

The amount $HgBr_2$ exceeded the solubility in CCl_4 after sample 4. This data was included to ensure that surface catalysis was not occurring.

Another possibility of $HgBr_2$ assistance could have been in the decomposition of the acyl hypobromide as shown below.



(1) S. J. Cristol and W. C. Firth, *J. Org. Chem.*, **26**, 280 (1961).

(2) P. W. Jennings, Masters Thesis, University of Colorado, 1961.

To test this intermediate, we fortified the reaction with $HgCl_2$. There was no evidence found to indicate any *n*-alkyl chloride formed.

Experimental Section

Preparation of Br_2O.—A solution of Br_2O in CCl_4 was prepared by mechanically stirring 6.8 ml (19.9 g, 0.125 mol) of Br_2, 60 g (0.278 mol) of red HgO, and 300 ml of CCl_4 in a 500-ml round-bottom flask fitted with a reflux condenser. The solution was maintained at 45° and light was excluded. After 90 min, the solution was cooled to −20° by a Dry Ice–methanol bath and 80 g (0.359 mol) of fresh HgO was added. Stirring was continued for 30 min followed by filtration to remove the $HgBr_2$ and unreacted HgO.

The filtrate was then connected to a vacuum line and the contents transferred slowly at −25°. The CCl_4 and Br_2 transfers first leaving a brownish green solid which when transferred and collected gives the uv spectrum reported for Br_2O.[3]

Preparation of the Alkyl Halide.—In a typical experiment, the Br_2O in CCl_4 solution is added, via a pressure equalized dropping funnel, to 250-ml flask containing 4.4 g (0.043 mol) of *n*-pentanoic acid which is dissolved in 50 ml of CCl_4. The solution was refluxed in the dark during the addition of Br_2O which took approximately 75 min. The solution was then allowed to reflux for an additional 15 min. Products were analyzed by isolation and vapor phase chromatography.

Registry No.—Br_2O, 21308-80-5.

(3) (a) W. Brenschede, and H. J. Schumaker, *Z. Physikol. Chem.*, **29B**, 356 (1935); (b) W. Brenschede, and H. J. Schumaker, *Z. Anorg. Chem.*, **226**, 370 (1936).

Photoisomerization of *cis*-Cyclooctene to *trans*-Cyclooctene[1]

JOHN S. SWENTON

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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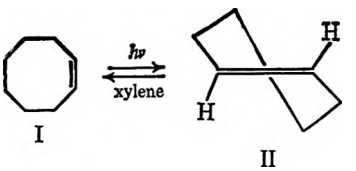
The need for modest quantities of *trans*-cyclooctene in connection with exploratory work in these laboratories coupled with the length of conventional syntheses[2,3] prompted us to explore a short direct route to this compound. The known benzene, toluene, and



I II

xylene sensitized isomerization of olefins[4] suggested the photosensitized isomerization of *cis*-cyclooctene as a potential route to the *trans* isomer. Since benzene is known to afford high yields of adduct when irradiated in the presence of cyclooctene,[5] xylene was chosen as sensitizer.

Irradiation of a solution of xylene and cyclooctene in purified cyclohexane followed by silver nitrate extraction and decomposition of the silver nitrate complex with concentrated ammonium hydroxide gave a two-component mixture. Preparative vpc isolation of the compounds followed by direct comparison with authentic materials showed the major product to be *trans*-cyclooctene (II) and the minor component to be 1,5-cyclooctadiene (III). That the 1,5-cyclooctadiene was not a photochemical product in this system was evident from the decrease in the percentage of III in the recycled irradiation mixtures (Table I). The

TABLE I

YIELD OF *trans*-CYCLOOCTENE AND 1,5-CYCLOOCTADIENE AS A FUNCTION RECYCLING PHOTOLYSIS MIXTURE

Number of cycles	Total yield, g	% II	% III
1	2.2	82	18
2	2.1	90	10
3	2.4	95	5
4	2.1	97	3

dramatic decrease in III upon repeated photolysis suggests that it is a minor impurity in commercial cyclooctene which coextracts with II.

This method has proven useful in conveniently preparing up to 2.5 g of *trans*-cyclooctene per irradiation cycle. Although initial irradiations yield mixtures of II and III, the high reactivity of II still renders the material synthetically useful. Continued irradiation of samples with an intervening distillation to remove higher boiling material affords II in good purity (>97%). The method, although limited in the amount of material obtained, requires only a small amount of manipulative operations and thus should be useful in preparation of modest amounts of II for exploratory and mechanistic work.

Experimental Section

Cyclooctene (600 ml) in 900 ml of olefin-free cyclohexane was extracted four times with 100 ml of 30% aqueous silver nitrate. After the extract was washed with water, dried over Drierite, and distilled through a 3-in. column, 150 ml of xylene was added to form the irradiation mixture. The material was irradiated in 500-ml portions for 36 hr under nitrogen using a 450-W Hanovia medium pressure source and a Corex filter sleeve. The use of a Vycor filter gave faster conversions initially but led to buildup of polymer on the immersion well. The combined irradiation solutions were extracted four times with 80 ml of 20% aqueous silver nitrate; the silver nitrate solution was washed with pentane twice, 70 ml) and decomposed by dropwise addition into 150 ml of concentrated ammonium hydroxide at 0°. The oily aqueous solution was extracted with pentane (thrice, 75 ml), the pentane layer dried, and the pentane distilled through a 6-in. Vigreux column. Short-path distillation of the remaining light yellow liquid afforded 2.2 g (0.02 mol) of colorless liquid, bp 75–6° (75 mm). Vpc inspection (20% β,β-oxydipropionitrile on 60–80 Chrom P, 10 ft × 0.25 in., 70°) showed three components with retention times of 10, 12, and 28 min. These products were identified as *cis*-cyclooctene, *trans*-cyclooctene, and 1,5-cyclooctadiene. The percentage of *cis*-cyclooctene in seven individual runs varied from 1 to 3% of the *trans* isomer.

For recycling, the light yellow photolysis solution was distilled at atmospheric pressure through a short column to yield 1400 ml

(1) A grant from the Eli Lilly Co., Indianapolis, Ind., is gratefully acknowledged.

(2) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, **75**, 3212 (1953); E. J. Corey and J. I. Shulman, *Tetrahedron Lett.*, 3655 (1968); E. J. Corey, F. A. Carey, R. A. E. Winter, *J. Amer. Chem. Soc.*, **87**, 934 (1965); E. J. Corey and R. A. Winter, *ibid.*, **85**, 2677 (1963).

(3) A recent improvement over these methods has been reported: J. N. Hines, M. J. Peagram, G. H. Whitham, and M. Wright, *Chem. Commun.*, 1593 (1968).

(4) For leading references, see P. J. Kropp and H. J. Krauss, *J. Amer. Chem. Soc.*, **89**, 5199 (1967).

(5) D. Bryce-Smith, A. Gilbert, and B. H. Orger, *Chem. Commun.*, 512 (1966).

of colorless distillate. To the distillate was added 50 ml of xylene and cyclohexane to afford a total volume of 1500 ml. The solution was then subjected to irradiation as shown above. The results of five recyclings are listed in Table I.

Registry No.—I, 931-87-3; II, 931-89-5; III, 111-78-4.

A Reexamination of the Effect of Benzophenone on Benzalazine Photochemistry[1]

ROGER W. BINKLEY

Department of Chemistry, The Cleveland State University, Cleveland, Ohio 44115

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Several years ago it was reported that the irradiation of a mixture of benzalazine and benzophenone in cyclohexane led in moderate yield to benzonitrile.[2] The authors of this report accounted for their observation by proposing the four-step sequence given in eq 1–4.

$$(C_6H_5)_2C{=}O \overset{h\nu}{\rightleftharpoons} (C_6H_5)_2C{=}O^* \quad (1)$$

$$(C_6H_5)_2C{=}O^* + C_6H_5CH{=}NN{=}CHC_6H_5 \rightleftharpoons C_6H_5\dot{C}{=}NN{=}CHC_6H_5 + (C_6H_5)_2\dot{C}OH \quad (2)$$

$$C_6H_5\dot{C}{=}NN{=}CHC_6H_5 + (C_6H_5)_2C{=}O \longrightarrow 2\ C_6H_5C{\equiv}N + (C_6H_5)_2\dot{C}OH \quad (3)$$

$$2\ (C_6H_5)_2\dot{C}OH \longrightarrow \text{benzpinacol} \quad (4)$$

More recently, other studies[3,4] have shown that, in the absence of benzophenone, benzalazine still reacts photochemically to give benzonitrile, although in lower yield; however, with reactions run with no benzophenone present, an approximately equal amount of benzaldimine (isolated as benzaldehyde, its hydrolysis product) also is formed. In an effort to understand the unusual influence of benzophenone upon the photochemistry of benzalazine, a detailed study of this reaction was undertaken.

$$C_6H_5CH{=}NN{=}CHC_6H_5 \xrightarrow{h\nu} \begin{cases} \xrightarrow{\text{benzophenone}} C_6H_5C{\equiv}N \\ \xrightarrow[\text{benzophenone}]{\text{no}} C_6H_5C{\equiv}N + C_6H_5CH{=}NH \end{cases}$$

When benzophenone and benzalazine were jointly irradiated in cyclohexane under nitrogen (run 1, Table I), the starting materials rapidly disappeared, but surprisingly, only trace amounts (<1%) of benzonitrile were formed. Since the original description of this reaction[2] did not comment on the exclusion of oxygen, a second set of experiments was conducted in which oxygen was purposely added during photolysis. In the presence of oxygen, the reported benzonitrile yield was realized, although a significant quantity of benzaldehyde was still isolated[5] (run 2, Table I). These second experiments clearly suggested that the critical factor in this reaction was the presence of oxygen and not benzophenone. To confirm this suggestion, benzalazine was irradiated under oxygen without benzophenone and was found to produce benzonitrile in high yield (run 3, Table I).

TABLE I

IRRADIATIONS OF BENZALAZINE IN CYCLOHEXANE[a]

Run	Atmosphere	Substance added	Time, hr	Completion	Product Yield,[b] mg: Benzonitrile	Product Yield,[b] mg: Benzaldehyde
1	Nitrogen	Benzophenone[c]	4.0	100	Trace	Trace
2	Oxygen	Benzophenone[c]	20.0	44	43 mg	15 mg
3	Oxygen	None	20.0	39	55 mg	15 mg
4	Nitrogen	None	10.0	40	15 mg	18 mg

[a] One millimole of benzalazine was irradiated in each run. [b] Product yield is given in mg of product per 100 mg of reactant consumed to avoid confusion, since each molecule of reactant can produce two molecules of product. [c] Two millimoles of benzophenone were added.

On the basis of these results, it is concluded that (a) the critical element responsible for the increased benzonitrile yield in the photochemistry of benzalazine is the presence of oxygen and not benzophenone; (b) the mechanism previously proposed[2] involving benzophenone in the photodecomposition of benzalazine is incorrect.

The observed influence of oxygen on this reaction is understandable in terms of the mechanism previously proposed for benzalazine decomposition under direct irradiation.[3] This mechanism, which has been shown to be consistent with the effect of hydrogen donors on benzalazine photolysis,[4] suggests that excitation of benzalazine results in a homolytic cleavage the nitrogen–nitrogen bond, producing two $C_6H_5CH{=}N$ radicals which may either react directly (a disproportionation reaction) to give benzonitrile and benzaldimine or may diffuse apart in solution. If the existence of $C_6H_5CH{=}N$ radicals in solution is combined with the fact that radicals of this type are known to be oxidized by molecular oxygen to nitriles[6] (eq 5),

$$RCH{=}NH + Cu(II) \longrightarrow H^+ + Cu(I) + [RCH{=}N\cdot] \xrightarrow{O_2} RC{\equiv}N + HO_2\cdot \quad (5)$$

the increased benzonitrile yield from the oxygenated irradiations of benzalazine is the logical result of the interaction between oxygen and $C_6H_5CH{=}N$ radical species.

Experimental Section

The irradiation and isolation procedure used in each of the reactions described in the text was identical; therefore, only one of these reactions will be described in detail.

Direct Irradiation of Benzalazine in Cyclohexane under Oxygen.—Benzalazine (208.3 mg, 1.0000 mmol) in 300 ml of cyclohexane was irradiated at 25.0° with constant stirring for 20.0 hr, using a 100-W Hanovia high-pressure quartz mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. Oxygen was passed through the solution for 1 hr prior to irradiation and a slow stream of oxygen was continued during photolysis.

After 20 hr, the solvent was removed by distillation *in vacuo* below 30°, producing a yellow oil. This oil was chromatographed

(1) Part IV in a series entitled "The Photochemistry of Unsaturated Nitrogen-Containing Compounds."

(2) J. E. Hodgkins and J. A. King, *J. Amer. Chem. Soc.*, **85**, 2630 (1963).

(3) R. W. Binkley, *J. Org. Chem.*, **34**, 2311 (1968).

(4) R. W. Binkley, *ibid.*, **34**, 2072 (1969).

(5) All attempts to isolate the benzhydrol indicated (ref 2) to be a reaction product (eq 4) have at present been unsuccessful. No evidence could be obtained for the formation of benzpinacol.

(6) W. Brackman and P. J. Smit, *Rec. Trav. Chim.*, **82**, 757 (1963).

on a 100 × 2.2 cm Florisil column slurry packed in 1:9 ether–hexane; 20-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane; 0.5 l. of 1:99 ether–hexane; 0.5 l. of 1:49 ether–hexane; 1.0 l. of 1:24 ether–hexane; 0.5 l. of 1:12 ether–hexane; and 0.5 l. of 1:6 ether–hexane.

Fractions 82–119 yielded 117 mg of benzalazine as yellow crystals, mp 91–94°. Fractions 121–131 gave 13.8 mg of a clear oil identified as benzaldehyde by comparison of ir and uv spectra with those of a known sample. Fractions 134–168 afforded 39.4 mg of a clear liquid identified as benzonitrile also by comparison of the ir and uv spectra of the photoproduct with those of a known sample of benzonitrile.

Registry No.—Benzophenone, 119-61-9; benzalazine, 588-68-1.

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Deoxygenation and Chlorination of Azoxybenzene by Acidic Halides[1]

JOHN F. VOZZA

The University of Wisconsin–Parkside, Racine Campus, Racine, Wisconsin 53403

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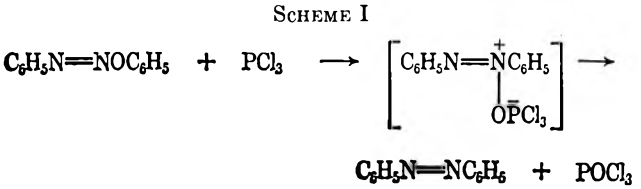
Recent investigations[2-4] of the mechanism of the Wallach rearrangement[5] of azoxybenzene to *p*-hydroxyazobenzene induced by chlorosulfonic acid led to the identification of small amounts of azobenzene and *p*-chloroazobenzene as additional products of this reaction.[6] This suggested the possibility of the initial formation of an intermediate product through chlorosulfonation of the oxygen of azoxybenzene followed either by rearrangement and decomposition to *p*-chloroazobenzene or by direct decomposition to azobenzene. This also indicated the possibility of a much simpler general method for preparing halogenated azo compounds than those that are now available.

Deoxygenation of Azoxybenzene.—Azoxybenzene is deoxygenated to azobenzene by certain acidic halides which can undergo oxidation. Scheme I, which suggests a possible way in which this transformation may occur in the deep red reaction mixture, shows phosphorus trichloride being oxidized to phosphorus oxychloride as azoxybenzene is reduced to azobenzene practically quantitatively. Other observations which appear in the Experimental Section show similar results that were obtained with several other inorganic acidic halides. Acetyl bromide and acetyl iodide also yield azobenzene in this reaction below 20°. At higher temperatures, these halides lead to the formation of some aniline and benzidine in addition to azobenzene.

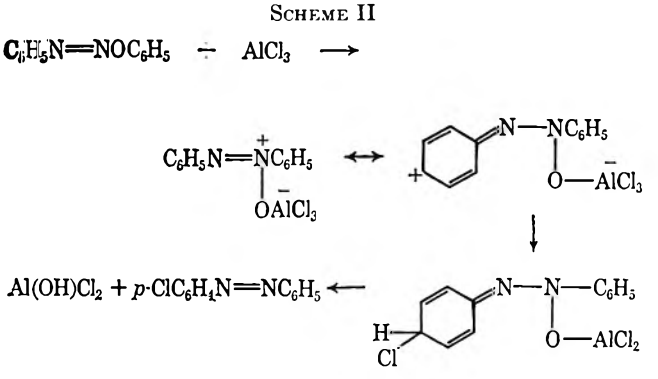
SCHEME I



Deoxygenation of Azoxybenzene with Chlorination.—The unusual deoxygenation and chlorination of azoxybenzene by aluminum chloride was observed under various conditions. A solid mixture of aluminum chloride and azoxybenzene reacts spontaneously and highly exothermically after a brief induction period. This reaction is violent at 40° in molten azoxybenzene. However, in refluxing carbon disulfide the red reaction mixture yields *p*-chloroazobenzene in 83% yield *via* a smooth reaction. Similar results are obtained in a refluxing acetyl chloride solution of molar equivalent amounts of azoxybenzene and aluminum chloride. Both of these procedures are recommended for the preparation of *p*-chloroazobenzene over the Curtin and Ursprung[7] method because of their simplicity and high yield of product.

Ferric chloride may replace aluminum chloride in this reaction, but the yield of *p*-chloroazobenzene is usually smaller. However, aluminum bromide and aluminum iodide reduce azoxybenzene to azobenzene even under mild conditions (0°). It was also noted that aluminum chloride fails to convert azoxybenzene to *p*-chloroazobenzene if any halide that deoxygenates azoxybenzene is present in the reaction mixture. This suggests that preferential deoxygenation of azoxybenzene by reducing halides prevents the aluminum chloride from reacting as proposed in Scheme II, which attempts to present a possible rationalization of the manner in which this reaction occurs under mild conditions.

SCHEME II



The reaction of azoxybenzene in benzenesulfonyl chloride in the presence of ferric chloride is more complex. A small amount of *p*-chloroazobenzene and a product which was characterized as a sulfone are formed in this reaction. As ferric chloride appears to function as a Friedel–Crafts catalyst in this reaction as well as the chlorinating agent, the yield of *p*-chloroazobenzene is improved by increasing the concentration of ferric chloride in the reaction mixture. Aluminum chloride is much less effective than ferric chloride in this reaction.

Azoxybenzene, aluminum chloride, and sulfuryl chloride react to form *p*-chloroazobenzene and *p,p'*-dichloroazobenzene. An increase in the molar ratio of alu-

(1) Supported in part by the Research Committee of the Graduate School of the University of Wisconsin from special funds voted by the State Legislature and by a research grant from the University of Wisconsin Center System.

(2) M. Shemyakin, V. Maimind, and B. Vaichunaite, *Chem. Ind.* (London), 755 (1958).

(3) M. Shemyakin, V. Maimind, and Ts. E. Agaadzhanyan, *ibid.*, 1223 (1961).

(4) P. Gore, *ibid.*, 191 (1959).

(5) O. Wallach and L. Belli, *Ber.*, **13**, 525 (1880).

(6) I. Pearl and A. Ronzio, *J. Org. Chem.*, **12**, 785 (1947).

(7) D. Curtin and J. Ursprung, *ibid.*, **21**, 1221 (1956).

minum chloride to azoxybenzene favors the formation of the dichloro compound. This simple preparative procedure, coupled with the ease of separating the monochloro compound from the dichloro compound with 95% ethanol in which the latter is much less soluble, makes *p,p'*-dichloroazobenzene much more easily available than by methods recorded in the literature.[8,9]

Azoxybenzene and aluminum chloride react in benzene to form *p*-phenylazobenzene in 84% yield. Apparently, in this reaction the electron-rich benzene ring replaces the chloride ion as the nucleophile, if the reaction proceeds in the manner suggested in Scheme II. The appearance of a deep red color in this reaction mixture was once suggested as a qualitative test for aromatic hydrocarbons.[10] Attempts to extend this reaction to biphenyl and fused aromatic ring systems failed to produce the expected azo compounds. Rather, certain amines were formed which were similar to those identified in reaction mixtures consisting of these hydrocarbons, aluminum chloride, and azobenzene.[11,12]

Fluoroazo compounds cannot be prepared by reactions of the type that have been described. Most inorganic fluorides, including aluminum fluoride and boron trifluoride, as well as organic fluorides do not react with azoxybenzene. Only those fluorides, such as antimony trifluoride, which can deoxygenate azoxybenzene, react to form azobenzene.

Experimental Section

The identity of every compound that was isolated in the following experiments was established by means of elemental analysis and by comparison of its ir spectrum and melting point with those of an authentic sample.

Deoxygenation and Chlorination of Azoxybenzene by Aluminum Chloride. A. *p*-Chloroazobenzene.—To a mixture of 4.0 g (0.03 mol) of $AlCl_3$ or 4.9 g (0.03 mol) of $FeCl_3$ in 50 ml of CS_2 or 30 ml of CH_3COCl in a three-neck flask equipped with a dropping funnel, mechanical stirrer, and a condenser protected by a $CaCl_2$ tube, a solution of 6.0 g (0.03 mol) of azoxybenzene in 50 ml of CS_2 or 20 ml of CH_3COCl was added slowly. The dark red mixture was stirred for 5 hr at reflux temperature and then distilled to dryness at reduced pressure. The dark residue was treated with 40 ml of 0.1 *N* HCl solution and then extracted with three 35-ml portions of ether. The ether solution was washed twice with water, 5.0% $NaHCO_3$ solution, and water and then dried over anhydrous $CaCl_2$. The crude product which was recovered from the ether solution was recrystallized from petroleum ether (bp 30–75°), yielding 5.4 g (83% with $AlCl_3$) or 4.1 g (63% with $FeCl_3$) of *p*-chloroazobenzene, mp 87–88° (lit.[13] 87–88°).

B. *p,p'*-Dichloroazobenzene.—To a mixture of 16.0 g (0.12 mol) of $AlCl_3$ in 35 ml of SO_2Cl_2, a solution of 6.0 g (0.03 mol) of azoxybenzene in 20 ml of SO_2Cl_2 was added. The mixture was refluxed for 5 hr and then worked up according to the procedure described in part A. The product obtained from the ether solution was treated with 25 ml of hot 95% ethanol. The undissolved material was filtered and dissolved in a hot mixture of 15 ml of acetone and 15 ml of 95% ethanol. From the concentrated, cold ethanol–acetone solution, 5.3 g (70%) *p,p'*-dichloroazobenzene, mp 186° (lit.[14] 187°), was obtained. From the concentrated, cold ethanol solution, 0.9 g (13%) *p*-chloroazobenzene was recovered.

C. Reaction in Benzenesulfonyl Chloride.—To a mixture of 4.9 g (0.03 mol) of $FeCl_3$ in 30 ml of benzenesulfonyl chloride, a solution of 6.0 g (0.03 mol) of azoxybenzene in 20 ml of benzenesulfonyl chloride was added and the mixture was stirred at 100° for 5 hr and then worked up according to the procedure described in part A. The product obtained from the ether solution was treated with 30 ml of petroleum ether and the residue was dissolved in 25 ml of 95% ethanol. From the concentrated, cold petroleum ether solution 0.7 g (10.7%) of *p*-chloroazobenzene was obtained. The cold, concentrated 95% ethanol solution yielded 1.1 g (10.0%) of a sulfone, mp 106°, ir ($CHCl_3$) 1160 cm^{-1} (O=S=O).

Anal. Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.91; H, 4.14; S, 9.46. Found: C, 63.86; H, 4.05; S, 9.39.

With 9.8 g (0.06 mol) of $FeCl_3$ in the reaction mixture, 2.0 g (30.7%) of *p*-chloroazobenzene and 0.55 g (5.0%) of sulfone were obtained.

***p*-Phenylazobenzene.**—To a mixture of 4.0 g (0.03 mol) of $AlCl_3$ in 40 ml of dry benzene, 6.0 g (0.03 mol) of azoxybenzene in 25 ml of benzene was added and the mixture was refluxed for 5 hr and then worked up according to the procedure described in part A. The ether solution yielded 6.1 g (84%) of *p*-phenylazobenzene (from ethanol), mp 150–151° (lit.[15] 150°).

Note: Addition of 0.03 mol of any of the halides listed below in the procedure entitled Deoxygenation of Azoxybenzene to any of the reaction mixtures described in the above procedures prevents the formation of the two chloroazo compounds or the *p*-phenylazobenzene. Instead, the reduction products described below (azobenzene, aniline, and benzidine) are formed.

Deoxygenation of Azoxybenzene. A. By Liquid Acidic Halides (PCl_3, $POCl_3$, $SOCl_2$, S_2Cl_2, CH_3COBr, and CH_3COI).—A solution of 6.0 g (0.03 mol) of azoxybenzene in 30 ml of each halide was refluxed for 3 hr except for the mixtures containing CH_3COBr and CH_3COI which were stirred at 20°. All mixtures were then worked up according to the procedure described earlier. The products obtained from the ether solutions in each case yielded azobenzene, mp 67–68° (lit.[16] 68°, *trans*), from petroleum ether in amounts ranging from 72% with S_2Cl_2 to 95% of the theoretical with PCl_3. From the $SOCl_2$ reaction product, *p*-chloroazobenzene (3.1%) and *p,p'*-dichloroazobenzene (5.2%) were obtained in addition to 75.3% azobenzene (see reaction with SO_2Cl_2 described earlier).

With CH_3COBr and CH_3COI azobenzene was obtained from the reaction mixtures which were stirred at 20° for 5 hr. At reflux temperatures these mixtures yielded aniline and benzidine.

B. By Solid Acidic Halides (AlI_3, $AlBr_3$, $ZnBr_2$, ZnI_2, and SbF_3) in CH_3COCl Solutions.—Following the procedure outlined in part A, a solution of 0.03 mol of azoxybenzene in 20 ml of CH_3COCl was added to a mixture of 0.03 mol of each halide in 30 ml of CH_3COCl and refluxed for 3 hr except for the mixtures containing AlI_3 and $AlBr_3$ which were stirred at 20°. The ether solutions obtained after working up the reaction mixtures according to the procedure described earlier yielded azobenzene in every case in amounts ranging from 55% with SbF_3 to 92% of the theoretical with ZnI_2.

In the aqueous acid solutions obtained from the hydrolysis of the reaction products in each experiment in part A the expected oxidation product of each halide was identified by the usual qualitative tests. PCl_3 and $POCl_3$ yielded phosphate ion; $SOCl_2$ yielded sulfate ion; S_2Cl_2 yielded S, SO_2, and some sulfate ion; CH_3COBr and CH_3COI yielded the free halogens. The solid iodides and bromides in part B yielded the free halogens, and SbF_3 yielded antimonate ion.

Registry No.—Azoxybenzene, 495-48-7.

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(10) R. Pummerer and J. Binapfl, *Ber.*, **54**, 2768 (1921).
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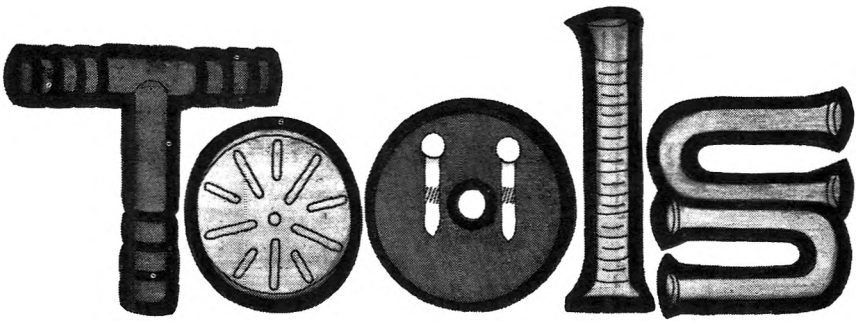
(12) R. Pummerer, J. Binapfl, R. Bittner, and K. Schuegraft, *ibid.*, **55**, 3099 (1922).
(13) J. Bamberger, *ibid.*, **29**, 2972 (1896).
(14) H. Willgerodt, *ibid.*, **14**, 2636 (1881).
(15) A. Locker, *ibid.*, **21**, 911 (1888).
(16) H. Henke and F. Brown, *J. Phys. Chem.*, **26**, 631 (1922).



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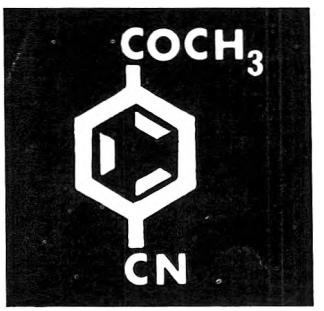

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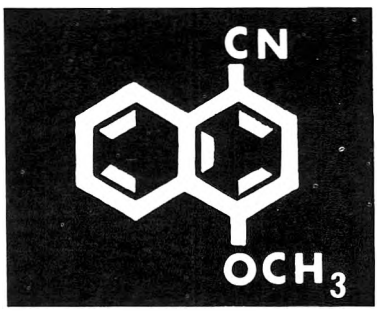

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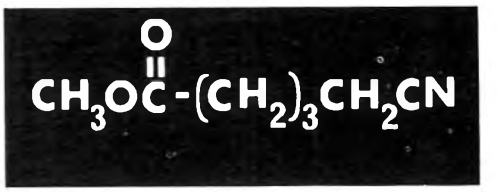

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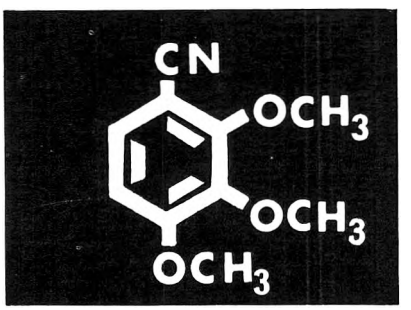

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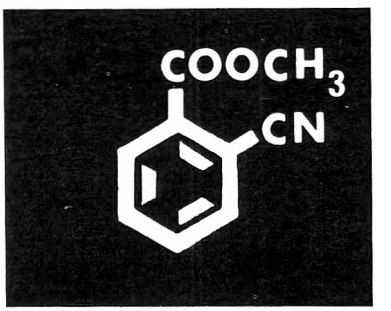

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