THE JOURNAL OF Organic Chemistry

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1971, 610 pp., $28.50

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by HARTWIG PERST, Institute of Organic Chemistry, University of Marburg, West Germany

Describes in detail the formation, modes of reaction, and preparative aspects of tertiary oxonium salts. Although the oldest class of these substances, pyrylium salts, has been investigated for 70 years and frequently reviewed, this is the first comprehensive review of the whole field of oxonium salts—including alkoxycarbonium, dialkoxycarbonium, and trialkyloxonium salts which have recently attained importance in theoretical and preparative investigations. In addition to its discussion of oxonium salts, the book includes a large section on tertiary oxonium ions which occur as intermediates, and which can be detected by low temperature nuclear magnetic resonance spectroscopy and by the isolation of oxonium salts.
May, June 1971, 202 pp., $15.00

NOTES

AUTHOR INDEX

Pyridylcyclobutanes. The Acid-Catalyzed Cycloaddition of Enamines to Vinylpyridines

DONALD E. HEITMEIER, JOHN T. HORTENSTINE, JR., AND ALLAN P. GRAY*[1]

Neisler Laboratories, Decatur, Illinois 62521, and Union Carbide Corporation, Tarrytown, New York 10591

Cycloaddition of enamines of α-disubstituted aldehydes to 2- and 4-vinylpyridines proceeds only in the presence of an acid catalyst to give pyridylcyclobutane derivatives in moderate to good yields. The reaction fails with a 3-vinylpyridine and yields other ultimate products with enamines bearing β hydrogens. It is considered that the acid protonates the vinylpyridine and thus polarizes and activates the double bond to attack. The pyridylcyclobutanes suffered facile ring opening in acid solution but were stable to strong base, and the anion of 3-(4-pyridyl)-2-morpholino-1,1-dimethylcyclobutane (1) could be alkylated to provide 3,3-disubstituted derivatives. 1 was selectively quaternized at the pyridine N but oxidized with a peracid at the morpholine N. Catalytic hydrogenation of 1 gave the piperidine derivative 19 which was much more stable to acid treatment.

As one outgrowth of our studies of pyridylcyclopropanes,[2] we were led to investigate compounds in which a substituted cyclobutane ring was directly attached to a pyridine nucleus. The present paper details our work on the synthesis of such compounds by the cycloaddition of enamines to 2- and 4- vinylpyridines, a reaction which was found to succeed only under conditions of acid catalysis and apparently only with enamines of α,α-disubstituted aldehydes (i.e., enamines without β hydrogens). Subsequent reactions of the pyridylcyclobutane products are also discussed.

At first glance a direct approach to the pyridylcyclobutane system seemed eminently feasible, patterned after the cycloaddition of enamines to α,β-unsaturated carbonyl compounds and nitriles, i.e., electrophilic olefins,[3-5] in which a vinylpyridine provided the electron-deficient double bond. Under a range of conditions as previously defined,[3-5] however, the morpholine and pyrrolidine enamines of isobutyraldehyde failed to add to 4-vinylpyridine, and only starting materials and polymeric resins were recovered from reaction mixtures.

4-Vinylpyridine apparently was not sufficiently reactive and it occurred to us that it might be possible to activate the double bond to attack by polarizing the molecule through protonation. Indeed, addition of a catalytic amount (ca. 2 mol %) of p-toluenesulfonic acid to reaction mixtures did promote facile cycloaddition

with enamines of α,α-disubstituted aldehydes, providing the cyclobutane derivatives described in Table I in yields up to 80%. As long as a small amount of acid was present, the reaction could be carried out in polar or nonpolar solvents or without solvent at temperatures up to 150° but proceeded most smoothly under mildest conditions (even at room temperature) and with least contamination from polymeric by-products in a polar solvent, notably acetonitrile. This fact suggests, in keeping with conclusions drawn from studies of the parallel reactions with α,β-unsaturated carbonyl compounds,[3-6] that cycloaddition is not concerted but is a two-step process going through a charged transition state. Although only a small amount of protonated vinylpyridine can be present at equilibrium, the effect of acid must mean that a protonated vinylpyridine participates in the rate-determining step,[7] which should

(1)
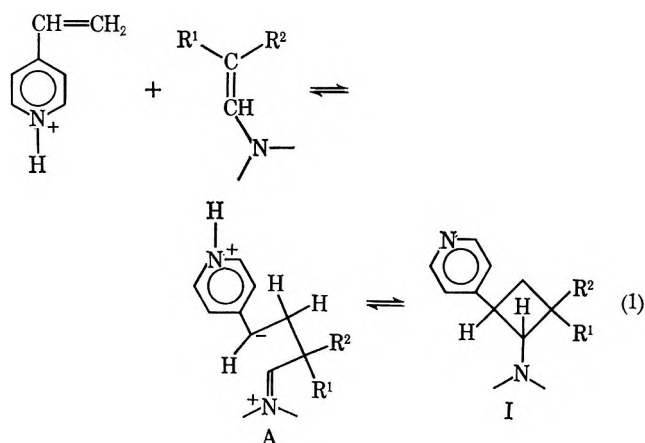
(1) Department of Pharmacology, Given Building, University of Vermont, Burlington, Vt. 05401.

(2) A. P. Gray and H. Kraus, J. Org. Chem., 31, 399 (1966); A. P. Gray, H. Kraus, D. E. Heitmeier, and R. H. Shiley, ibid., 33, 3007 (1968).

(3) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelley, ibid., 26, 625 (1961); ibid., 29, 801 (1964).

(4) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, ibid., 29, 813 (1964).

(5) I. Fleming and J. Harley-Mason, J. Chem. Soc, 2165 (1964).

(6) A. Risaliti, E. Valentin, and M. Forchiassin, Chem. Commun., 233 (1969).

(7) A. P. Gray and W. L. Archer, J. Amer. Chem. Soc., 79, 3554 (1957).

TABLE I

PYRIDYLCYCLOBUTANES
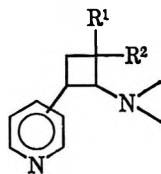
Compd[a]	Pyridyl isomer	R[1]	R[2]	−N<	Mp, °C	Yield, %
1	4	Methyl	Methyl	Morpholino	93–94	64
2	2	Methyl	Methyl	Morpholino	83–85	48
	Maleate salt				144–145	
3	2-(Maleate salt)	Methyl	Methyl	Pyrrolidino	127–128	13
4	4	Methyl	Methyl	Pyrrolidino	95–96	35
5	4	Methyl	Methyl	Dimethylamino	55–56	80
6	4	Methyl	Ethyl	Morpholino	99–100	40
7	4	Methyl	Phenyl	Morpholino	119–120	23
8	4	Ethyl	Ethyl	Morpholino	71–72	38
9	4	Methyl	*n*-Nonyl	Morpholino	61–62	39
10	4	$\langle^{R^1}_{R^2}$ = cyclohexylidene		Morpholino	152–153	61
11	4	$\langle^{R^1}_{R^2}$ = 3-cyclohexenylidene		Morpholino	166–167	60
12	4	$\langle^{R^1}_{R^2}$ = 5-norbornen-2-ylidene		Morpholino	Brown glass	48

[a] Satisfactory analytical values for C, H, and N ($\pm 0.35\%$) were obtained for all compounds except as follows. Calcd for 2: N, 11.38. Found: N, 10.89. Calcd for 3 maleate salt: N, 8.09. Found: N, 7.72. Calcd for 12: C, 76.98; mol wt, 296.4. Found: C, 76.58; mol wt (Rast), 300.0.

be the initial addition of the enamine to it. Without attempting a precise formulation of the transition state, we picture the reaction as proceeding somewhat as indicated for 4-vinylpyridine (eq 1).

Only a single isomer of the cycloadduct I was isolated in each of the additions to enamines in which $R^1 = R^2$. This was clearly indicated by the nmr spectral data and by examination with tlc. In fact, surprisingly, even the cycloadducts (6, 7, 9, 11) derived from enamines of asymmetrically substituted aldehydes, which involve three asymmetric centers in the cyclobutane ring, appeared to be (by tlc; nmr data were not helpful) uncontaminated by isomeric products, although here the evidence for homogeneity cannot be considered unequivocal. It was then reassuring in a negative way to find that at least 12, derived from the enamine of

12
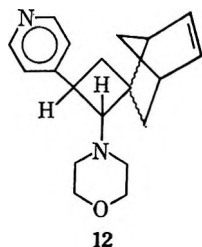
norbornenecarboxaldehyde, was indeed a mixture of isomers presumably dependent on orientation of the norbornene system with respect to the cyclobutane ring. That the products are cyclobutane derivatives having the designated gross structures is clear from the nmr spectral data (see Experimental Section), which were consistent throughout the series.[8] In the absence of suitable models and more detailed analysis, the data do not permit establishment of stereochemistry. The

unequivocal evidence that an analogous cycloaddition is a reversible process leading to the thermodynamically more stable cyclobutane product,[6] however, makes it reasonable to suppose that the present reaction is likewise thermodynamically controlled. If this be true, then it seems likely that the amine and pyridine substituents would be attached trans to each other on the cyclobutane ring as pictured in I. Little can be said with any degree of confidence about the stereochemical disposition of the R^1 and R^2 substituents where these are different.

Cycloaddition proceeded less well with 2- than with 4-vinylpyridine. In this connection it is instructive to note that reaction of the morpholine enamine of isobutyraldehyde with 2-vinylpyridine gave 2 in reasonable yield (48%), the corresponding reaction with the pyrrolidine enamine provided 3 in very poor yield (13%), and reaction with the dimethylamine analog afforded no isolable product although reaction of the same enamine with 4-vinylpyridine had given 5 in 80% yield, the best realized in this series. Explanation may lie in the fact that 4-vinylpyridine is significantly more basic ($pK_a = 5.62$) than 2-vinylpyridine ($pK_a = 4.92$).[9] Thus, if the reactive species is the protonated form of the vinylpyridine as shown in eq 1, it may well be that the equilibrium for protonation of 2-vinylpyridine in the presence of the more basic enamines lies too far to the right (*e.g.*, eq 2).

In line with the idea that the vinylpyridine must be activated and that this is what is accomplished by addition of acid is the finding that a 3-vinylpyridine failed to undergo cycloaddition.[10] Under forcing conditions, reaction of 2-methyl-5-vinylpyridine with 1-morpholino-1-isobutene afforded, in addition to polymers and

(8) For a tabulation of nmr data for related cyclobutane derivatives, see I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).

(9) A. Pietrzyk, R. Wiley, and D. McDaniel, *J. Org. Chem.*, **22**, 83 (1957).

(10) In unpublished work from this laboratory, 3-pyridyl analogs have been prepared by an alternative cycloaddition process.
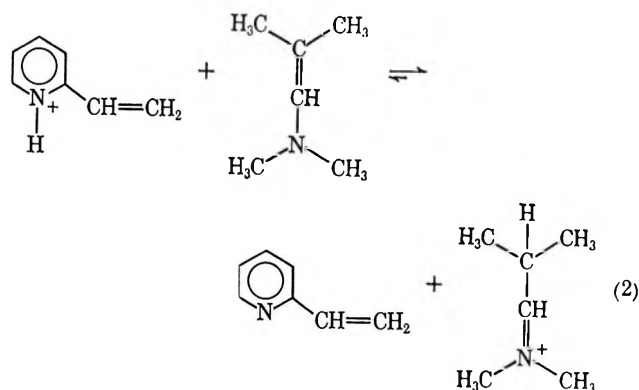
recovered starting materials, a small amount of a product which ir and nmr spectral data suggest to be the aldol-type condensation product **26**. Also unrespon-
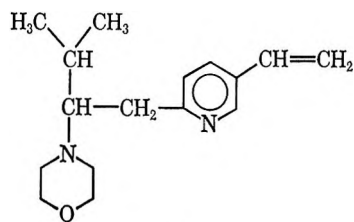
26

sive to this cycloaddition were 4-vinylpyridines bearing terminal substituents such as methyl, phenyl, or even the electron-withdrawing carbomethoxy group. 2-Vinylquinoline did, however, give a cycloadduct **25** with 1-morpholino-1-isobutene, although the reaction went in poor yield.

In contrast to experience with other electrophilic olefins,[3-6,11] only enamines derived from α-disubstituted aldehydes, and therefore enamines not possessing β hydrogens, appeared to undergo the acid-catalyzed cycloaddition to vinylpyridines. Reaction of the morpholine enamine of propionaldehyde with 4-vinylpyridine gave no isolable cycloadduct but only a 45% yield of 4-(morpholinoethyl)pyridine (**28**), identical with material prepared by the pyridylethylation of morpholine.[12] The obvious explanation for this result would be that the enamine had hydrolyzed in the course of reaction and the released morpholine had added to the 4-vinylpyridine. Although the reaction was carried out, and repeated, under optimum conditions for cycloaddition, under which no hydrolysis of β-disubstituted enamines was detected (a catalytic amount of *p*-toluenesulfonic acid monohydrate in undried acetonitrile at room temperature), the greater lability of enamines bearing β hydrogens[3] makes this rationalization perfectly plausible.[13] It is obviously important to learn if the cycloaddition could be effected under anhydrous conditions.

Although cyclohexanone enamines give cycloadducts in many cases,[4-6,11] in numerous others they are reported to give straightforward Michael adducts[14] and

this has been ascribed to the lability and facile ring opening under the reaction conditions of cycloadducts derived from enamines bearing β hydrogens and/or to intramolecular proton transfer from the corresponding dipolar intermediates.[4-6,14] In the present work reaction of the morpholine enamine of cyclohexanone with 4-vinylpyridine did not proceed smoothly except under forcing conditions (catalytic amount of toluenesulfonic acid without solvent at 140°) and then yielded the Michael adduct, 2-(4-pyridylethyl)cyclohexanone (**27**), which is also produced by the reaction of the pyrrolidine enamine with vinylpyridine at higher temperatures without acid catalysis.[15] Either ring opening or proton transfer could account for this result. Hydrogens not present in products derived from enamines of α-disubstituted aldehydes could participate in both processes.

Although formed in the presence of a catalytic amount of acid, the pyridylcyclobutanes were found to be quite labile to acid treatment. Attempts to prepare hydrochloride salts or dissolution of the bases in dilute hydrochloric acid resulted in extensive breakdown. Allowing **1** to stand in glacial acetic acid at room temperature produced a 74% yield of 2,2-dimethyl-4-pyridinebutyraldehyde (**29**), the product which would have been expected if the initial reaction had proceeded by direct Michael-type addition. The acid-catalyzed conversion to the Michael adduct could result from electron withdrawal through the protonated pyridine ring (eq 3). Of course the morpholine N
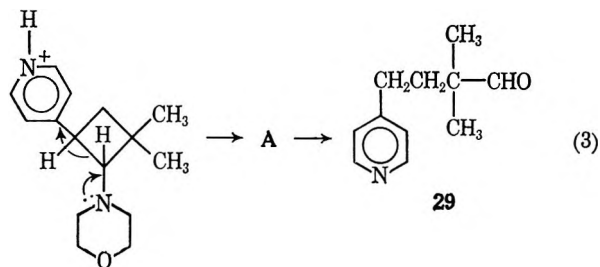
would also be protonated but reaction would occur only when it became free to participate.

Catalytic hydrogenation of **1** in solutions containing excess hydrochloric acid proceeded with opening of the cyclobutane ring and resulted in products derived from the hydrogenation of **29**.[16] When **1** was hydrogenated over Adams platinum oxide in ethanol solution containing just slightly more than 2 equiv of hydrochloric acid, however, ring opening did not occur and the piperidine derivative **19** was obtained in 88% yield. Acylation gave derivatives of **19** (R = acyl). Lithium aluminum hydride reduction of the *N*-benzoyl deriva-

19, R = H
21, R = benzyl

(11) J. Elguero, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. Fr.*, 1149 (1968).

(12) A. P. Phillips, *J. Amer. Chem. Soc.*, **78**, 4441 (1956).

(13) An alternate explanation would involve substitution of the enamine at N rather than C followed by degradation of the resultant dipolar intermediate *via* intramolecular proton transfer.

(14) *E.g.*, G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); A. Risaliti, M. Forichassin, and E. Valentin, *Tetrahedron Lett.*, 6331 (1966); A. Risaliti, M. Forchiassin, and E. Valentin, *Tetrahedron*, **24**, 1889 (1968); N. F. Firrell and P. W. Hickmott, *Chem. Commun.*, 544 (1969).

(15) G. Singerman and S. Danishefsky, *Tetrahedron Lett.*, 2249 (1964).

(16) Unpublished work from this laboratory.

tive gave 3-(1-benzyl-4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane (21). Supporting the thesis that cyclobutane ring opening involved electron transmission *via* the protonated pyridine ring was the finding that the corresponding piperidine derivatives were quite stable to acid, could be recovered without loss from acid solutions, and converted to stable hydrochloride salts. It may be noted that the influence of electron transmission through the pyridine ring here is opposite to that observed in the not really analogous pyridylcyclopropane series[2] where the pyridine substituent *stabilized* the carbocyclic ring to acid attack. In the earlier case ring opening is considered to be initiated by protonation of the α-hydroxyl group followed by electron flow away from rather than toward the pyridine ring. Electron withdrawal through a protonated pyridine would stabilize in the former and destablize in the latter situation. Thus, it appears that under the conditions used for the hydrogenation of 1 reduction of the pyridine ring precedes ring opening and provides a product stabilized to acid attack. Hydrogenation of 1 in the absence of acid over a rhodium catalyst also afforded 19, but the yield was poor (35%).

Treated at room temperature with excess methyl iodide, 1 gave a dimethiodide salt 13; treated carefully with 1 equiv, a monomethiodide 14 could be isolated, but the ease of diquaternization of 1 could be considered supportive of the postulated trans arrangement of the pyridine and morpholine groups. Both 13 and 14 retained the cyclobutane ring. The uv, ir, and nmr spectra of 14 showed unequivocally that the product was the pyridine–methiodide as shown. Although labile, 14 was sufficiently stable to be isolated and char-

14
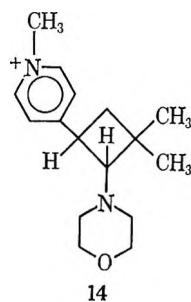
acterized (Table II). Careful treatment of 1 with benzyl bromide gave a crude monobenzyl quaternary salt which was also shown to be a pyridinium salt since catalytic hydrogenation afforded the same product (21) obtained by the lithium aluminum hydride reduction of the *N*-benzoyl derivative of 19 (Table III).

On the other hand, oxidation of 1 with 1 equiv of *m*-chloroperbenzoic acid yielded a mono *N*-oxide which was shown to be the morpholine *N*-oxide 15. The uv

15
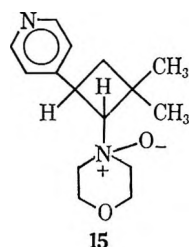
spectrum in acid and base was that of a typical pyridine, the ir spectrum showed no shift in the 1600-cm⁻¹ band,[17]

TABLE II
4-PYRIDYLCYCLOBUTANE DERIVATIVES
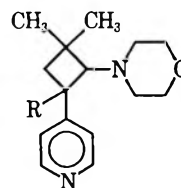
Compd	Derivative	R	Mp, °C	Analyses[a]
13	Dimethiodide	H	230–231	C, H, I[a]
14	Pyridine–methiodide	H	254–256	C, H, N
15	Morpholine *N*-oxide	H	163–164	C, H, O[a]
	Dimaleate salt		134–135	C, H, N
16		Benzyl	157–158	C,[a] H, N
17		Methyl	90–91	C, H, N
18		Phenyl	135–140	C, H, N

[a] Satisfactory analytical values for the indicated elements (±0.35%) were obtained for all compounds except as follows. Calcd for **13**: I, 47.88. Found: I, 48.24. Calcd for **15**: O, 12.20. Found: O, 12.82. Calcd for **16**: C, 78.54. Found: C, 77.97.

TABLE III
4-PIPERIDYLCYCLOBUTANE DERIVATIVES
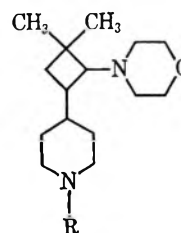
Compd	R	Mp, °C	Analyses[a]
19	H	66–67	C, H, N
20	Benzoyl	104–107	C, H, N
	Hydrochloride salt	268–270	C, H, Cl
21	Benzyl	96–97	C, H, N
	Dihydrochloride salt	208–210	C, H, Cl[a]
22	Acetyl	121–122	C, H, N
	Hydrochloride salt	192–193	C,[a] H, Cl
23	3,4,5-Trimethoxy-benzoyl	109–111	C, H, N
	Hydrochloride salt	259–260	C, H, Cl[a]
24	*n*-Butylcarbamoyl	105–106	C, H, N

[a] Satisfactory analytical values for the indicated elements (±0.35%) were obtained for all compounds except as follows. Calcd for **21** 2HCl: Cl, 17.08. Found: Cl, 16.72. Calcd for **22** HCl: C, 61.70. Found: C, 61.33. Calcd for **23** HCl: Cl, 7.34. Found: Cl, 7.71.

and in the nmr there was a marked alteration and displacement of the pattern of signals from the morpholine protons and a slight shift (compared to 1) to lower rather than higher[18] fields for the pyridine proton signals. It would thus appear that relative basicity was the controlling factor in oxidation and directed initial reaction to the more basic morpholine N whereas steric hindrance about the morpholine and, perhaps, polarizability of the pyridine directed alkylation first to the pyridine N.

The pyridylcyclobutanes were remarkably stable to harsh alkaline treatment. Subjection of 1, 4, and 5 to

(17) *Cf.* A. R. Katritzky, C. R. Palmer, F. J. Swinbourne, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.*, **91**, 636 (1969).

(18) A. R. Katritzky and J. M. Lagowski, *J. Chem. Soc.*, **43** (1961); unpublished results from this laboratory.

TABLE IV

ENAMINES OF DISUBSTITUTED ACETALDEHYDES

$$\underset{R^2}{\overset{R^1}{\diagdown}}C{=}CH{-}N\underset{\diagdown}{\overset{\diagup}{}}$$
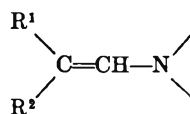
R¹	R²	Registry no.	—N<	Bp, °C (mm)[a]	Ref bp, °C (mm)[a]	Ir,[b] ν_{max}, cm⁻¹, C=CN	Yield, %
Methyl	Methyl		Morpholino	65–70 (15)	56–57 (11)[c]		89
Methyl	Methyl		Dimethylamino	85–87	87–89 (760)[d]		35
Methyl	Methyl		Pyrrolidino	70–73 (40)	70–71 (38)[c]		84
Methyl	Ethyl	28478-25-3	Morpholino	86–89 (17)		1660	70
Ethyl	Ethyl	28478-26-4	Morpholino	90–93 (15)		1645	92
Methyl	Phenyl	28478-27-5	Morpholino	64–65[e]		1625	68
Methyl	n-Nonyl	28478-28-6	Morpholino	130–131 (0.05)		1665	61
Cyclohexylidene		16963-29-4	Morpholino	105–107 (6)		1650	79
3-Cyclohexenylidene		28487-14-1	Morpholino	90–94 (0.05)		1665	52
5-Norbornen-2-ylidene			Morpholino	128–133 (13)	132–135 (14)[f]		77

[a] Satisfactory analytical values for N (±0.2%) were obtained for all new compounds listed. [b] Spectra were obtained in chloroform solution. [c] Reference 20. [d] Reference 3. [e] Melting point. [f] L. A. Paquette, *J. Org. Chem.*, 29, 2851 (1964).

conditions such as sodamide in boiling tetrahydrofuran, sodium ethoxide in boiling ethanol, or sodium hydride in hot dimethylformamide resulted only in recovery of starting material (75–90%). Although I can be viewed as a Mannich-type base, the amino group could neither be eliminated nor displaced by introduction of suitable nucleophiles. Since alkylation with Mannich bases undoubtedly proceeds through an elimination-addition mechanism, these results accord with the high energy of activation for introducing a double bond in a cyclobutane ring. Of course, if selective quaternization of the amino N had been possible, the difficulty might have been circumvented.[3] Experiments with the N-oxide 15 gave anomalous results.

Treatment of 1 with sodamide in liquid ammonia did, however, produce the anion by removal of the proton α to the pyridine ring and subsequent alkylation with benzyl chloride and with methyl iodide afforded the 3,3-disubstituted cyclobutanes 16 and 17, respectively.
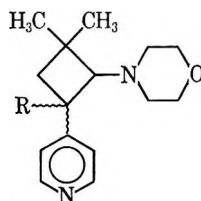
16, R = benzyl
17, R = methyl
18, R = phenyl

Treatment with bromobenzene gave the phenyl derivative 18 in poor yield and even this required 2 equiv of sodamide in line with intervention of a benzyne intermediate. The nmr spectra of 16–18 clearly indicated their gross structure but nothing can be said about stereochemistry.

Many of the 4-pyridylcyclobutanes listed in Table I showed significant antidepressant and stimulant properties in rodents but were not pursued owing to their marked barbiturate-potentiating activity, probably mediated by inhibition of metabolism.

Experimental Section[19]

Materials. The enamines of disubstituted acetaldehydes used in this investigation are listed in Table IV and where indicated were prepared by methods described in the literature. New enamines were prepared by the method of Benzing[20] and were characterized by their infrared spectra and "basic" nitrogen analyses. 1-Morpholino-1-propene, bp 58–66° (10 mm), was prepared using method B of Brannock.[3] 1-Morpholino-1-cyclohexene showed bp 120–123° (20 mm) [lit.[21] bp 117–120 (10 mm)] and 2-vinylquinoline showed bp 116–119° (4 mm) [lit.[22] bp 120–125° (7 mm)]. All other materials were commercially available and were used without further purification.

Reaction of Enamines with Vinylpyridines. 3-(4-Pyridyl)-2-morpholino-1,1-dimethylcyclobutane (1). Method A.—To a solution of 8 g of p-toluenesulfonic acid monohydrate in 500 ml of acetonitrile under nitrogen was added 157.6 g (1.5 mol) of 4-vinylpyridine followed by the dropwise addition of 217.4 g (1.54 mol) of 1-morpholino-1-isobutene. The mixture was heated for 2 hr on the steam bath and concentrated under reduced pressure to a red oil that solidified on cooling. The crude solid was recrystallized from hexane to give 237 g (64%) of 1 as colorless crystals: mp 93–94°; uv max (0.1 N HCl) 256.5 mμ (log ε 3.71); uv max (0.1 N NaOH) 258.0 mμ (log ε 3.36); ir (CHCl₃) 1600 (pyridine); nmr (CDCl₃) δ 8.40 (m, 2, α-pyridine protons), 7.05 (m, 2, β-pyridine protons), 3.50 (m, 4, morpholine OCH₂), 3.10 (q, 1, J = 9 Hz, proton on pyridine-attached cyclobutane carbon), 2.57 (d, 1, J = 9 Hz, proton on morpholine-attached cyclobutane carbon), 2.10 (m, 4, morpholine NCH₂), 1.88 and 1.48 (each, d, 1, J = 9 Hz, cyclobutane CH₂), 1.20 (s, 6, gem-dimethyl).

Method B.—A mixture of 45 g (0.43 mol) of 4-vinylpyridine, 64 g (0.45 mol) of 1-morpholino-1-isobutene, and 2 g of p-toluenesulfonic acid monohydrate in 125 ml of acetonitrile was allowed to stand at room temperature for 3 days. Concentration of the reaction mixture left a thick red oil that solidified on standing; recrystallization afforded 62.3 g (59%) of 1, mp 92–93°.

3-(4-Pyridyl)-2-morpholino-1,1-dimethylcyclobutane Dimethiodide (13).—A solution of 5.0 g of 1 in 25 ml of acetonitrile and 20 ml of methyl iodide, allowed to stand at room temperature for

(19) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded with a Beckman Model IR-5 spectrophotometer; peak positions are given in reciprocal centimeters. Nmr spectra were determined with a Varian Model A-60 spectrometer; pertinent chemical shifts are expressed in parts per million downfield from tetramethylsilane and coupling constants in cycles per second.

(20) E. Benzing, *Angew. Chem.*, 71, 521 (1959).

(21) S. Hunig, E. Benzing, and E. Lucke, *Chem. Ber.*, 90, 2833 (1957).

(22) G. B. Bachman and D. D. Micucci, *J. Amer. Chem. Soc.*, 70, 2381 (1948).

3 days, deposited 7.2 g of solid that crystallized from methanol to give 4.9 g of **13** as amber plates, mp 230–231°.

3-(4-Pyridyl)-2-pyrrolidino-1,1-dimethylcyclobutane (4).—A mixture of 103 g (0.98 mol) of 4-vinylpyridine, 123.6 g (0.98 mol) of 1-pyrrolidino-1-isobutene, and 4 g of *p*-toluenesulfonic acid monohydrate was heated for 6.5 hr on the steam bath in a nitrogen atmosphere. Dilution of the mixture with 25 ml of acetone afforded a crystalline precipitate which was recrystallized from acetone to give 77 g (35%) of **4** as large colorless crystals: mp 95–96° (no additional product could be isolated by further work-up of the mother liquors); ir (CHCl₃) 1600 (pyridine); nmr (CDCl₃) δ 8.42 (m, 2, α-pyridine protons), 7.13 (m, 2, β-pyridine protons), 3.15 (q, 1, *J* = 9 Hz, proton on pyridine-attached cyclobutane carbon), 2.50 (d, 1, *J* = 9 Hz, proton on pyrrolidine-attached cyclobutane carbon), 2.20 (m, 4, pyrrolidine NCH₂), 1.97–1.47 (complex m, 6, pyrrolidine CH₂CH₂ and cyclobutane CH₂), 1.21 and 1.17 (two s, 6, *gem*-dimethyl).

3-(2-Quinolyl)-2-morpholino-1,1-dimethylcyclobutane (25).—A solution of 10.0 g (0.07 mol) of 1-morpholino-1-isobutene, 11.0 g (0.07 mol) of 2-vinylquinoline, and 0.4 g of *p*-toluenesulfonic acid monohydrate in 25 ml of acetonitrile was allowed to stand under nitrogen for 3 days. The red solution was concentrated to dryness and the residue crystallized from pentane to give 2.4 g (11.6%) of **25** as colorless needles: mp 123–124°; nmr (CDCl₃) δ 8.10 (d, 2, quinoline 3,4 protons), 7.53 (m, 4, quinoline 5,6,7,8-protons), 3.62 (m, 4, morpholine OCH₂), 3.32 (m, 1, proton on quinoline-attached cyclobutane carbon), 2.90 (d, 1, *J* = 9 Hz, proton on morpholine-attached cyclobutane carbon), 2.24 (m, 4, morpholine NCH₂), 1.98 and 1.60 (each, d, 1, poorly resolved cyclobutane CH₂), 1.28 (s, 6, *gem*-dimethyl).

Anal. Calcd for C₁₉H₂₄N₂O: C, 76.98; H, 8.16; N, 9.45. Found: C, 77.01; H, 8.24; N, 9.41.

Other pyridylcyclobutanes, prepared similarly (usually as described for **1**, method B) from the appropriate enamine (Table IV), *p*-toluenesulfonic acid monohydrate, and 2- or 4-vinylpyridine, are listed in Table I. The reactions could also be carried out in other polar solvents such as isopropyl alcohol or dimethylformamide although acetonitrile was generally used since less resinous by-product formed in this solvent.

2-(2-Morpholino-3-methyl-1-butyl)-5-vinylpyridine (26).—A mixture of 60 g (0.5 mol) of 2-methyl-5-vinylpyridine, 71 g (0.5 mol) of 1-morpholino-1-isobutene, and 2.0 g of *p*-toluenesulfonic acid monohydrate was heated in a nitrogen atmosphere at 140° for 8 hr. The mixture was cooled to room temperature and diluted with hexane to precipitate polymeric material. The hexane solution was decanted, concentrated, and vacuum distilled to give 60 g of material, bp 60–75° (16 mm), which from the infrared spectrum was a mixture of enamine and vinylpyridine. Distillation of the residue yielded 9.8 g (7.5%) of what is presumed to be **26**: bp 118–121° (0.1 mm); ir (neat) 1630 (vinyl), 1595 (pyridine); nmr (CCl₄) δ 8.43 (broad s, 1, α-pyridine proton), 7.52 (d, 1, γ-pyridine proton), 7.03 (m, 1, β-pyridine proton), 6.58 (m, 1, vinyl CH), 5.50 (broad q, 2, vinyl CH₂), 3.48 (m, 4, morpholine OCH₂), 2.82 (broad s, 3), 2.42 (m, 4, morpholine NCH₂), 1.7 (broad band, 1), 1.0 (q, 6, *gem*-dimethyl).

Anal. Calcd for C₁₆H₂₄N₂O: C, 73.80; H, 9.29; N, 10.76. Found: C, 73.85; H, 9.37; N, 10.53.

2-(4-Pyridylethyl)cyclohexanone (27).—A mixture of 25.5 g (0.15 mol) of 1-morpholino-1-cyclohexene, 17.0 g (0.16 mol) of 4-vinylpyridine, and 1 g of *p*-toluenesulfonic acid monohydrate was heated at 140° for 9 hr under nitrogen and vacuum distilled to give 22.0 g (72%) of **27**: bp 134–148° (0.5 mm); ir (CHCl₃) 1700 (ketone C=O), 1600 (pyridine); picrate, mp 127–130° [lit.¹⁵,²³ bp 134–139° (0.3 mm); ir 1705, 1590; picrate, mp 129.5–131°].

4-(Morpholinoethyl)pyridine (28).—A solution of 30.0 g (0.23 mol) of 1-morpholino-1-propene, 24 g (0.23 mol) of 4-vinylpyridine, and 1 g of *p*-toluenesulfonic acid monohydrate in 75 ml of acetonitrile was allowed to stand in a stoppered flask for 7 days. The dark red solution was concentrated *in vacuo* and the residue was distilled through a molecular still to give 20 g (45%) of **28**, which solidified on standing, mp 49–50° unchanged on recrystallization from pentane. The mixture melting point with material (49–50°) prepared by the pyridylethylation of morpholine¹² was not depressed.

Anal. Calcd for C₁₁H₁₆N₂O: N, 14.57. Found: N (basic), 14.31.

Reactions of 3-(4-Pyridyl)-2-morpholino-1,1-dimethylcyclobutane (1). Ring Opening. 2,2-Dimethyl-4-pyridinebutyralde-

hyde (29).—A solution of 32.0 g (0.13 mol) of **1** in 375 ml of glacial acetic acid was allowed to stand at room temperature for 2 days. Concentration *in vacuo* at 50° left a yellow oil which was dissolved in ice water. The aqueous solution was made basic with 20% sodium hydroxide and extracted with ether. Drying and removal of the ether followed by distillation of the residue gave 17.0 g (74%) of **29** as a pale yellow oil: bp 104–107° (0.1 mm); *n*²⁰D 1.5048; ir (neat) 1710 (C=O) and 1590 (pyridine); nmr (CDCl₃) δ 9.58 (s, 1, aldehyde proton), 8.46 (m, 2, α-pyridine protons), 7.08 (m, 2, β-pyridine protons), 2.50 (m, 2), 1.75 (m, 2), 1.15 (s, 6, *gem*-dimethyl).

Anal. Calcd for C₁₁H₁₅NO: C, 74.53; H, 8.53; N, 7.91. Found: C, 74.77; H, 8.81; N (basic), 7.82.

Stability of 1 and Other Cyclobutanes to Base.—To a solution of 12.5 g (0.05 mol) of **1** in 50 ml of dimethylformamide was added 2.2 g (0.05 mol of NaH) of a 56% sodium hydride–oil dispersion and the mixture was heated on the steam bath for 3 hr. Cautious addition of 250 ml of water with cooling precipitated 11.5 g (92% recovery) of **1** as a white solid, mp 90–93°. The mixture melting point with pure **1** (93–94°) was not depressed. **1** was also perfectly stable to boiling for 15 min with 10% aqueous sodium hydroxide.

Similar results obtained when cyclobutane **4** was treated with sodium amide in liquid ammonia followed by boiling in tetrahydrofuran (80% recovery of **4**) or when **5** was heated at reflux with sodium ethoxide in ethanol (73% recovery of **5**).

3,3-Disubstituted Cyclobutanes.—To a slurry of 4.3 g (0.11 mol) of sodium amide in 200 ml of liquid ammonia was added in portions 25.0 g (0.1 mol) of **1**. The red mixture was stirred for 30 min and treated, dropwise (5 min), with 17.2 g (0.12 mol) of methyl iodide in 25 ml of dry tetrahydrofuran, which treatment discharged the red color. As the ammonia evaporated it was replaced with 200 ml of tetrahydrofuran and the mixture was finally heated at reflux for 3 hr. The filtered tetrahydrofuran solution was evaporated to a solid residue that was twice recrystallized from hexane to give 10.8 g (40%) of **3-(4-pyridyl)-3-methyl-2-morpholino-1,1-dimethylcyclobutane (17)** as colorless crystals: mp 90–91°; nmr (CDCl₃) δ 8.58 (m, 2, α-pyridine protons), 7.26 (m, 2, β-pyridine protons), 3.68 (m, 4, morpholine OCH₂), 2.77 (s, 1, proton on morpholine-attached cyclobutane carbon), 2.26 (m, 4, morpholine NCH₂), 1.83 (s, 2, cyclobutane CH₂), 1.60 (s, 3, CH₃ attached to 3 carbon of cyclobutane), 1.37 and 1.18 (each, s, 3, *gem*-dimethyl).

Compounds **16** (46%) and **18** (10%, using 2 equiv of sodium amide) were similarly prepared by reaction with benzyl chloride and bromobenzene, respectively.

Morpholine N-Oxide.—To a solution of 25.0 g (0.1 mol) of **1** in 100 ml of methylene chloride was added, dropwise, a solution of 24.0 g (0.12 mol) of 87% *m*-chloroperbenzoic acid in 500 ml of methylene chloride. After being allowed to stand for 20 hr at room temperature the mixture was washed with a nearly saturated solution of potassium carbonate, dried, and concentrated to leave a tan solid. Two recrystallizations from acetone yielded 9.2 g (35%) of **3-(4-pyridyl)-2-morpholino-1,1-dimethylcyclobutane morpholine N-oxide (15)** as colorless crystals: mp 163–164°; uv max (0.1 N HCl) 254.5 mμ (log ε 3.68); uv max (0.1 N NaOH) 257.5 mμ (log ε 3.23); ir (CHCl₃) 1600 (pyridine); nmr (CDCl₃) δ 8.58 (m, 2, α-pyridine protons), 7.36 (m, 2, β-pyridine protons), 4.3–2.1 (complex m, 12, morpholine and cyclobutane protons), 1.61 and 1.40 (each, s, 3, *gem*-dimethyl).

The dimaleate salt of **15**, prepared in chloroform and recrystallized from isopropyl alcohol, melted at 134–135°.

Selective Pyridine Quaternization.—To a solution of 24.6 g (0.1 mol) of **1** in 200 ml of benzene at room temperature was added, dropwise over a 2-hr period, a solution of 15.6 g (0.11 mol) of methyl iodide in 30 ml of benzene. The mixture was stirred for 16 hr to give 15 g of tan crystals, mp 234–238°. Recrystallization from methanol yielded 9.0 g (23%) of **3-(4-pyridyl-2-morpholino-1,1-dimethylcyclobutane pyridine methiodide (14)**: mp 254–256°; uv max (0.1 N HCl) 258.0 mμ (log ε 3.63); uv max (0.1 N NaOH) 257.5 mμ (log ε 3.72); ir (CHCl₃) 1638 (pyridinium); nmr (CDCl₃) δ 9.37 (m, 2, α-pyridine protons), 8.05 (m, 2, β-pyridine protons), 4.70 (s, 3, pyridinium NCH₃), 3.60 (m, 4, morpholine OCH₂), 2.15 (m, 4, morpholine NCH₂), 1.25 (s, 6, *gem*-dimethyl). Other cyclobutane protons are accounted for in the integration but absorptions are not resolved.

3-(1-Benzyl-4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane (21). A. *Via* **Hydrogenation of the Benzyl Quaternary Salt of 1.**—To 24.6 g (0.1 mol) of **1** in 100 ml of benzene was added, dropwise over a 5-hr period, 19.0 g (0.11 mol) of benzyl bromide

(23) G. Magnus and R. Levine, *J. Org. Chem.*, **22**, 270 (1957).

in 25 ml of benzene. The mixture was stirred for 16 hr and the precipitate collected and dried to give 49 g of an uncrystallizable solid melting at 80–82° with foaming.

A solution of 21.0 g of the solid in 200 ml of ethanol was shaken with 2 g of a 5% rhodium-on-carbon catalyst for 20 hr at room temperature in an Adams–Parr apparatus under 50 psi of hydrogen. The filtered solution was concentrated to an oil that was dissolved in water; the aqueous solution was treated with solid potassium carbonate and extracted with ether. Evaporation of the ether left 6 g of oil that solidified, mp 91–93°; mixture melting point with pure (mp 96–97°) 21 (see below) was not depressed.

B. Via Hydrogenation of 1.—To a solution of 40.0 g (0.16 mol) of 1 in 200 ml of ice-cold ethanol was slowly added 37 ml of concentrated hydrochloric acid and the mixture was shaken at room temperature with 1.5 g of platinum oxide catalyst at an initial pressure of 50 psi of hydrogen. Reduction was complete in 10 hr after which the catalyst was filtered off, the filtrate was concentrated *in vacuo*, and the residual oil was dissolved in 200 ml of water. The aqueous solution was made strongly basic with 50% sodium hydroxide and extracted with benzene. Drying and removal of the benzene left an oil that solidified on standing. Recrystallization from pentane gave 36 g (88%) of 3-(4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane (19) as colorless crystals: mp 66–67°; ir (CHCl₃) 3220 (NH), pyridine absorption absent; nmr (CDCl₃) δ 3.68 (m, 4, morpholine OCH₂), 2.30 (m, 4, morpholine NCH₂), 1.65 (s, 1, NH), 1.07 and 1.05 (two s, 6, *gem*-dimethyl). Other absorptions were unresolved between 3.2 and 1.3 but all protons are accounted for in the total integration.

The catalytic hydrogenation of 1 was also carried out in ethanol solution without any added hydrochloric acid using a 5% rhodium-on-carbon catalyst (8 g of catalyst for 15 g of 1) at 50° to give a 35% yield of 19, mp 66–67° undepressed on admixture with 19 prepared with added hydrochloric acid.

An ice-cooled solution of 11.0 g (0.04 mol) of 19 in 150 ml of benzene and 20 ml of triethylamine was treated, dropwise, with 8.5 g (0.06 mol) of benzoyl chloride in 15 ml of benzene. The mixture was stirred for 5 hr at room temperature, washed twice with water, dried, and concentrated to an oil that solidified. Recrystallization from hexane provided 14.5 g (92%) of colorless crystals of 3-(1-benzoyl-4-piperidyl)-2-morpholino-1,1-dimethylcyclobutane (20): mp 102–104°; mp 104–107° after one additional recrystallization; ir (CHCl₃) 1625 (amide —C=O), 1585 (phenyl).

The hydrochloride salt of 20, prepared in ethyl acetate and recrystallized from isopropyl alcohol–hexane, showed mp 268–270°.

The acetyl (22) and the 3,4,5-trimethoxybenzoyl (23) derivatives (Table III) were similarly prepared.

To a slurry of 2.0 g (0.05 mol) of lithium aluminum hydride in 200 ml of dry tetrahydrofuran was added, dropwise, a solution of 10.0 g (0.03 mol) of 20 in 100 ml of dry tetrahydrofuran. The mixture was stirred for 2 hr at room temperature and then heated at reflux for 2 hr. The cooled mixture was treated with 5 ml of water followed by 25 ml of 20% sodium hydroxide. The coagulated aluminum hydroxide was filtered off and the filtrate was dried and concentrated leaving a solid that was crystallized from pentane to give 5.6 g (58%) of 21: mp 93–95°; mp 96–97° after further recrystallization; nmr (CDCl₃) δ 7.33 (s, 5, phenyl protons), 3.68 (m, 4, morpholine OCH₂), 3.51 (s, 2, benzyl CH₂), 2.35 (m, 4, morpholine NCH₂), 1.08 and 1.05 (two s, 6, *gem*-dimethyl). All other protons were unresolved between 3.1 and 1.3 and accounted for in total integration.

The dihydrochloride salt of 21 was recrystallized from isopropyl alcohol and showed mp 208–210°.

3-[1-(*n*-Butylcarbamoyl)-4-piperidyl]-2-morpholino-1,1-dimethylcyclobutane (24).—To a cold solution of 12.6 g (0.05 mol) of 19 in 25 ml of benzene was added 10.0 g (0.1 mol) of *n*-butyl isocyanate in 15 ml of benzene. The solution was allowed to stand for 16 hr at room temperature and concentrated *in vacuo* and the residual oil was crystallized from hexane to give 16 g (91%) of 24 as glistening plates: mp 105–106°; ir (CHCl₃) 3390 (NH), 1635 (urea C=O).

Hydrolysis of Halopyridines at 250–350°. Formation of a Rearranged Product from 3-Halopyridines

JOHN A. ZOLTEWICZ* AND A. A. SALE

Department of Chemistry, University of Florida, Gainesville, Florida 32601

3-Chloro-, 3-bromo-, or 3-iodopyridine when heated with 4 *M* aqueous potassium hydroxide at 250–350° gives mixtures of 3-hydroxypyridine and 4-pyridone. The ratio of the yields of these products as indicated by nmr analysis of the reaction mixtures decreases in the order Cl > Br > I. 3-Iodopyridine gives more rearranged than unrearranged product; it also gives pyridine. Under the same conditions 2- or 4-chloro-, bromo-, and iodopyridines give 2- or 4-pyridone, respectively. 3-Hydroxypyridine is stable under the hydrolysis conditions but 2- and 4-pyridone degrade at the higher temperatures; nonaromatic products were characterized. It is suggested that the hydrolysis reactions of 3-halopyridines may involve competing direct substitution and elimination-addition reactions. The latter involves the formation of 3,4-pyridyne as an intermediate.

It has been known for many years that halobenzenes undergo alkaline hydrolysis at 250–350° to give phenols.[1,2] The mechanisms for this reaction are said to include direct substitution and aryne (elimination-addition) pathways, the aryne route being favored at higher temperatures.[3] The formation of structurally

rearranged hydrolysis products is cited as evidence for the aryne route (eq 1). When only aryne formation
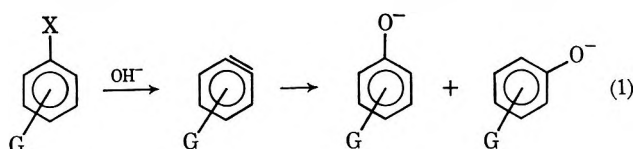
takes place, the ratio of rearranged to unrearranged products is independent of the identity of the leaving

(1) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.
(2) W. Hale and E. C. Britton, *Ind. Eng. Chem.*, **20**, 114 (1928).
(3) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **79**, 1458 (1957).

halide ion. When halobenzenes react by both pathways concurrently, the product ratio is sensitive to the halogen.

Although a variety of halogenated carbocyclic aromatic compounds have been hydrolyzed by the high temperature method, curiously, halogenated heteroaromatic compounds have not been treated with aqueous alkali under conditions which might be expected to lead to hetaryne intermediates.[1,4-7]

We report the results of studies with isomeric halopyridines heated at 250–350° with 4 *M* potassium hydroxide. In addition to the nonaromatic degradation products found in all the reaction mixtures, direct substitution products from the reactions of 2- and 4-halopyridines were observed, but 3-halopyridines gave mixtures of 3-hydroxypyridine and 4-pyridone, the ratio depending on the identity of the halogen. In addition, pyridine was formed from 3-iodopyridine.

Results and Discussion

Since halopyridines are expected to hydrolyze to hydroxypyridines, control experiments were carried out to determine the stability of the expected products. The results in Table I show that only 3-hydroxypyri-

TABLE I
CONTROL RUNS TO DETERMINE THE STABILITY OF 2- AND
4-PYRIDONE AND 3-HYDROXYPYRIDINE IN 4 *M* AQUEOUS
POTASSIUM HYDROXIDE SOLUTION[a]

Pyridine derivative	Furnace T, °C	Time, min	% unreacted pyridine[b]
2	350	30	23[c]
2	300	60	70[c]
2	250	240	97[c]
3	350	30	100
3	300	60	100
4	350	30	81[d]
4	300	60	>95[d]

[a] 0.020 mol of the substrate was heated with 25 ml of 4 *M* KOH containing 0.0066 mol of isobutyric acid as internal standard. [b] From nmr analysis of the reaction mixtures. [c] Acetate ion is also present. [d] Formate and acetate ions present as well as acetone.

dine is completely stable toward 4 *M* KOH at 300–350°. About 19% degradation of 4-pyridone in 4 *M* KOH occurs after 30 min at 350°; almost no degradation results after 1 hr at 300°. 2-Pyridone undergoes extensive fragmentation.[8] After 30 min at 350°, for example, only 23% of 2-pyridone remained; 2 equiv of acetate ion were formed. At lower temperatures the 2-pyridone is more stable. At 300° for 1 hr and at 250° for 4 hr only 30% and ~3% degradation results, respectively. These results indicate that there will be some difficulty in detecting 2-pyridone as a hydrolysis product but that 3-hydroxypyridine and 4-pyridone, owing to their greater thermal stability, can easily be detected.

(4) H. J. den Hertog and H. C. van der Plas, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 17.

(5) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocycl. Chem.*, 4, 121 (1965).

(6) T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, 4, 543 (1965).

(7) R. W. Hoffmann, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 16.

(8) By comparison, 2-chloroquinoline is quantitatively converted to 2-quinolone on heating at approximately 300° in 4 *M* KOH for 2.5 hr. Thus, 2-quinolone appears to be more stable than 2-pyridone in aqueous alkali.

Also detected (nmr analysis) in the reaction mixture of 4-pyridone showing degradation were formate and acetate ions as well as acetone.[9] These nonaromatic products were commonly found in small, variable quantities in other reaction mixtures where decomposition of the aromatic substrate took place. In control experiments it was shown that formate ion and acetone can survive under the conditions employed for halopyridine hydrolysis. For example, after heating acetone at 300° for 30 min with 4 *M* KOH, 12% could be detected in the mixture. Similarly, 30% of the original formate ion remained after heating for 30 min at 350°. Ammonia and carbon dioxide also were detected when the heteroaromatic substrate decomposed.

In all of our studies reaction mixtures were analyzed by nmr.[10] Isobutyric acid generally was added to reaction mixtures prior to heating to serve as an internal standard. Control runs indicated that the standard was thermally stable and that mixtures could be analyzed quantitatively by this method. The nmr standard had no influence on the ratio of halopyridine hydrolysis products.

In spite of the degradation of 2-pyridone which occurs at 300–350°, we elected to employ these higher temperatures in studies of the hydrolysis of halopyridines. In our systems, dehydrohalogenation reactions are expected to have energies of activation which are greater than those for direct substitution processes. Hence, the higher energy reaction becomes relatively more favorable with increasing temperatures.[3]

Table II summarizes the results of hydrolysis experiments with the 2 and 4 isomers of chloro-, bromo-, and iodopyridines at 300–350° in 4 *M* KOH. The 2-halo-

TABLE II
CONDITIONS AND RESULTS OF THE HYDROLYSIS OF 2- AND
4-HALOPYRIDINES WITH 4 *M* POTASSIUM HYDROXIDE

Halopyridine	Furnace T, °C	Time, min	% corresponding hydroxypyridine[a]
2-Cl	350	30	22
2-Br	350	30	25
2-I	350	30	34
4-Cl	350	30	60
4-Cl	300	15	62[b]
4-Br	350	30	52
4-Br	300	5	46[b,c]
4-Br	300	10	61[b]
4-I	350	30	38

[a] Nonaromatic products present as well. [b] 12–17% 4-aminopyridine also formed. Amount varies with run. [c] 11% of starting material unreacted.

pyridines gave 22–34% of 2-pyridone. No 3-hydroxypridine or 4-pyridone could be detected. The 4-halopyridines gave rise to 38–62% of 4-pyridone and also 12–17% of 4-aminopyridine. No 2-pyridone or 3-hydroxypyridine products could be found.

Although the 4-aminopyridine product could arise from a reaction between 4-halopyridine and liberated

(9) The 2,4-dinitrophenylhydrazone derivative of acetone was recovered from a reaction mixture.

(10) Nmr spectra of 2- and 4-pyridones and 3-hydroxypyridine in 4 *M* potassium hydroxide as well as nmr spectra of typical 3-halopyridine hydrolysis reaction mixtures will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N. W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

TABLE III

CONDITIONS AND RESULTS OF THE HYDROLYSIS OF 3-HALOPYRIDINES WITH 4 M POTASSIUM HYDROXIDE
TO 3-HYDROXYPYRIDINE AND 4-PYRIDONE

Halogen	Furnace T, °C	Time, min	% hydroxypyridines[a] 3	3:4	4	Other pyridines[b]
Cl	350	30	68	77:23	20	
Cl	350	150	47			
Cl	300	30	63	76:24	20	14% 3-Cl
Cl	300	45	70	78:22	21	9% 3-Cl
Cl	300	60	72	80:20	18	8% 3-Cl
Cl[c]	300	150		80:20		
Cl	250	120	43	89:11	5	36% 3-Cl
Cl	250	240	64	86:14	10	10% 3-Cl
Br	350	30	22	44:56	27	
Br[c]	350	90		59:41		
Br	300	60	27	41:59	39	
Br[c]	300	150		43:57		
Br	250	240	25	45:55	30	
I	350	30	15	32:68	33	25–30% pyridine
I	350	30	18	36:64	32	pyridine
I[c]	350	90		42:58		pyridine
I	300	60	16	33:67	34	11–32% pyridine
I	300	60	17	31:69	39	16–19% pyridine
I	300	60	19	30:70	44	20–27% pyridine
I[c]	300	150		34:66		pyridine
I	250	240	8	40:60	12	pyridine

[a] This ratio is calculated solely in terms of the amounts of hydroxy pyridines formed. No corrections have been made for the formation of other products. [b] In the case of 3-iodopyridine, the range in the percentage of pyridine formed results from two methods of analysis. [c] No isobutyric acid internal standard present.

ammonia, another route is possible. This involves reaction of the halopyridine to give 1-(4'-pyridyl)-4-pyridone which degrades to 4-aminopyridine and 4-pyridone (eq 2). Treatment of this pyridylpyridone

$$(2)$$
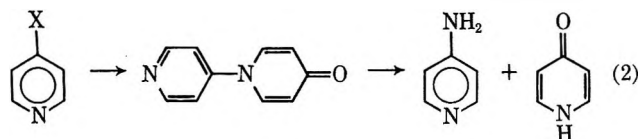
with 4 M KOH at 300° for 15 min resulted in the formation of 28% 4-aminopyridine, 22% 4-pyridone, and nonaromatic products.

4-Aminopyridine is also converted to 4-pyridone in the presence of 4 M KOH. After 60 min at 300°, 75% of 4-pyridone was formed; 23% of the amino compound was unchanged.

3-Halopyridines, on the other hand, clearly give rise to both 3-hydroxypyridine and 4-pyridone hydrolysis products (eq 3).[11] It was not possible to detect 2-

$$(3)$$
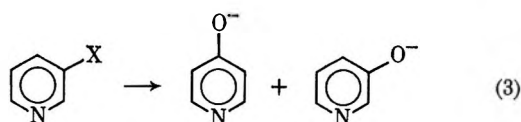
pyridone in the presence of the other two isomers by means of nmr, owing to peak overlap. However, this difficulty was circumvented by analysis using thin layer chromatography; by this means the three hydroxypyridine isomers are clearly separated. No 2-pyridone was detected in 3-chloro- and 3-bromopyridine reaction mixtures, but no conclusion was reached concerning the presence of 2-pyridone in 3-iodopyridine reaction mix-

(11) No evidence has been found for the formation of rearranged substitution products in the reactions of 3-chloro- and 3-bromopyridine with sodium methoxide in methanol at 218°.[12]

(12) J. A. Zoltewicz and A. A. Sale, *J. Org. Chem.*, **35**, 3462 (1970).

tures, owing to streaking of the chromatograms. Note that spots fluorescing under ultraviolet light also were present in the chromatograms. These materials were not identified.

Total yields of pyridines from 3-chloropyridine generally were ~90% but yields from 3-bromo- or 3-iodopyridine mixtures were considerably reduced, owing to extensive decomposition. In spite of the decomposition of 3-iodopyridine reaction mixtures, repeated experiments gave hydroxypyridines in reproducible quantities. Note that, when 3-iodopyridine was heated with 4 M potassium chloride in the absence of alkali at 350° for 30 min, extensive carbonization resulted and no pyridine could be detected. This demonstrates the thermal instability of the aryl iodide.

The molar ratio of 3-hydroxypyridine to 4-pyridone products is highly dependent on the identity of the halogen leaving group and only slightly dependent on the reaction temperature in the region 250–350° (Table III). At 350° this ratio increases with reaction time, owing to decomposition of 4-pyridone. Excluding those cases where there is decomposition of this hydrolysis product, the % 3-OH:4-OH ratios and their ranges are for Cl, 76:24–89:11; Br, 41:59–45:55; I, 30:70–40:60. Increasing amounts of rearranged product are formed in the order Cl < Br < I. In addition, unreacted 3-chloropyridine was detected and in the case of 3-iodopyridine pyridine was formed. It is to be noted that pyridine can also undergo degradation reactions. Approximately half the pyridine was destroyed when it was exposed to 4 M KOH at 350° for 30 min. A substantial amount of acetate ion was detected by nmr in the mixture.

Before interpreting our results it is worth noting that 3- and 4-halopyridines can be dehydrohalogenated by the action of strong nitrogen bases to give 3,4-pyridyne (I). There is no compelling evidence for the formation

of 2,3-pyridyne (II) by a dehydrohalogenation route.[4-6,13] Also noteworthy is the occasional formation of reductive dehalogenation products in these reactions.[5]

In view of these amination results and those from the high temperature hydrolysis of halobenzenes, it may be concluded that 2- and 4-halopyridines on treatment with aqueous alkali only undergo direct substitution reactions. Our results do not provide evidence for the formation of pyridynes. No structurally rearranged product, 3-hydroxypyridine, was detected in reaction mixtures.

It may, however, be postulated that the formation of a rearranged product from 3-halopyridines is due to the presence of 3,4-pyridyne (I). Moreover, since the hydroxypyridine product ratio depends on the identity of the leaving halide ion, the presence of concurrent substitution and 3,4-pyridyne pathways also is suggested.

It is interesting to compare our results with those from a series of haloaromatics reacting by concurrent elimination–addition and direct substitution pathways. Halotoluenes when treated with aqueous sodium hydroxide at 250–340° give rise to direct substitution and rearranged products. The amount of direct substitution product increases in the order Cl < Br < I.[3] In the pyridine series the relative amount of direct substitution product increases in the reverse order I < Br < Cl. Both of these orders are compatible with concurrent elimination–addition and direct substitution pathways. Halogen leaving group orders for both types of reactions are markedly dependent on the nature of the reactants as well as the reaction conditions.[14-16]

In addition to the pyridyne hypothesis other mechanisms should be considered. Another possibility includes halogen migration reactions[17] involving the formation of polyhalopyridines which then undergo substitution and reductive dehalogenation. These reactions are not without precedent. Halopyridines are known to undergo base-catalyzed halogen rearrangement reactions.[18] There is an authentic example (thiophene series[19]) of the formation of a rearranged substitution product resulting from a halogen migration sequence. Note that chlorine atoms migrate less readily than bromine or iodine atoms.[17]

The pyridine which is produced in the reaction of 3-iodopyridine could arise by several routes. These include halogen transfer and radical reactions. The radical process could be similar to that involving the

reduction of *m*-iodochlorobenzene to chlorobenzene under basic conditions.[20]

Our experiments provide the first examples of the formation of rearranged substitution products in the hydrolysis of hetaryl halides. No doubt, other aromatic heterocyclic halides will give similar results.

Experimental Section

Materials.—2-[21] and 4-iodopyridine,[22] 3-methoxypyridine,[23] and 1-(4'-pyridyl)-4-pyridone[24] were prepared. Other pyridines and 2-chloroquinoline are available from Aldrich Chemical Co.

Calibration Curves for the Rates of Heating–Cooling of the Reaction Bomb.—The Inconel bomb (series 4740, Parr instrument Co.) used in the hydrolysis studies was filled with 25 ml of oil and placed into an electrically heated aluminum furnace. A Honeywell Pyr-O-Vane was used to control temperatures. After the furnace was preheated to the desired temperature, the bomb was added. It took 20–25 min for the bomb and its contents to come to the preset temperature (±5°). On removing the bomb and allowing it to air cool, the temperature rapidly fell about 50° in five min; after 30 min the oil temperature was <150°. Temperatures were measured with a copper-constantan thermocouple.

Control Run Used to Establish the Analytical Method.—Nmr was used to quantitatively analyze reaction mixtures, the signal from the methyl groups of isobutyric acid serving as an internal standard.

A mixture consisting of 0.545 g (0.00500 mol) of 3-methoxypyridine,[23] 0.0145 g (0.00165 mol) of isobutyric acid, and 6.25 ml of 4 *M* KOH was heated at 300° for 1 hr. Methanol was added to the cold mixture to make it homogeneous and the nmr spectrum was recorded. Unreacted 3-methoxypyridine and also 3-hydroxypyridine were present. The ratio of the area of the appropriate peaks of the pyridines (Table IV) to the area of the

TABLE IV

CHEMICAL SHIFTS AND ASSOCIATED PROTONS USED TO
IDENTIFY PRODUCTS IN ALKALINE REACTION MIXTURES

Compd	τ^a	Proton(s)
2-Pyridone[b]	2.6, 3.6	H-4, H-3,5
3-Hydroxypyridine[b]	2.4, 3.0	H-6, H-4,5
4-Pyridone[b]	2.0, 3.5	H-2,6, H-3,5
3-Chloropyridine	1.6	H-2
3-Bromopyridine	1.6	H-2,6
3-Iodopyridine	1.4	H-2
3-Methoxypyridine	2.0, 2.7	H-2,6, H-4,5
4-Aminopyridine	3.4	H-3,5
Pyridine	1.5	H-2,6
Formic acid[b]	1.5–1.6	H
Acetic acid[b]	8.1	CH₃
Acetone	8.0	CH₃

a The methyl doublet (τ 9.0) of the isobutyrate ion served as standard. Values refer to alkaline solutions. The approximate center of a multiplet is listed. *b* Exists as its conjugate base in the alkaline solution.

internal standard were employed to calculate yields: 14% 3-methoxypyridine and 86% 3-hydroxypyridine. The mass balance was quantitative.

As a check, the reaction mixture then was extracted with methylene chloride and 3-methoxypyridine (79 mg) was recovered, the amount agreeing with that indicated by nmr.

General Method of Hydrolysis.—A mixture of a halo- or hydroxypyridine (0.020 mol), isobutyric acid (0.0066 mol) internal standard, and 25 ml of 4 *M* KOH (0.10 mol) was sealed in an Inconel bomb which then was lowered into the preheated furnace. The reaction times recorded in the tables indicate the

(13) W. Adam, A. Grimison, and R. Hoffmann, *J. Amer. Chem. Soc.*, **91**, 2590 (1969).

(14) G. Illuminati, *Advan. Heterocycl. Chem.*, **3**, 285 (1964).

(15) F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

(16) R. Huisgen in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, Chapter 2.

(17) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963); J. F. Bunnett and D. J. McLennan, *ibid.*, **90**, 2190 (1968).

(18) M. J. Pieterse and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **81**, 855 (1962).

(19) M. G. Reinecke and H. W. Adickes, *J. Amer. Chem. Soc.*, **90**, 511 (1968).

(20) J. F. Bunnett and C. C. Wamser, *ibid.*, **89**, 6712 (1967).

(21) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 118 (1955).

(22) E. Sergely and T. Iredale, *J. Chem. Soc.*, 3226 (1953).

(23) D. A. Prins, *Recl. Trav. Chim. Pays-Bas*, **76**, 58 (1957).

(24) F. Arndt and A. Kalischek, *Chem. Ber.*, **63**, 587 (1930); F. Arndt, *ibid.*, **65**, 92 (1932).

time the bomb was in contact with the furnace. The bomb was then withdrawn and allowed to air cool.

The contents of the cooled bomb were filtered to remove carbonaceous materials. When unreacted halogenated starting material was present, methanol was added until the reaction mixture became homogeneous. An nmr of the solution was taken using a Varian A-60A spectrometer. Peaks were repeatedly integrated and average areas were employed. Table IV lists the identity of the signals used to calculate the product yields.

In order to determine whether 2-pyridone was present in 3-halopyridine reaction mixtures, the following was employed. 3-Halopyridine reaction mixtures were thoroughly extracted with chloroform and the aqueous phase was acidified to pH 7 with dilute hydrochloric acid. The neutralized phase was extracted with chloroform and dried ($MgSO_4$). (Control runs showed that the hydroxypyridines could be removed from aqueous solutions by this method.) Thin layer chromatography using silica gel plates and acetone containing a small amount of acetic acid as eluent showed that mixtures of the hydroxypyridines could be clearly separated. The order of increasing R_f value is 4-pyridone, 2-pyridone, and 3-hydroxypyridine. No attempt was made to establish the lower limits of detection of 2-pyridone by tlc.

The pyridine content of 3-iodopyridine reaction mixtures was obtained as follows. The nmr spectra of alkaline reaction mixtures were recorded before and after extraction with methylene chloride. Spectra taken before extraction provide a measure of hydroxypyridines as well as of pyridine. Spectra after extraction measure the hydroxypyridines. The amount of pyridine present was obtained by subtraction. In addition the dried ($MgSO_4$) methylene chloride extracts were concentrated and the amount of pyridine present was determined by weight. The two results, Table III, are in reasonable agreement but it is to be noted that both methods assume impurities are not present. These results, then, should be regarded as giving the maximum amounts. The recovered pyridine was distilled and compared with authentic material. Aqueous solutions were neutralized and analyzed for 2-pyridone content as described above.

Isolation of 3-Hydroxypyridine and 4-Pyridone from the Hydrolysis of 3-Bromopyridine.—After 3.16 g (0.20 mol) of 3-bromopyridine was hydrolyzed at 300° for 1 hr with 4 M po-

tassium hydroxide (no isobutyric acid), the aqueous solution was acidified to pH 7 with dilute HCl and evaporated to dryness under reduced pressure. The solid was extracted with acetone and then the insoluble portion was dissolved in a minimum amount of water. After adjusting to pH 8, the evaporation-extraction process was repeated. The process was repeated a third time at pH 6. The acetone extracts were dried ($MgSO_4$) and the solvent was removed. The crude mixture of 3-hydroxypyridine and 4-pyridone was sublimed at 140–160° (0.5 Torr). The sublimate was chromatographed on a silica gel column. Elution with 4% methanol in chloroform (v/v) gave 0.40 g (21%) of 3-hydroxypyridine which on recrystallization from benzene showed mp and mmp 127–129° (lit.[25] mp 129°). Elution with 60% methanol in chloroform (v/v) gave 0.48 g (25%) of 4-pyridone which on recrystallization from chloroform–hexane showed mp and mmp 145–149° (lit.[25] 148.5°).

Isolation of 4-Aminopyridine from the Hydrolysis of 4-Bromopyridine.—A mixture of 3.89 g (0.092 mol) of 4-bromopyridine hydrochloride and 25 ml of 4 M potassium hydroxide was heated at 300° for 10 min. The cold mixture was extracted with methylene chloride and dried ($MgSO_4$). Removal of the solvent gave 0.226 g (12%) of 4-aminopyridine, mp and mmp 158–159° (lit.[25] mp 158°). Nmr analysis of the aqueous solution indicated that 61% of 4-hydroxypyridine was present.

(25) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.

Independent Syntheses of the Products of Acid- and Base-Catalyzed Rearrangements of 2-(1-Isoquinolyl)-3,3,5-triarylpyrrolenines

William E. McEwen,* David H. Berkebile, Tsung-Kai Liao, and Yun-Shan Lin

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01002

2-(1-Isoquinolyl)-3,4,5-triphenylpyrrole (4) and 2-(1-isoquinolyl)-3-*p*-anisyl-4,5-diphenylpyrrole (6) have been synthesized by unambiguous methods. The synthetic samples are identical with the products of the acid- or base-catalyzed isomerization of 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine (3) and the base-catalyzed isomerization of 2-(1-isoquinolyl)-3-*p*-anisyl-3,5-diphenylpyrrolenine (21), respectively. By inference, 2-(1-isoquinolyl)-4-*p*-anisyl-3,5-diphenylpyrrole (7) is the product of the acid-catalyzed isomerization of 21. These facts provide additional support for the mechanisms of the isomerization reactions proposed in previous papers.

Mainly by a series of tracer studies, but also on the basis of other evidence, it has been established that the acid-catalyzed condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (1) with 1,1-diphenylethylene (2) affords a mixture of 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine (3) and 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (4).[1] It was also established that 3 can be isomerized to 4 by the action of acid or by fusion with potassium hydroxide. Mechanisms were suggested for the formation of 3 and its isomerization to 4. It was also pointed out in a footnote of a previous paper[1] that 2-(1-isoquinolyl)-3-*p*-anisyl-3,5-diphenylpyrrolenine (21), obtained by the acid-catalyzed condensation of 1 with 1-*p*-anisyl-1-phenylethylene (5), gives two isomeric pyrroles, one

predominating in the acid-catalyzed isomerization and the other in the potassium hydroxide fusion. It was suggested that the two pyrroles are 2-(1-isoquinolyl)-3-*p*-anisyl-4,5-diphenylpyrrole (6) and 2-(1-isoquinolyl)-4-*p*-anisyl-3,5-diphenylpyrrole (7). Based on mechanistic considerations, it was further suggested that 6 should be the product of the alkali fusion reaction and 7 that of the acid-catalyzed isomerization. We have now developed unambiguous syntheses of 4 and 6, and these results serve to complete the proofs of structure of the compounds and to provide a firm foundation for the mechanistic considerations.

2,3,4-Triphenylpyrrole (8), prepared by the procedure of Pollak and Tisler,[2] was the principal starting material in the unambiguous synthesis of 4. The key step

(1) W. E. McEwen, T. T. Yee, T.-K. Liao, and A. P. Wolf, *J. Org. Chem.*, **32**, 1947 (1967).

(2) A. Pollak and M. Tisler, *Tetrahedron Lett.*, 253 (1964).

1

3

4, R = R′ = phenyl
6, R = p-anisyl; R′ = phenyl
7, R = phenyl; R′ = p-anisyl
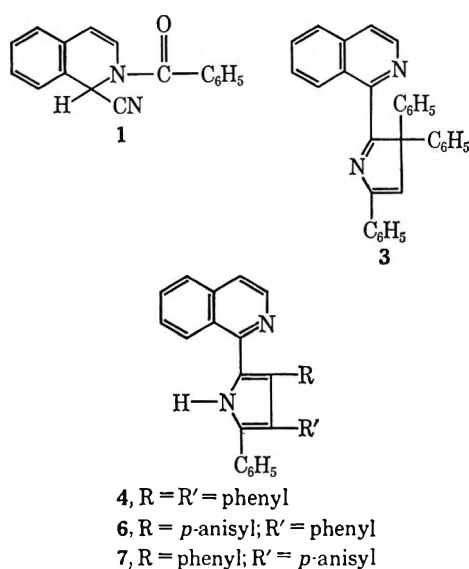
in the preparation of **8** consists of the treatment of 4,5,6-triphenyl-3(2H)-pyridazinethione (**9**) with Raney nickel W-6 catalyst and ammonia in alcohol solution. Pollak and Tisler[2] did not suggest a mechanism for this reaction, nor did they report the formation of other products.

9, R = phenyl
16, R = p-anisyl

Ni(R) / [H]

8, R = phenyl
17, R = p-anisyl
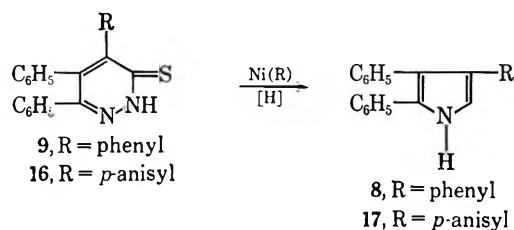
Ethyl 3,4,5-triphenylpyrrole-2-carboxylate (**10**) was obtained by treatment of **8** first with ethylmagnesium bromide and subsequently with ethyl chloroformate.[3] Reaction of **10** with β-phenethylamine gave N′-(2-phenethyl)-3,4,5-triphenylpyrrole-2-carboxamide (**11**), which was converted to 2-(3,4-dihydro-1-isoquinolyl)-3,4,5-triphenylpyrrole (**12**) by the action of polyphosphoric acid at 120–140° in a typical Bischler–Napieralski reaction. Dehydrogenation of **12** to **4** was effected by use of 10% palladium on charcoal in refluxing tetralin.

11, R = phenyl
19, R = p-anisyl

12, R = phenyl
20, R = p-anisyl
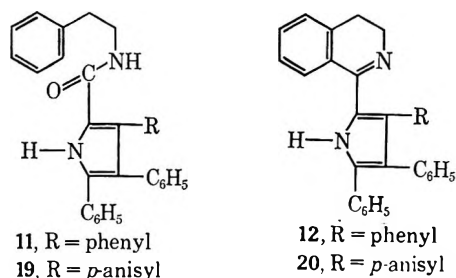
The initial step in the preparation of **6** was the condensation of benzil monohydrazone (**13**) with ethyl p-anisylacetate (**14**) to give 4-p-anisyl-5,6-diphenyl-3-(2H)-pyridazone (**15**). Conversion of **15** to 4-p-anisyl-5,6-diphenyl-3(2H)-pyridazinethione (**16**) was effected by the action of phosphorus pentasulfide in toluene

(3) *Cf.* H. Fischer and B. Walach, *Justus Leibigs Ann. Chem.*, **450**, 125 (1926).

solution. The remaining steps paralleled those employed for the independent preparation of **4**. The action of Raney nickel and ammonia on **16** in ethanol solution gave 2,3-diphenyl-4-p-anisylpyrrole (**17**). Treatment of **17** first with ethylmagnesium bromide and then with ethyl chloroformate gave ethyl 4,5-diphenyl-3-p-anisylpyrrole-2-carboxylate (**18**). Condensation of **18** with β-phenethylamine afforded N′-(2-phenethyl)-3-p-anisyl-4,5-diphenylpyrrole-2-carboxamide (**19**), which was cyclized to 2-(3,4-dihydro-1-isoquinolyl)-3-p-anisyl-4,5-diphenylpyrrole (**20**) by the action of phosphorus oxychloride. Dehydrogenation of **20** with 10% palladium on charcoal in refluxing decalin gave **6**.

Detailed mechanisms for both the acid-catalyzed and base-catalyzed isomerization of **3** to **4** have been published.[1] When the same mechanisms are applied to 2-(1-isoquinolyl)-3-p-anisyl-3,5-diphenylpyrrolenine (**21**), it is obvious that, if 2-(1-isoquinolyl)-3-p-anisyl-4,5-diphenylpyrrole (**6**) is the major product of the potassium hydroxide fusion reaction, then 2-(1-isoquinolyl)-4-p-anisyl-3,5-diphenylpyrrole (**7**) must be the isomeric product produced in the acid-catalyzed isomerization. These results are completely reasonable in that the base-catalyzed process requires migration of an aryl group carrying a net negative charge,[4] while the acid-catalyzed process requires migration of an aryl group carrying a net positive charge. Clearly, a phenyl group is better able to undergo the former migration than a p-anisyl group, and *vice versa* for the latter migration.[5]

21

H+ →

7

OH−

6
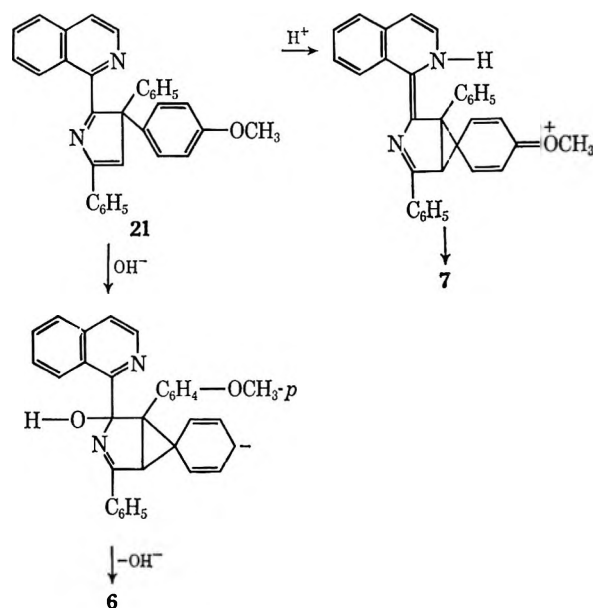
An attempt was made to synthesize **7** by a scheme similar to that used for the synthesis of **6**. However, this synthesis was abandoned when the reaction of p-methoxybenzil (**22**) with hydrazine hydrate gave a mixture of two isomeric monohydrazones which could not be separated.[6]

(4) Whether "classical" structures or "phenanion" and "anisonium" ion structures, respectively, are the best representations of the transition states for the aryl migrations is not known.

(5) H. E. Zimmerman and A. Zweig, *J. Amer. Chem. Soc.*, **83**, 1196 (1961).

(6) Reaction of the mixture of the two monohydrazones with ethyl phenyl-acetate gave a mixture of 4,6-diphenyl-5-p-anisyl-3(2H)-pyridazone and 4,5-diphenyl-6-p-anisyl-3(2H)-pyridazone. We were not able to separate these isomers either.

An attempt was made to reproduce some results reported previously,[7] viz., that the acid-catalyzed condensation of 1 with benzhydrol gives α,α-diphenylacetophenone. The only neutral, solid product which could be isolated was benzhydryl ether (23). We do not know why the previously reported results could not be confirmed.

Experimental Section[8]

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (1) with 1-p-Anisyl-1-phenylethylene (5).—To a solution of 10.0 g (0.31 mol) of 1 and 10.0 g (0.048 mol) of 5 in 200 ml of purified dioxane was added gradually, with vigorous stirring, 20 ml of concentrated sulfuric acid, and the mixture was stirred for 26 hr. The mixture was filtered to remove 0.97 g of isoquinaldamide bisulfate salt, and the filtrate was concentrated at room temperature by application of a jet of air. The residual syrupy orange solution was mixed with about 1000 ml of water and stirred vigorously. After having been allowed to stand at room temperature for a few hours, the mixture deposited an orange-yellow solid. This was collected by filtration, washed with 100 ml of hot ethanol, and recrystallized from chloroform–ethanol to give 5.80 g of colorless 2-(1-isoquinolyl)-3-p-anisyl-3,5-diphenylpyrrolenine (21), mp 204.5–205.8°.

Anal. Calcd for $C_{32}H_{24}N_2O$: C, 84.94; H, 5.35; N, 6.21. Found: C, 85.17; H, 5.34; N, 6.21.

The 100 ml of ethanol wash solution was concentrated and filtered to remove a small amount of 5 which had crystallized. After further concentration of the mother liquor a small amount of orange solid precipitated. This was collected by filtration and recrystallized from ethanol–ether to give 1.0 g of the bisulfate salt of 2-(1-isoquinolyl)-4-p-anisyl-3,5-diphenylpyrrole (7), mp 277–281°.

Anal. Calcd for $C_{32}H_{24}N_2O \cdot H_2SO_4$: C, 69.81; H, 4.72; N, 5.09; S, 5.81. Found: C, 69.99; H, 4.86; N, 5.37; S, 5.86.

Isolation of 2-(1-Isoquinolyl)-4-p-anisyl-4,5-diphenylpyrrole (7).—To a mixture of 1.0 g of the bisulfate salt of 7, mp 277–281°, and 10 ml of ethanol was added dilute sodium hydroxide solution, with stirring of the mixture and heating on the steam bath, until the orange color changed to yellow. A solid which had formed was collected by filtration, washed with water, and crystallized from chloroform–ethanol to give 0.5 g of 7, mp 237–238°.

Anal. Calcd for $C_{32}H_{24}N_2O$: C, 84.93; H, 5.35; N, 6.19. Found: C, 84.64; H, 5.29; N, 6.28.

Acid-Catalyzed Isomerization of 2-(1-Isoquinolyl)-3-p-anisyl-3,5-diphenylpyrrolenine (21).—A mixture of 2.0 g of 21 and 30 ml of 12 N sulfuric acid was heated under reflux for 4 hr. The mixture, which was orange in color, was filtered, and 2.1 g of the bisulfate salt of 7 was obtained, mp 275–280° after crystallization from ethanol–ether. Decomposition of this salt with sodium hydroxide solution gave 7, mp 237–238° after crystallization from chloroform–ethanol.

Alkali Fusion of 2-(1-Isoquinolyl)-3-p-anisyl-3,5-diphenylpyrrolenine (21).—To a molten mixture of 20 g of potassium hydroxide and 2 ml of water contained in a nickel crucible was added 2.0 g of 21, and the mixture was heated at 250–260° for 20 min, with occasional stirring. The cooled mixture was treated with 200 ml of water, and a brown solid which had precipitated was separated from the alkaline solution by decantation. Several crystallizations of the crude precipitate from ethanol and then from ethanol–chloroform gave 0.3 g of colorless 2-(1-isoquinolyl)-3-p-anisyl-4,5-diphenylpyrrole (6), mp 212–213°.

Anal. Calcd for $C_{32}H_{24}N_2O$: C, 84.93; H, 5.35; N, 6.19. Found: C, 84.93; H, 5.43; N, 6.18.

2,3,4-Triphenylpyrrole (8).—A mixture of 14.0 g (0.041 mol) of 4,5,6-triphenyl-3(2H)-pyridazinethione (9),[2] the amount of Raney nickel W-6 catalyst obtainable from 250 g of nickel-aluminum alloy powder (W. R. Grace and Co., No. 2913),[9] 110 ml of concentrated ammonia water, and 600 ml of 95% eth-

anol was heated under reflux with mechanical stirring for 3 hr. The hot reaction mixture was filtered to remove metallic nickel, and the filtrate was concentrated to 30 ml *in vacuo* at room temperature. A total of 5.0 g (41%) of colorless, needlelike 8, mp 164.5–165.5° (lit.[2] mp 168°), crystallized from this solution.

Ethyl 3,4,5-Triphenylpyrrole-2-carboxylate (10).—The following procedure is a modification of a method which has been used to prepare ethyl 2,3,4-trimethylpyrrole-5-carboxylate.[3]

To 24 g (0.1 g-atom) of magnesium turnings was added a few milliliters of a solution of 11 g (0.1 mol) of ethyl bromide in 20 ml of absolute ether. When the reaction started, 100 ml of ether was added, and then the remaining ethyl bromide solution was added as fast as the rate of refluxing permitted. After a period of reflux of 45 min, a solution of 18 g (0.06 mol) of the pyrrole 8 in 240 ml of anhydrous ether was added as fast as possible, consistent with maintenance of control of the frothing due to ethane evolution, and the mixture was refluxed for 30 min.

The reaction mixture was cooled to room temperature, and a solution of 9 g (0.083 mol) of ethyl chloroformate in 20 ml of anhydrous ether was added dropwise. The solution first turned pink and then became cloudy. At the end of the addition, a white solid precipitated. The mixture was heated with magnetic stirring for 2.5 hr; then it was allowed to stand overnight at room temperature. At this stage all of the solid had precipitated.

The mixture was hydrolyzed by the addition of 100 ml of saturated ammonium chloride solution and then 100 ml of water. The light pink powder which had formed was collected on a Büchner funnel and then washed with ether. Recrystallization from 4 l. of 95% ethanol gave a pink, fluffy, crystalline solid, 11 g (50%), mp 220–221°.

Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.71; H, 5.77; N, 3.81. Found: C, 81.52; H, 5.67; N, 4.08.

N'-(2-Phenethyl)-3,4,5-triphenylpyrrole-2-carboxamide (11).—A mixture of 2.0 g (5.45 mmol) of the ester 10 and 2.4 g (20 mmol) of β-phenethylamine was heated at 270° (bath temperature) for 8 hr with magnetic stirring. When the reaction mixture was cooled to room temperature, it solidified. The solid was triturated with a small amount of ether and Skelly B solvent. The white insoluble solid was collected by filtration and washed with ether. After recrystallization from 95% ethanol (800 ml), 1.3 g (54.1%) of 11, mp 248.5–250.2°, was obtained.

Anal. Calcd for $C_{31}H_{26}N_2O$: C, 84.12; H, 5.93; N, 6.33. Found: C, 83.96; H, 5.81; N, 6.44.

2-(3,4-Dihydro-1-isoquinolyl)-3,4-5-triphenylpyrrole (12).—A mixture of 2.0 g of the amide 11 and 20 g of phosphorus pentoxide in 30 ml of toluene was heated under reflux for 6 hr in a stream of nitrogen gas with stirring. The toluene layer was decanted from the insoluble residue while hot. The black residue was poured into water (500 ml) with stirring, and the greenish-yellow precipitate which formed was collected by filtration, washed with ether, and treated with a small volume of concentrated sodium hydroxide solution. The mixture was then diluted with water. The mixture was neutralized with 6 N sulfuric acid and stirred overnight. The crude, dark greenish colored solid which had formed was collected by filtration and weighed 1.6 g. Its melting point was 212–214°. The solid was dissolved in a hot mixture of Skelly B solvent and methyl alcohol, and the solution was concentrated to 100 ml. It was then allowed to stand at room temperature overnight; 0.66 g (34.4%) of yellow prisms of 12 crystallized, mp 229.5–230°.

Anal. Calcd for $C_{31}H_{24}N_2$: C, 87.68; H, 5.71; N, 6.60. Found: C, 87.69; H, 5.54; N, 6.63.

2-(1-Isoquinolyl)-3,4,5-triphenylpyrrole (4) by the Dehydrogenation of 12.—A mixture of 0.3 g (0.7 mmol) of the dihydroisoquinoline 12 and 0.1 g of 10% palladium-on-carbon catalyst in 10 ml of decalin was refluxed in a nitrogen atmosphere with magnetic stirring for 5 hr. The hot reaction mixture was filtered to remove the catalyst. When the filtrate had cooled to room temperature, 0.23 g (76%) of a greenish-yellow solid crystallized. A pale yellow solid was obtained in a yield of 0.15 g (50%), mp 262.5–263.5° after recrystallization from a mixture of methyl alcohol and Skelly B solvent. This compound showed no depression in the melting point when mixed with the compound of the same melting point produced in the reaction between 2-benzoyl-1,2-dihydroisoquinaldonitrile and 1,1-diphenylethylene in the presence of concentrated sulfuric acid.[1] Also, the uv, ir, and nmr spectra of both samples were found to be identical.

4-p-Anisyl-5,6-diphenyl-3(2H)-pyridazone (15).—A solution of sodium ethoxide was prepared from 18.4 g (0.8 g-atom) of sodium and 3200 ml of absolute ethanol. The solution was placed in a 5-

(7) T. K. Liao and W. E. McEwen, *J. Org. Chem.*, **26**, 5257 (1961).

(8) Melting points are uncorrected. All nmr spectra were taken on a Varian A-60 spectrometer at a sweep width of 500 cps. Deuteriochloroform was used as the solvent with TMS as an internal standard. Microanalyses were carried out by C. Meade and V. Giridhar.

(9) H. R. Billica and H. Adkins, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 176.

l. flask, and 179.2 g (0.8 mol) of benzil monohydrazone[10] and 155.2 g (0.8 mol) of ethyl *p*-anisylacetate were added. The reaction mixture was refluxed, with mechanical stirring, for 3 hr, allowed to cool to room temperature, and then filtered. The filtrate was concentrated to about one-third of its original volume *in vacuo.*

The concentrated filtrate was diluted with an equal volume of cold water, and the resulting mixture was acidified with 2 N HCl to pH 5. The mixture was filtered to give 229.8 g (81.1%) of yellow solid. The crude product was recrystallized from ethyl ether to yield 145 g of white solid, mp 265.5–266.2°.

Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.97; H, 5.08; N, 7.91. Found: C, 78.21; H, 5.17; N, 7.91.

4-*p*-Anisyl-5,6-diphenyl-3(2*H*)-pyridazinethione (16).—In a typical run, a mixture of 14.16 g (0.04 mol) of 4-*p*-anisyl-5,6-diphenyl-3(2*H*)-pyridazone (15), 24 g of phosphorus pentasulfide, and 400 ml of toluene was refluxed for 1 hr. The supernatant toluene layer of the hot mixture was slowly decanted, leaving solid in the flask. The toluene solution was concentrated to about one-half of its original volume *in vacuo,* and a solid precipitated. The resulting mixture was filtered to give a bright yellow solid, which was recrystallized several times from 95% ethanol.

About 200 ml of 95% ethanol was added to the solid remaining in the original reaction flask, and the mixture was refluxed for several hours. The first crystals obtained from the resulting solution when it was cooled were separated from the mother liquor before substantial sulfur crystallization took place, and these crystals were repeatedly recrystallized from 95% ethanol.

The product from both sources was either yellow or chartreuse in color and was obtained in the form of needles with mp 275.5–277°. The average yield obtained from this reaction was 66%, and the maximum yield obtained was 98.7%.

Anal. Calcd for $C_{23}H_{18}N_2OS$: C, 74.59; H, 4.89; N, 7.57; S, 8.65. Found: C, 74.51; H, 4.91; N, 7.47; S, 8.71.

2,3-Diphenyl-4-*p*-anisylpyrrole (17).—The amount of Raney nickel W-6 catalyst obtainable from 250 g of nickel–aluminum alloy powder (W. R. Grace and Co., No. 2813) was added to 10 g (0.027 mol) of 4-*p*-anisyl-5,6-diphenyl-3(2*H*)-pyridazinethione (16), 400 ml of absolute ethanol, and 75 ml of concentrated ammonium hydroxide. The reaction mixture was heated to reflux with stirring for 3 hr.

The hot reaction mixture was filtered to remove the metallic catalyst, and the filtrate was concentrated to about one-half volume by magnetic stirring, at room temperature, under reduced pressure.

The white solid which was obtained by filtration was recrystallized from cyclohexane, and a light purple crystalline solid, mp 180–182°, was obtained. Both the white solid and the recrystallized purple form had superimposable infrared and nmr spectra, indicating that the color change was not due to decomposition of the product. The white solid also turned to a purple color if the concentration of the original filtrate was carried out until near dryness.

Further reactions were usually carried out with the white form without further purification. The average yield, obtained from this step of the synthesis, was 19%, and the best yield was 37%.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.92; H, 5.85; N, 4.31. Found: C, 84.76; H, 5.85; N, 4.23.

Ethyl 4,5-Diphenyl-3-*p*-anisylpyrrole-2-carboxylate (18).—The same method was used for the preparation of 18 as described previously for the preparation of 10, 2,3-diphenyl-4-*p*-anisylpyrrole (17) being used in place of 2,3,4-triphenylpyrrole (8).

The product obtained was sometimes a light pink and sometimes a light blue or purple, but both forms had mp 196–198° after recrystallization from 95% ethanol, and the infrared and nmr spectra of the two were superimposable. The average yield

obtained was 65%, with a yield of 87.4% being realized in the best reaction.

Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.59; H, 5.79; N, 3.53. Found: C, 78.75; H, 5.82; N, 3.85.

N'-(2-Phenethyl)-3-*p*-anisyl-4,5-diphenylpyrrole-2-carboxamide (19).—A mixture of 6.06 g (0.05 mol) of freshly distilled β-phenethylamine and 2.0 g (0.005 mol) of the ester 18 was heated at reflux temperature, with magnetic stirring, for 8 hr. At the end of the reflux period, the reaction mixture was cooled by means of an ice bath, and a clear yellow solution resulted. A mixture of 30 ml of ethyl ether and 30 ml of Skelly B solvent was added, and the resulting solution was thoroughly mixed by high-speed magnetic stirring. After 10–30 min, a white precipitate formed, and this was collected by filtration and washed with ether. After recrystallization from 95% ethanol, the product had mp 227–230°.

Purification of the product proved to be difficult because of inclusion of β-phenethylamine and/or ethanol. A prolonged period of heating, at reduced pressure, was required before an analysis could be obtained with a nitrogen percentage within experimental error of the expected figure. The average yield obtained from this reaction was 44%, and the highest yield obtained was 54%.

Anal. Calcd for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 79.75; H, 6.32; N, 5.86.

2-(3,4-Dihydro-1-isoquinolyl)-3-*p*-anisyl-4,5-diphenylpyrrole (20).—A solution of 0.472 g (0.001 mol) of the amide 19 in 20 ml of toluene was heated to the reflux temperature. Phosphorus oxychloride (1 ml) was added dropwise, causing the solution to turn pink. The reaction mixture was refluxed for 1 hr, and during this time the color of the solution turned dark. Following the reflux period, the solution was cooled and extracted several times with water.

The aqueous layer was adjusted to a pH value of 7.5 by addition of sodium hydroxide solution and allowed to stand, in the cold, overnight. Since no precipitation was observed at this point, the solution was adjusted to pH 7.0 by addition of a 5% solution of hydrochloric acid and extracted three times with ether. Evaporation of the ether layer left no residue.

The toluene layer, which had yielded only a small amount of solid when allowed to stand for 1 day at room temperature, was placed in the cold room overnight, and 0.187 g (38.6%) of cream-colored product, mp 195–197°, crystallized.

Anal. Calcd for $C_{32}H_{26}N_2O$: C, 84.55; H, 5.77; N, 6.16. Found: C, 84.85; H, 5.77; N, 6.31.

2-(1-Isoquinolyl)-3-*p*-anisyl-4,5-diphenylpyrrole (6).—A suspension of 175 mg (0.385 mmol) of the dihydroisoquinoline 20 and 0.06 g of 1% palladium on powdered charcoal in 6 ml of decalin was refluxed, under a nitrogen atmosphere, with magnetic stirring for 5 hr. The reaction mixture was filtered hot to remove the catalyst. Solid began to crystallize as soon as the solution was allowed to cool. About 20 mg (11.5%) of light yellow product was obtained. The melting point of this compound was 211.5–213°. A mixture melting point with a sample of 6 obtained by fusion of 21 with alkali showed no depression. Also, the infrared and nmr spectra of the two samples were found to be superimposable.

(10) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1957, p 856.

Rearrangement of 3-Amino-1-benzylindazole to 4-Amino-2-phenylquinazoline

NEVILLE FINCH* AND HEINZ W. GSCHWEND

Research Department, CIBA Pharmaceutical Company, Summit, New Jersey 07901

Attempts to prepare 3-amino-1-benzylindazole (4) by cyclization of o-(1-benzylhydrazino)benzonitrile (2) yielded instead a rearranged and oxidized product 4-amino-2-phenylquinazoline (3). A mechanism for this transformation is proposed. The intermediates postulated have been synthesized and subjected to rearrangement conditions. Some comments are made about the chemistry of dihydroquinazolines.

3-Aminoindazoles **1** (R = H) have been obtained by various routes.[1-4] The preparation of specifically 1-substituted 3-aminoindazoles (R ≠ H) seemed trivial in view of the literature reports[1,3] on the ease of cyclizing o-hydrazinobenzonitriles. Since we were interested in
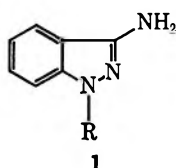
such compounds, we decided to synthesize the undescribed 3-amino-1-benzylindazole (**4**) by this approach.

o-(1-Benzylhydrazino)benzonitrile (**2**) was prepared by nitrosation and subsequent reduction of N-benzylanthranilonitrile. However, compound **2** resisted all our numerous attempts to effect cyclization (NaOEt–EtOH, HCl, SnCl₄, pyrolysis), only starting material being recovered. Complete transformation of the starting material was achieved by strenuous basic conditions, namely NaH in refluxing diethylene glycol dimethyl ether. To our surprise, however, the product (32% isolated yield) was the known 4-amino-2-phenylquinazoline[5] (**3**). The identity of our product was confirmed by melting point, mixture melting point, and spectral comparison with a sample prepared by the literature procedure.[5] A mechanism could be proposed for this process (Scheme I) but it seemed desirable to provide further experimental support for it.

The desired 3-amino-1-benzylindazole (**4**) was prepared unambiguously by Curtius degradation of the known 1-benzylindazole-3-carboxylic acid.[6]

When this indazole **4** was subjected to the cyclization conditions, i.e., NaH–refluxing diethylene glycol dimethyl ether, 4-amino-2-phenylquinazoline (**3**) could be isolated in 68% yield. This yield thus precludes a disproportionation type mechanism for the oxidation process involved in product formation. It also provides support for the contention that **4** is on the reaction pathway from **2** to **3** (Scheme I).

4-Amino-1,2-dihydroquinazolines are mentioned only once in the literature,[7] and the work by Carrington describes only 2,2-dimethyl compounds which are
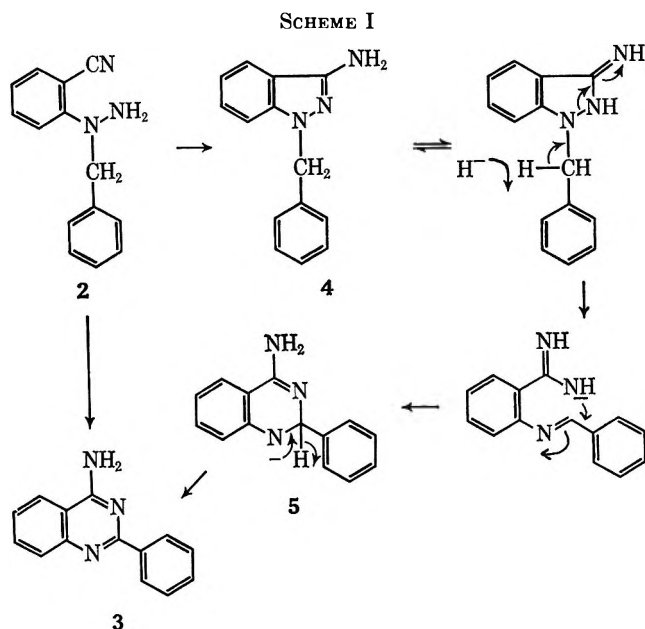
SCHEME I

thus blocked to aromatization. Nevertheless, his procedure worked well to provide 4-amino-2-phenyl-1,2-dihydroquinazoline (**6a**) by condensation of o-aminobenzamidine with benzaldehyde (Scheme II).

SCHEME II

6a, R = Ph
b, R = CH₂Ph

3, R = Ph
7a, R = CH₂Ph
7b, R = H
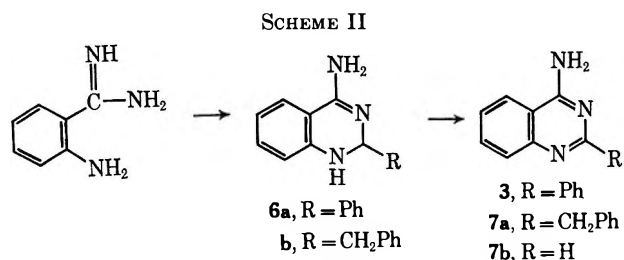
Reaction of this new substance **6a** with NaH in refluxing diethylene glycol dimethyl ether again gave a good yield (70%) of 4-amino-2-phenylquinazoline (**3**) thus providing additional support for our mechanistic scheme (Scheme I) which involves the anion derived from **6a**, namely **5**, as an intermediate in the rearrangement.

The chemistry of 1,2-dihydroquinazolines has had only limited attention. A precedent for the ease of aromatization can be cited, though, in the aerial oxidation (or by potassium ferricyanide) of 2-aminoalkyl-4-aryl-1,2-dihydroquinazolines.[8] However, it is important to emphasize that oxidation of **6a** to **3** occurs with sodium hydride in an aprotic solvent under nitrogen and in 70% yield. This attests to a special type of reactivity in this system, imparted by the stability of

(1) (a) M. A. Aron and J. A. Elvidge, *Chem. Ind. (London)*, 1234 (1958); (b) F. C. Cooper, *J. Chem. Soc.*, 4212 (1958).

(2) (a) E. W. Parnell, *ibid.*, 4930 (1961); (b) M. W. Partridge and M. F. G. Stevens, *ibid.*, 3663 (1964).

(3) J. J. Lafferty, D. H. Tedeschi, and C. L. Zirkle, U. S. Patent 3,133,081 (1964); *Chem. Abstr.*, **61**, 4364 (1964).

(4) G. Beck, E. Degener, and H. Heitzer, *Justus Liebigs Ann. Chem.*, **716**, 47 (1968).

(5) H. Meerwein, P. Laasch, R. Mersch, and I. Spille, *Chem. Ber.*, **89**, 224 (1956).

(6) K. v. Auwers and W. Schaich, *ibid.*, **54**, 1756 (1921).

(7) H. C. Carrington, *J. Chem. Soc.*, 2527 (1955).

(8) A. Marxer, U. Salzmann, and F. Hofer, *Helv. Chim. Acta*, **52**, 2351 (1969).

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the radical anion or perhaps the ability of the C_2 hydrogen to leave as hydride (Scheme III).

SCHEME III
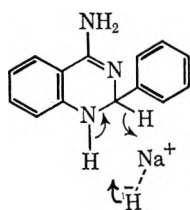
A recent publication by Pakrashi[9] describes a surprising transformation which bears on this point. Reduction of 2-benzyl-3-methyl-4-quinazolinone with sodium borohydride in methanol yields 3-methyl-4-quinazolinone, *i.e.*, borohydride effects debenzylation from carbon! Viewed in terms of the mechanism of Scheme III, this suggests that a 1,2-dihydroquinazoline anion given a choice between expelling hydride or benzyl anion, chooses, not unreasonably, the latter. (Of course, a radical mechanism cannot be excluded.) To confirm this point to our satisfaction, 4-amino-2-benzyl-1,2-dihydroquinazoline (6b), prepared from *o*-aminobenzamidine and phenylacetaldehyde dimethyl acetal, was reacted with sodium hydride in refluxing diethylene glycol dimethyl ether. The known 4-aminoquinazoline[10] (7b) was the sole isolable product in 43% yield. A mass spectrum of the mother liquors indicated trace amounts of 4-amino-2-benzylquinazoline (7a) suggesting that hydride loss is still present as a minor pathway.

Reaction of 4-amino-2-benzyl-1,2-dihydroquinazoline (6b) with sodium carbonate and potassium ferricyanide in aqueous ethanol at room temperature also gave 4-aminoquinazoline (45%) as the only isolable product. Further work is required to clarify the actual nature of the bond-breaking process at C_2 to determine whether it is homolytic or heterolytic.

Experimental Section[11]

o-(1-Benzylhydrazino)benzonitrile (2).—Anthranilonitrile (10.8 g, 91.5 mmol), 12 g of NaHCO₃, and 10.9 ml of benzylbromide (91.5 mmol) were refluxed in ethylene glycol dimethyl ether for 44 hr. The solvent was evaporated, and the residue was taken up in methylene chloride, washed with water, and dried over Na₂SO₄. After removal of the solvent the residue was crystallized from benzene to give a total of 10 g of analytically pure *N*-benzylanthranilonitrile (mp 114–116°).[12]

This anthranilonitrile (5.2 g, 25 mmol) was stirred at 0° in 300 ml of 6 *N* hydrochloric acid. Over a period of 3 hr, 2 g of NaNO₂ in 100 ml of water was added. Stirring was continued for an additional 2 hr. The precipitate was then filtered, washed successively with water, and dried *in vacuo* to give 5.8 g (97.5%) of pure *N*-nitroso-*N*-benzylanthranilonitrile (mp 69–71°; ν_{max}^{Nujol} 2230, 1490, 1435, 1060 cm⁻¹).

Anal. Calcd for C₁₄H₁₁N₃O: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.27; H, 4.56; N, 17.57.

N-Nitrosoamine (2.7 g, 11.4 mmol) was stirred in 30 ml of water under an atmosphere of nitrogen. Then 2.34 g of zinc dust and dropwise 3.9 ml of acetic acid were added. The temperature was then raised to 60–65° and maintained at this level

for 0.5 hr. After cooling, the aqueous solution was made basic with sodium carbonate and the product extracted into methylene chloride. After drying and evaporating the solvent, 2.4 g of solid was obtained. A part thereof was recrystallized from ether to give an analytically pure sample of *o*-(1-benzylhydrazino)benzonitrile (2) (mp 109–111°; $\nu_{max}^{CH_2Cl_2}$ 3440, 3370, 3200, 2230, 2210, 1605, 1575, 1530, 1490 cm⁻¹).

Anal. Calcd for C₁₄H₁₃N₃: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.43; H, 5.77; N, 18.67.

3-Amino-1-benzylindazole (4).—1-Benzylindazole-3-carboxylic acid[6] (22 g, 87 mmol) was refluxed for 1.5 hr in 150 ml of thionyl chloride. The excess reagent was then removed *in vacuo* and the residue dissolved in 200 ml of acetone. Then a solution of 42 g of NaN₃ in 200 ml of water was added to the cold solution of the acid chloride. The precipitated azide was stirred for 2 hr. Crushed ice was then added and after 1.5 hr more the product was filtered and dried at room temperature *in vacuo*. The azide was then dissolved in 700 ml of ethanol and refluxed for 20 hr to give the corresponding urethane (mp 114–116°; ν_{max}^{Nujol} 3200, 1730, 1715 cm⁻¹), which did not have to be isolated for the next step. The ethanolic solution was reduced to about half its volume and then refluxed for 20 hr with 200 ml of 30% aqueous KOH. The ethanol was then distilled off, and the aqueous solution was cooled and diluted with water to precipitate the amine. The product was filtered off, washed with water, and dried to yield 17.4 g (mp 114–116°) or 90% overall from the acid.

A 300-mg sample was recrystallized from ethanol to give shiny needles: mp 115–116°; nmr (CDCl₃) δ 4.18 (singlet, 2 H), 5.3 (singlet, 2 H), 6.8–7.6 (multiplet, 9 H); $\lambda_{max}^{CH_3OH}$ 232 mμ (ε 16,770), 318 (4800); ν_{max}^{Nujol} 3440, 3305, 3200, 1623, 1606, 1572, 1535 cm⁻¹.

Anal. Calcd for C₁₄H₁₃N₃: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.44; H, 5.74; N, 18.85.

4-Amino-2-phenylquinazoline (3). A.—*o*-(1-Benzylhydrazino)benzonitrile (5.9 g, 26.5 mmol) and 1.55 g of 55% NaH (washed three times with anhydrous ether, 1.2 equiv) were dissolved and refluxed under nitrogen in 120 ml of dry diethylene glycol dimethyl ether for a period of 16 hr. The solvent was then removed *in vacuo*, water was added, and excess oase was neutralized with 2 *N* HCl to a pH of 8. The product was extracted into CH₂Cl₂. After drying and removing all solvent, the dark residue was dissolved in ether and treated with charcoal. From ether–hexane 1.9 g of quinazoline was obtained (mp 140–143°). Recrystallization from ether gave an analytically pure sample (mp 143–145°).

B.—3-Amino-1-benzylindazole (1.0 g, 4.5 mmol) and 260 mg of 55% NaH (washed three times with ether) was refluxed as described in A in 20 ml of dry diethylene glycol dimethyl ether. After the work-up procedure (as described in A), a total of 680 mg of quinazoline were obtained (68%). Recrystallization from ether–hexane gave 530 mg of a pure sample (mp 144.5–145.5°). The products from A and B showed identical analytical and spectroscopic properties (ir, uv, nmr, mass spectrum).

C.—4-Amino-2-phenyl-1,2-dihydroquinazoline hydrochloride (1.3 g, 5 mmol) was worked up to the free base using sodium carbonate and dichloromethane. The organic layer was dried over Na₂SO₄ and the solvent removed to complete dryness. The gummy residue was dissolved in 20 ml of dry diglyme and refluxed together with 260 mg of NaH (55%, washed three times with dry ether) for 16 hr under a nitrogen atmosphere. The solvent was then removed *in vacuo* (water aspirator), ice and water were added to the residue, and the mixture was transferred into a separating funnel using methylene chloride. The aqueous phase was made neutral with 2 *N* HCl and then basic with dilute sodium carbonate solution and the product extracted into methylene chloride. After drying over Na₂SO₄ and removal of the solvent *in vacuo*, 1 g of solid material was obtained. Recrystallization from ether–hexane gave 330 mg (mp 144–145°) as a first crop and 400 mg (mp 138–142°) as a second crop (70%). The material was identical in all respects (analysis, melting point, ir, uv, mass spectrum) with the 4-amino-2-phenylquinazoline obtained under A and B.

4-Amino-2-phenyl-1,2-dihydroquinazoline (6a).—*o*-Aminobenzamidine dihydrochloride[7] (10.4 g, 50 mmol) and 5 ml of benzaldehyde (50 mmol) were refluxed for 1 hr in 180 ml of ethanol under an atmosphere of nitrogen. The warm solution was filtered to remove a small amount of insoluble material. After concentrating the reaction mixture to about one-half of its original volume, ether was added until the solution turned very slightly turbid. The product crystallized as a monohydrochloride (8.8 g, mp 211–215°). Analytically pure material was ob-

(9) S. C. Pakrashi and A. K. Chakravarti, *Chem. Commun.*, 1443 (1969).

(10) J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, 1354 (1959).

(11) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument.

(12) A. M. Simonov, B. K. Martsokha, and F. T. Pozharskii, *Zh. Obshch. Khim.*, **32**, 2388 (1962).

tained by recrystallizing a sample from ethanol-ether: mp 216–219°; $\nu_{cm^{-1}}^{Nujol}$ 1660, 1626, 1605; $\lambda_{max}^{CH_3OH}$ 228 mμ (ϵ 37,300,)258 (7540), 348 (2080), 370 (3280).

Anal. Calcd for $C_{14}H_{13}N_3 \cdot HCl$: C, 64.75; H, 5.43; N, 16.18. Found: C, 64.54; H, 5.73; N, 16.18.

4-Amino-2-benzyl-1,2-dihydroquinazoline (6b).—*o*-Amino-benzamidine hydrochloride[7] (8.4 g, 40 mmol) and 6.65 g of phenylacetaldehyde dimethyl acetal (40 mmol) were refluxed for 3 hr in 170 ml of ethanol. After cooling the reaction mixture, the ethanol was evaporated *in vacuo*, the residue taken up in methylene chloride and washed with an aqueous sodium carbonate solution under an atmosphere of N_2, and the organic layer dried over Na_2SO_4. The solvent was then removed and the residue dissolved in hot benzene. Upon cooling 5.6 g (59%) of product was obtained which after recrystallization from benzene showed mp 145–147°; $\nu_{cm^{-1}}^{Nujol}$ 3455, 3370, 1660, 1620, 1605; $\lambda_{max}^{CH_3OH}$ 232 mμ (ϵ 50,800), 261 (9100), 359 (2200); nmr (DMSO-d_6) δ 6.4–7.5 (m, 9 H), 5.9 (s, 1 H exchange), 5.4 (s, 2 H exchange), 4.92 (t, $J = 6$ Hz, 1 H), 3.91 (d, $J = 6$ Hz, 2 H).

Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.97; H, 6.50; N, 17.43.

4-Amino-2-benzyl-1,2-dihydroquinazoline (6b) → **4-Amino-quinazoline (7b). A.**—4-Amino-2-benzyl-1,2-dihydroquinazoline (480 mg, 2 mmol) and 120 mg of NaH (55%, washed three times with anhydrous ether) were refluxed under an atmosphere of N_2 in 12 ml of dry diethylene glycol dimethyl ether for a period of 16 hr. After cooling, the reaction mixture was diluted

with CH_2Cl_2, washed with dilute $NaHCO_3$ solution, and dried over Na_2SO_4. After removal of the solvent the residue (170 mg) was crystallized from CH_2Cl_2–ether to give 120 mg of 4-amino-quinazoline (7b): mp 258–260° (lit.[10] 259–260° and 267°); mass spectrum *m/e* 145 (Calcd for $C_8H_7N_3$: 145.064. Found: 145.063.).

B.—4-Amino-2-benzyl-1,2-dihydroquinazoline (480 mg, 2 mmol) were stirred at room temperature in 20 ml of ethanol with a solution of 3 g of $K_3Fe(CN)_6$ and 1.7 g of K_2CO_3 in 22 ml of water for 2 hr. The solvent was then partially removed and, after the addition of 4 ml of 10 N NaOH solution, the mixture was extracted with CH_2Cl_2. From the residue (170 mg), 130 mg of 4-aminoquinazoline (7b), mp 257–260°, was obtained (45%).

Quinazolines and 1,4-Benzodiazepines. LII.[1] Rearrangement of 1-Alkyl-7-chloro-1,3-dihydro-3-acetoxy-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-ones with Base

A. WALSER,* G. SILVERMAN, J. BLOUNT, R. IAN FRYER, AND L. H. STERNBACH

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

The preparation and rearrangement of the title compounds (**2a,b**) to 2,5-epoxy-1,4-benzodiazepin-3-ones (**3a,b**) are described. The further rearrangement of the 2,5-epoxy compound **3a** to the corresponding 3-hydroxy-1,4-benzodiazepin-2-one **4a** is shown, and the possible mechanisms involved in these conversions are discussed. The determination of the structure of **3a** by single X-ray diffraction analysis is also presented.

Although considerable attention has been devoted to 3-substituted 1,4-benzodiazepines, 3-hydroxy-3-methyl derivatives are not reported in the literature. Bell and coworkers[2] attempted the preparation of 7-chloro-1,3-dihydro-3-hydroxy-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one by hydrolysis of the corresponding 3-acetoxy derivative. Using either acid or base, they obtained only 2-acetyl-6-chloro-4-phenylquinazoline.

Since 1,4-benzodiazepines bearing an alkyl substituent in the 1 position cannot undergo a similar rearrangement to quinazolines, we were able to prepare 7-chloro-1,3-dihydro-1,3-dimethyl-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**4a**) by acid hydrolysis of the corresponding acetate **2a** (Scheme I).

The benzodiazepine structure assigned to **4a** is based on spectroscopic data which would not satisfy the alternate 2-acetyl-2-hydroxy-1,2-dihydroquinazoline structure (intermediate A in Schemes II and III). The uv spectra of **4a** and **2a** do not differ from those of other related benzodiazepine derivatives. The intermediate A would be expected to show the uv characteristics of compound **7**, the hydrochloride of which has a strong maximum at 450–454 mμ.[3] An absorption of this kind is not observed for compound **4a** in 0.1 N hydrochloric acid. The carbonyl band at 1660 cm^{-1} in

the ir spectrum of **4a** certainly speaks for the benzodiazepine structure. The same argument holds for the chemical shift of the methyl group which is not compatible with an acetyl group free of unusual shielding. The conformational equilibrium observed in dimethyl sulfoxide solution gives additional support to the assigned structure, for such conformational equilibria have been found with other benzodiazepines.[4]

Surprisingly, the use of sodium methoxide in methanol did not lead to the 3-hydroxybenzodiazepine **4a** but to compound **3a**. The same reagent also effected the conversion of **4a** to **3a**. A plausible mechanism for these rearrangements is shown in Scheme II. If R represents hydrogen, the intermediate A would convert readily to 2-acetyl-6-chloro-4-phenylquinazoline (**6**) by dehydration.

We were able to reverse this rearrangement and obtained the 3-hydroxy-3-methylbenzodiazepine **4a** by treatment of compound **3a** with hydrogen chloride in ethanol. The proposed mechanism is shown in Scheme III and is envisioned as proceeding through the same intermediate A.

We also looked into the possible formation of 7-chloro-1,3-dihydro-3-hydroxy-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one by controlled acid-catalyzed ethanolysis of the 1-methoxymethyl derivative **2b**. While mild ethanolysis allowed the preparation of com-

(1) Paper LI: N. W. Gilman and L. H. Sternbach, *J. Heterocycl. Chem.*, **8**, 297 (1971).

(2) S. C. Bell, *et al.*, *ibid.*, **33**, 457 (1968).

(3) Compare G. F. Field, *Chem. Commun.*, 886 (1969).

(4) P. Linscheid and J. M. Lehn, *Bull. Soc. Chim. Fr.*, 992 (1967).

SCHEME I

SCHEME II

SCHEME III

a, R = CH₃
b, R = CH₂OCH₂
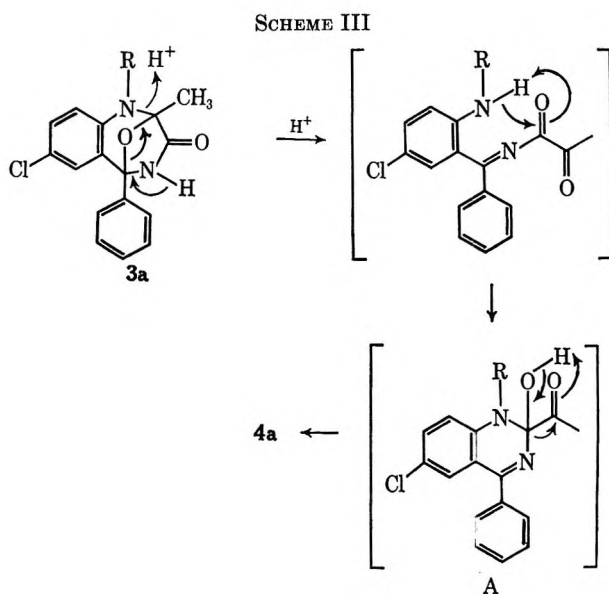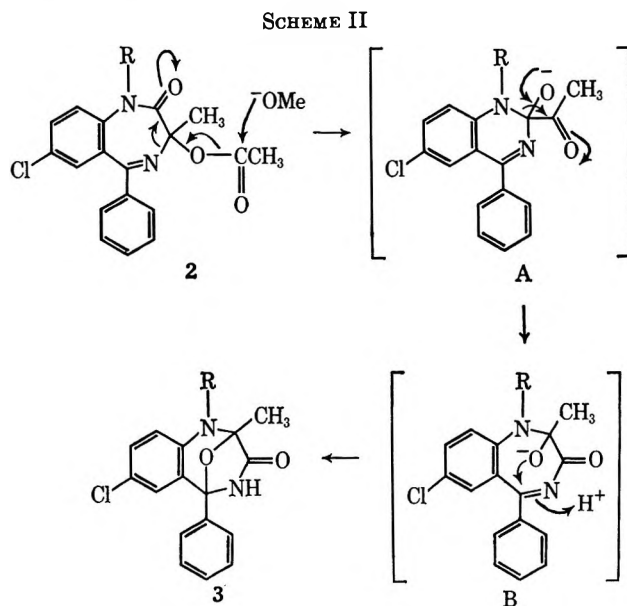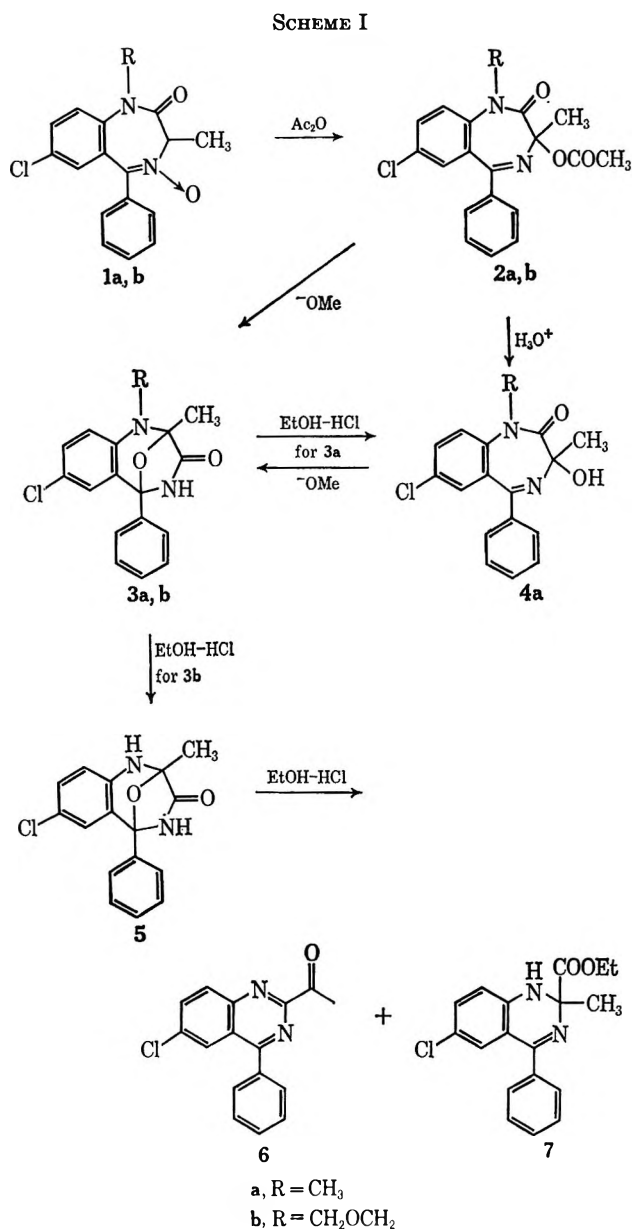
pound **5**, more vigorous conditions produced a mixture of the anticipated 1,2-dihydroquinazoline **7** and the 2-acetylquinazoline **6**.

The structure of **3a** was established by single-crystal X-ray diffraction analysis. The numbering scheme adopted for the crystallographic analysis is shown below. The bond lengths and angles involving the non-

hydrogen atoms are given in Tables I and II. The average C–H distance is 1.01 Å. N(2) and O(2) participate in intermolecular hydrogen bonding, the N(2)–O(2) distance being 2.99 Å. For the molecule located at (x, y, z), N(2) is hydrogen bonded to O(2) in the molecule
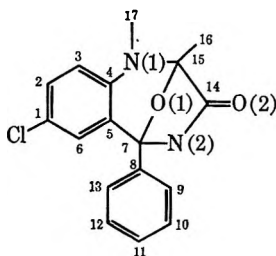
located at $(-\frac{1}{2} + x, \frac{3}{2} - y, 1 - z)$ and O(2) is hydrogen bonded to N(2) in the molecule located at $(\frac{1}{2} + x, \frac{3}{2} - y, 1 - z)$, so that the hydrogen bonding network extends in infinite chains parallel to the a axis. Figure 1 is a stereoscopic view of **3a** showing the conformation of the molecule in the solid state.

Determination of the Crystal Structure.—The position of the chlorine atom was determined from a three-dimensional Patterson synthesis. For the initial electron density synthesis based on the phases calculated for the chlorine atom, the x coordinate of the chlorine atom was displaced 0.04 Å from $x = 0$, the value obtained from the Patterson, in order to destroy the additional symmetry that otherwise would have been introduced. A total of four electron density syntheses based on successively more complete partial structures were required to locate all the nonhydrogen atoms. Four cycles of full matrix least squares gave a disagreement index (R) of 9.7% for an isotropic model. Two more cycles of full matrix least squares in which the atoms were assigned anisotropic thermal parameters reduced R to 6.6%. A difference map calculated at this point clearly showed all 15 hydrogen atoms. The structure
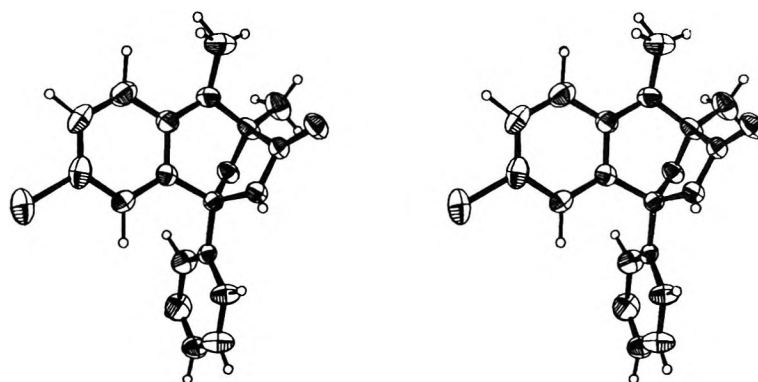
Figure 1.—Stereoscopic view of **3a**. The anisotropic thermal ellipsoids are scaled to include 50% probability; the hydrogens are represented as spheres of arbitrary size.

TABLE I

BOND LENGTHS (Å)^a IN **3a** AVERAGED OVER THERMAL MOTION^b

C(1)–Cl	1.734 (6)	C(2)–C(3)	1.367 (9)
		C(3)–C(4)	1.410 (8)
C(7)–O(1)	1.461 (6)	C(4)–C(5)	1.395 (7)
C(15)–O(1)	1.417 (7)	C(5)–C(6)	1.402 (7)
C(14)–O(2)	1.246 (6)	C(5)–C(7)	1.519 (7)
		C(7)–C(8)	1.498 (7)
C(4)–N(1)	1.397 (7)	C(8)–C(9)	1.406 (7)
C(15)–N(1)	1.476 (8)	C(8)–C(13)	1.417 (7)
C(17)–N(1)	1.490 (8)	C(9)–C(10)	1.395 (9)
C(7)–N(2)	1.477 (6)	C(10)–C(11)	1.373 (10)
C(14)–N(2)	1.341 (6)	C(11)–C(12)	1.381 (10)
		C(12)–C(13)	1.361 (9)
C(1)–C(2)	1.382 (9)	C(14)–C(15)	1.536 (7)
C(1)–C(6)	1.381 (8)	C(14)–C(16)	1.522 (8)

^{a} Estimated standard deviation of last significant figures appears in parentheses. ^{b} Second atom is assumed to ride on first: W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **17**, 142 (1964).

TABLE II

BOND ANGLES (DEGREES)^a IN **3a**

Cl–C(1)–C(2)	119.5 (4)	C(9)–C(8)–C(13)	119.3 (5)
Cl–C(1)–C(6)	118.0 (5)	C(8)–C(9)–C(10)	119.5 (5)
C(6)–C(1)–C(2)	112.5 (5)	C(9)–C(10)–C(11)	121.4 (5)
C(1)–C(2)–C(3)	119.0 (5)	C(10)–C(11)–C(12)	118.2 (5)
C(2)–C(3)–C(4)	121.7 (5)	C(11)–C(12)–C(13)	121.9 (5)
C(3)–C(4)–C(5)	117.6 (5)	C(12)–C(13)–C(8)	119.6 (5)
C(3)–C(4)–N(1)	121.8 (5)	C(15)–C(14)–N(2)	105.6 (4)
C(5)–C(4)–N(1)	120.6 (5)	C(15)–C(14)–O(2)	126.1 (4)
C(4)–C(5)–C(6)	121.0 (5)	N(2)–C(14)–O(2)	128.2 (5)
C(4)–C(5)–C(7)	116.0 (4)	C(14)–C(15)–C(16)	115.2 (4)
C(6)–C(5)–C(7)	123.0 (4)	C(14)–C(15)–N(1)	107.3 (4)
C(5)–C(6)–C(1)	118.1 (5)	C(14)–C(15)–O(1)	101.7 (4)
C(5)–C(7)–C(8)	116.4 (4)	C(16)–C(15)–N(1)	115.2 (5)
C(5)–C(7)–N(2)	109.9 (4)	C(16)–C(15)–O(1)	108.4 (5)
C(5)–C(7)–O(1)	104.8 (4)	N(1)–C(15)–O(1)	108.1 (5)
C(8)–C(7)–N(2)	114.7 (4)	C(4)–N(1)–C(15)	117.1 (4)
C(8)–C(7)–O(1)	108.1 (4)	C(4)–N(1)–C(17)	119.7 (5)
N(2)–C(7)–O(1)	101.2 (4)	C(15)–N(1)–C(17)	117.6 (5)
C(7)–C(8)–C(9)	121.0 (4)	C(7)–N(2)–C(14)	110.0 (4)
C(7)–C(8)–C(13)	119.7 (4)	C(7)–O(1)–C(15)	103.9 (4)

^{a} Estimated standard deviation of last significant figure appears in parentheses.

was further refined by block diagonal least squares (9 × 9 blocks for the heavy atoms and 4 × 4 blocks for the hydrogen atoms) until the shifts in all parameters of the heavy atoms were less than one-fifth of the corresponding standard deviations. The final *R* value is 4.3%. A difference Fourier based on the final parameters has no features greater than 0.3 e/A^3 in magni-

tude. The final atomic parameters and the observed and calculated structure factors appear in the microfilm edition of this journal.[5]

Experimental Section

Melting points were determined microscopically on a hot stage. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer; nmr spectra were recorded with a Varian A-60 instrument. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–135 mesh) was used for chromatography. Petroleum ether refers to a fraction of bp 30–60°.

7-Chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide.—A solution of 28.6 g (0.1 mol) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide[6] in 150 ml of dimethylformamide was cooled to −20° with stirring under nitrogen. After addition of 8.1 g (0.15 mol) of sodium methoxide, the temperature was lowered to −40° and 12 ml (0.15 mol) of chloromethyl methyl ether was added dropwise. Cooling was discontinued and when the temperature had reached 0° the reaction mixture was poured into ice water. The precipitate was collected by filtration, washed with water, and dissolved in methylene chloride. The solution was dried over sodium sulfate and evaporated. Crystallization of the residue from methanol yielded 22.4 g (68%) of product. The analytical sample was recrystallized from ethanol, mp 164–166°.

Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.55; H, 4.60; N, 8.50.

7-Chloro-1,3-dihydro-1-methoxymethyl-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (1b).—Potassium *tert*-butoxide (23 g, 0.2 mol) was added to a solution of 50 g (0.15 mol) of 7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide in 250 ml of dimethylformamide cooled to −30°. After stirring under nitrogen for 5 min, 12.5 ml (0.2 mol) of methyl iodide was added. The temperature was allowed to reach 0° and the reaction mixture was then poured into ice water. The collected precipitate was dissolved in methylene chloride and the solution was dried and evaporated. Crystallization of the residue from ethanol gave 28.8 g (55%) of product; mp 133–136° after recrystallization from ethanol; nmr (CDCl₃) δ 1.68 (d, 3, *J* = 6.5 Hz, C₃ CH₃), 3.4 (s, 3, OCH₃), 4.52 (q, 1, *J* = 6.5 Hz, C₃ H), 5.03 5.45 (AB, 2, *J* = 10 Hz, NCH₂O), 7–7.8 (m, 8).

Anal. Calcd for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.79; H, 4.89; N, 8.12.

3-Acetoxy-7-chloro-1,3-dihydro-1,3-dimethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (2a).—A mixture of 15.8 g (0.015 mol) of 7-chloro-1,3-dihydro-1,3-dimethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide,[7] 150 ml of toluene, and 75 ml of acetic anhydride

(5) Listings of structure factors, coordinates, and thermal parameters will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

(6) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(7) Paper L: A. Walser, G. Silverman, R. Ian Fryer, L. H. Sternbach, and J. Hellerbach, *ibid.*, **36**, 1248 (1971).

was heated under reflux for 3 hr. During this time, 110 ml of toluene was removed by distillation. The reaction mixture was evaporated under reduced pressure and the residue was crystallized from a mixture of methylene chloride and hexane to yield 7.2 g of product. Chromatography of the concentrated mother liquor on 250 g of silica gel using 10% (v/v) ethyl acetate in methylene chloride for elution afforded an additional 4.6 g of **2a**: yield 66%; mp 150–152; ir (CHCl₃) 1730, 1680 cm⁻¹ (C=O); uv max 235–237 mμ (ε 28,200), infl 260 (16,300), max 325–328 (2280); nmr (CDCl₃) δ 1.35 (s, C₃ CH₃), 2.14 (s, 3, COCH₃), 3.45 (s, 3, NCH₃).

Anal. Calcd for C₁₉H₁₇ClN₂O₃: C, 63.96; H, 4.80; N, 7.85. Found: C, 63.87; H, 4.89; N, 7.83.

3-Acetoxy-7-chloro-1,3-dihydro-1-methoxymethyl-3-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (2b).—A mixture of 17.3 g (0.05 mol) of **1b** was dissolved in a mixture of 200 ml of toluene and 75 ml of acetic anhydride and was heated for 3 hr with distillation of 150 ml of solvent. Work-up of the reaction mixture as for **2a** afforded 11 g of product which was crystallized from a mixture of ether and hexane. The analytical sample was recrystallized from a mixture of methylene chloride, ether, and hexane: mp 154–157°; ir (CHCl₃) 1730, 1680 cm⁻¹ (C=O); nmr (CDCl₃) δ 1.4 (s, 3, C₃ CH₃), 2.12 (s, 3, COCH₃), 3.48 (s, 3, OCH₃), 4.86, 5.60 (AB, 2, J = 10 Hz, NCH₂O).

Anal. Calcd for C₂₀H₁₉ClN₂O₄: C, 62.10; H, 4.95; N, 7.24. Found: C, 62.11; H, 4.74; N, 7.39.

7-Chloro-1,2-dimethyl-2,5-epoxy-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepin-3-one (3a).—A solution of 7.2 g (0.02 mol) of **2a** in 200 ml of warm methanol was treated with 2.7 g (0.05 mol) of sodium methoxide. The reaction mixture was heated to boiling and the solvent was partly removed under reduced pressure. The residue was diluted with water, and the precipitated crystals were collected, washed with water, dried, and recrystallized from a mixture of methylene chloride and methanol to yield 4.7 g (74%) of product: mp 227–230° dec; ir (KBr) 3260 (NH), 1730, 1705 cm⁻¹ (C=O); uv infl 207 mμ (ε 33,000), max 265–266 (12,900), 310–313 (2580); nmr (DMSO-d) δ 1.73 (s, 3, C₂ CH₃), 2.98 (s, 3, NCH₃), 6.18 (d, 1, J = 2.5 Hz, C₆ H), 6.9 (d, 1, J = 9 Hz, C₉ H), 7.3 (q, 1, J_AB = 9 Hz, J_AX = 2.5 Hz, C₈ H), 7.53 (s, 5, C₆H₅), 10.3 (broad s, 1, NH).

Anal. Calcd for C₁₇H₁₅ClN₂O₂: C, 64.86; H, 4.80; N, 8.90; Cl 11.26. Found: C, 64.93; H, 5.14; N, 9.10; Cl, 11.32.

This compound was also obtained from **4a** under the same conditions.

7-Chloro-2,5-epoxy-1-methoxymethyl-2-methyl-5-phenyl-1,2,-4,5-tetrahydro-3H-1,4-benzodiazepin-3-one (3b).—A solution of 7.75 g (0.02 mol) of **2b** in 200 ml of warm methanol was cooled to 30° when 2.25 g (0.04 mol) of sodium methoxide was added. The mixture was kept at room temperature for 15 min. The solvent was partly removed *in vacuo* and the residue was partitioned between water and methylene chloride. The methylene chloride layer was dried over sodium sulfate and evaporated. The crystalline residue was slurried with ether and filtered to yield 6.4 g (93%) of product: mp 220–225° dec after recrystallization from a mixture of methylene chloride and hexane; ir (KBr) 3240 (NH), 1730, 1690 cm⁻¹ (C=O); uv max 253 mμ (ε 13,000), 300 (2400); nmr (DMSO-d) δ 1.76 (s, 3, C₂ CH₃), 3.33 (s, 3, OCH₃), 4.79 (s, 2, OCH₂N), 6.3 (d, 1, J = 2.5 Hz, C₆ H), 7.05 (d, 1, J = 9 Hz, C₉ H), 7.3 (q, 1, J_AB = 9 Hz, J_AX = 2.5 Hz, C₈ H), 7.53 (s, 5, C₆H₅), 10.3 (broad s, 1, NH).

Anal. Calcd for C₁₈H₁₇ClN₂O₃: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.59; H, 4.99; N, 8.08.

7-Chloro-1,3-dihydro-1,3-dimethyl-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (4a). 1.—A mixture of 3.6 g (0.01 mol) of **2a** and 30 ml of concentrated sulfuric acid was stirred at room temperature until solution was complete. The mixture was then poured on ice and made alkaline by the addition of ammonia. The precipitated product was collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization of the residue from a mixture of methylene chloride and hexane gave 2.5 g (79%) of **4a**: mp 156–158° dec; ir (CHCl₃) 3450 (OH), 1660 cm⁻¹ (C=O); uv max 232–234 mμ (ε 28,750), infl 260 (1400), max 321–327 (1800); nmr (CDCl₃) δ 1.15 (s, 3, C₃ CH₃), 3.56 (s, 3, NCH₃), 5.5 (s, 1, OH), 7.2–7.9 (m, 8); nmr (DMSO-d) mixture of two conformers.

Anal. Calcd for C₁₇H₁₅ClN₂O₂: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.93; H, 4.64; N, 8.95.

2.—A mixture of 2 g of **3a**, 20 ml of methylene chloride, and 20 ml of (1.6 N) ethanolic hydrogen chloride was heated under reflux for 27 hr. After evaporation of the solvents, the residue

was partitioned between aqueous sodium bicarbonate and methylene chloride. The organic layer was separated, dried, and concentrated. Partial crystallization of the residue from a mixture of ether and petroleum ether yielded 0.5 g (25%) of product identical in every respect with the compound described above.

7-Chloro-2,5-epoxy-2-methyl-5-phenyl-1,2,4,5-tetrahydro-3H-1,4-benzodiazepin-3-one (5).—A mixture of 1 g of **3b**, 20 ml of methylene chloride, 20 ml of ethanol, and 5 ml of (1.6 N) ethanolic hydrogen chloride was heated under reflux for 1 hr. The orange-colored solution was diluted with water and extracted with methylene chloride. The organic layer was washed with 1 N hydrochloric acid, dried over sodium sulfate, and evaporated. The crystalline residue was slurried in ether, collected, and recrystallized from a mixture of acetone and hexane to yield 0.5 g (57.5%) of product. The analytical sample was recrystallized from methanol: mp 220–225°; ir (KBr) 1720 cm⁻¹ (C=O); uv max 261–262 mμ (ε 10,800), 309–310 (2340); nmr (DMSO-d) δ 1.57 (s, 3, C₂ CH₃), 6.2 (d, 1, J = 2 Hz, C₆ H), 6.67 (d, 1, J = 8 Hz, C₉ H), 7.14 (q, 1, J_AB = 8 Hz, J_AX = 2 Hz, C₈ H), 7.5 (s, 5, C₆H₅), 7.62 (s, 1, NH), 10.02 (broad s, 1, NHCO).

Anal. Calcd for C₁₆H₁₃ClN₂O₂: C, 63.90; H, 4.35; N, 9.31. Found: C, 63.78; H, 4.22; N, 9.49.

Ethyl 6-Chloro-1,2-dihydro-2-methyl-4-phenylquinazoline-2-carboxylate (7).—A mixture of 2 g of **3b**, 50 ml of methylene chloride, and 50 ml of (1.6 N) ethanolic hydrogen chloride was refluxed for 20 hr. The red solution obtained was evaporated and the residue was crystallized from acetone and recrystallized from a mixture of methanol and acetone to yield 0.8 g (38%) of the hydrochloride: mp 150–160° dec; ir (KBr) 1750 cm⁻¹ (C=O); uv max 238–240 mμ (ε 28,200), 285–290 (9300), 450–454 (3450).

Anal. Calcd for C₁₈H₁₈Cl₂N₂O₂: C, 59.19; H, 4.96; N, 7.66. Found: C, 59.23; H, 4.93; N, 7.64.

The free base was crystallized from a mixture of ether and hexane, mp 98–101°. It was found identical with a sample prepared from ethyl pyruvate, 2-amino-5-chlorobenzophenone, and ammonium acetate.

The original mother liquor was evaporated and the residue was partitioned between aqueous sodium carbonate and methylene chloride. The organic layer was separated, dried, and concentrated. Crystallization of the residue from ethanol and recrystallization of the collected material from the same solvent yielded 0.27 g (16%) of the known 2-acetyl-6-chloro-4-phenylquinazoline,[2] mp and mmp 132–134°.

Crystallography.—Crystals of **3a** (C₁₇H₁₆ClN₂O₂, mol wt 314.74) were grown from a methylene chloride–methanol mixture. The crystal data are $a = 8.413 \pm 0.002$, $b = 7.918 \pm 0.001$, $c = 22.840 \pm 0.004$ Å (at 21°, λ = 1.5418 Å for Cu Kα), $V = 1521.5$ Å³, $D_m = 1.40$ g cm⁻³, $D_c = 1.38$ g cm⁻³ for $Z = 4$, $F(000) = 1256$. The space group is $P2_12_12_1$ (D_2^4, no. 19)[8] (h00 absent for h odd, 0k0 absent for k odd, and 00l absent for l odd). The intensities of 1066 independent reflections with $2\theta < 140°$ were measured on a Hilger & Watts Model Y290 four-circle diffractometer by a moving crystal-moving counter method using Ni-filtered Cu Kα radiation. The data were corrected for Lorentz and polarization effects but not for absorption (μ = 22.6 cm⁻¹). The crystal used was a rectangular prism with dimensions 0.12 × 0.18 × 0.25 mm.

All calculations were performed on a GE-635 computer. Local modifications of the Busing–Martin–Levy ORFLS[9] crystallographic least-squares program was used for the refinement in which $\Sigma w(|F_o| - |F_c|)^2$ was minimized. In the final cycles of least-squares refinement, the weights were taken as $w = 1/(8.5 + F_0 + 0.021F_0^2)$. The scattering curves of Cromer and Waber[10] were used for Cl, O, N, and C and that of Stewart, Davidson, and Simpson[11] for hydrogen.

Registry No.—**1b**, 28506-46-9; **2a**, 28506-47-0; **2b**, 28506-48-1; **3a**, 28506-49-2; **3b**, 28506-50-5; **4a**, 28506-51-6; **5**, 28506-52-7; **7**, 28638-51-9; 7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide, 28506-53-8.

(8) "International Tables for X-Ray Crystallography," Vol. I, Kynoch Press, Birmingham, England, 1965.

(9) W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn.

(10) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965).

(11) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

Mass Spectra and Pyrolyses of Tetrachloro-*o*-phenylene Carbonate and Tetrachloro-*o*-benzoquinone[1a,b]

D. C. DeJongh,* David A. Brent,[1b,c] and R. Y. Van Fossen[1b]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

The mass spectra of tetrachloro-*o*-phenylene carbonate (**6**) and of tetrachloro-*o*-benzoquinone (**7**) have been compared. The M − CO ion from **6**, which is part of a minor fragmentation pathway, may be the same as the molecular ion from **7**. The major fragmentation pathway of the molecular ion of **6** involves initial loss of CO_2. When **6** is pyrolyzed in the gas phase by passing it through a heated quartz tube in a stream of nitrogen, products are isolated which can be associated with initial pyrolytic loss of CO_2, and other products can be associated with initial pyrolytic loss of CO. For example, $C_{10}Cl_{10}$, $C_{10}Cl_8$, and C_9Cl_8 compounds have been associated with initial CO_2 loss, whereas tetrachlorobut-1-en-3-yne (**11**) and dichloro-1,3-dibutadiyne (**12**) have been associated with initial CO loss. When **7** is pyrolyzed, **11** and **12** are isolated, as well as the dimer of tetrachlorocyclopentadienone; this indicates **7** is the intermediate formed in that pyrolytic pathway of **6** involving initial CO loss. A ketocarbene could be the intermediate formed in that pyrolytic pathway of **6** involving initial CO_2 loss. Thus, these electron-impact and pyrolytic fragmentations appear to be qualitatively similar.

The mass spectra of a number of organic carbonates and cyclic sulfites have been compared with the products isolated from their pyrolyses, and similarities and differences have been noted.[2-6] For example, the mass spectrum of *o*-phenylene carbonate (**1**) shows the loss of CO_2 followed by CO to be the major fragmentation of the molecular ion; a minor path involves successive losses of CO for a total of 3CO lost.[5] When **1** is pyrolyzed in a stream of nitrogen in the presence of methanol, an intermediate ketene **2** is trapped and isolated as dimers of methyl cyclopentadiene-1-carboxylate (**3**) (44% at 810°) (eq 1).[5] This path is similar to

(1)
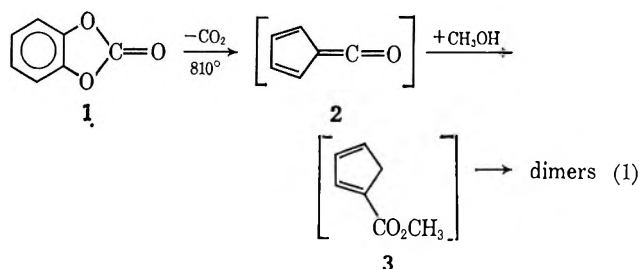
the major fragmentation of the molecular ion of **1**, *i.e.*, CO_2 is initially eliminated. A dimer **4** of cyclopentadienone is also obtained (14% at 810°) *via* a pathway (eq 2) involving loss of 2CO. This path is similar to the minor fragmentation of the molecular ion of **1**, *i.e.*, CO is initially lost.

The molecular ion of *o*-phenylene sulfite (**5**) eliminates SO followed by CO. When **5** is pyrolyzed, **4** is isolated in 30% yield (eq 3); cyclopentadienone forms *via* loss of SO followed by CO.[6]

(2)

(3)
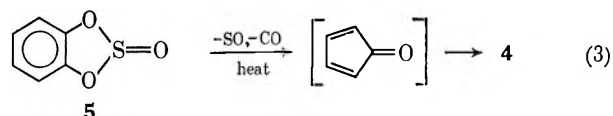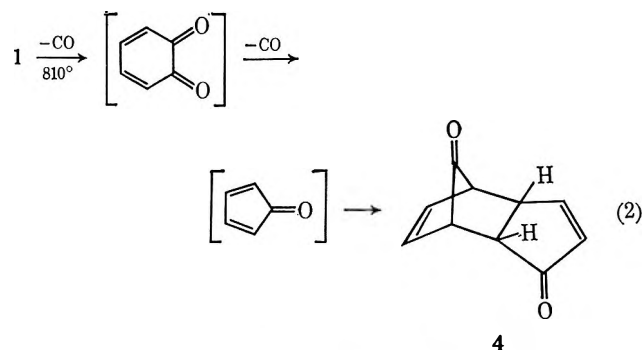
Tetrachloro-*o*-phenylene carbonate (**6**) has been studied with pyrolytic and electron-impact techniques, and we report the results in this article. *o*-Benzoquinone (**7**) has also been studied in order to determine the extent to which it functions as one of the intermediates in the pyrolysis of **6**.

6   **7**
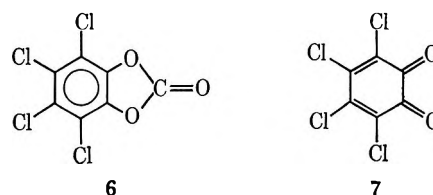
Experimental Section

Infrared spectra were recorded with a Perkin-Elmer Infracord. Mass spectra were obtained from an Atlas CH4 or an A.E.I. MS 902 mass spectrometer. All glpc work was carried out with a Hewlett-Packard 5750 research chromatograph with a thermal conductivity detector. Ultraviolet and visible spectra were determined with a Perkin-Elmer 202 or Cary 14 spectrophotometer. Chemical analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind.

Preparation of Tetrachloro-*o*-phenylene Carbonate (6).—Tetrachlorocatechol (Aldrich), 50 g, was added to a solution of 18 g of

(1) (a) This investigation was supported in part by the Alfred P. Sloan Foundation, 1967–1969. (b) This manuscript was taken from the Ph.D. Dissertations of D. A. Brent and of R. Y. Van Fossen, Wayne State University, Detroit, Mich., 1970. (c) D. A. Brent acknowledges the financial support of the Frank Knoller and Detroit New Research Fellowships.

(2) P. Brown and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 2469 (1966).

(3) G. G. Smith and B. Koesters, *Chem. Ber.*, **93**, 2400 (1960).

(4) A. David and J. H. Golden, *J. Chem. Soc. B*, 40 (1968).

(5) D. C. DeJongh and D. A. Brent, *J. Org. Chem.*, **35**, 4204 (1970).

(6) D. C. DeJongh, R. Y. Van Fossen, and C. F. Bourgeois, *Tetrahedron Lett.*, 271 (1967).
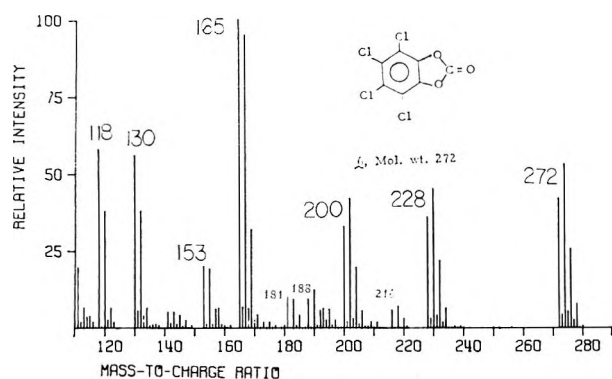
Figure 1.—The 70-eV mass spectrum of tetrachloro-*o*-phenylene carbonate (6) (the peak at m/e 244 is present in <0.1% relative intensity).
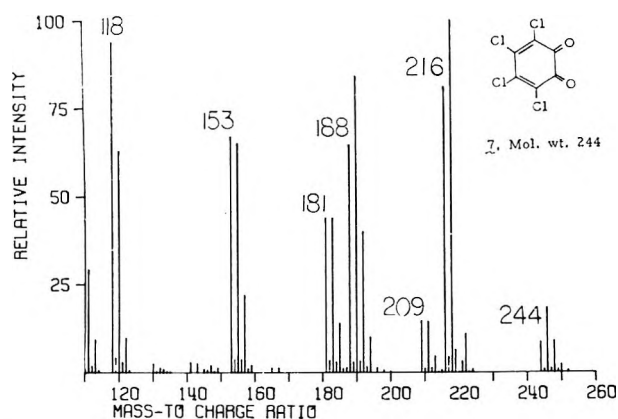
Figure 2.—The 70-eV mass spectrum of tetrachloro-*o*-benzoquinone (7).

sodium hydroxide in 50 ml of deaerated water (under nitrogen). After the addition of 150 ml of toluene, the solution was cooled to 0–5°. Phosgene (J. T. Baker) was slowly bubbled through the mixture for 1 hr. The mixture was stirred under nitrogen at 5° for another hour, after which the reaction was allowed to come to room temperature. The solution was filtered and the toluene layer was evaporated to dryness. (Unreacted phosgene might still be present in the toluene at this point. Therefore, evaporation was carried out in the hood.) A 31% yield of 6 was obtained: mp 167–168.5° (lit.[7] 172–173°); ir bands 1890, 1850, 1825 cm^{-1}; mass spectrum (70 eV); see Figure 1.

Anal. Calcd for C$_7$Cl$_4$O$_3$: C, 30.68; Cl, 51.80. Found: C, 30.98; Cl, 51.56.

Tetrachloro-*o*-benzoquinone (7).—Tetrachloro-*o*-benzoquinone (7) was used as purchased (Aldrich) without further purification, mass spectrum (70 eV); see Figure 2.

Preparation of Bis(pentachlorocyclopentadienyl) (8).—Bis(pentachlorocyclopentadienyl) (8) was prepared from hexachlorocyclopentadiene (Matheson Coleman and Bell) using the procedure of McBee, Idol, and Roberts:[8] yield, 29%; mp 118–120° (lit.[8] 120–121°); mass spectrum (70 eV) m/e (rel intensity) 470 (5), 400 (5.5), 330 (7.5), 295 (2.0), 270 (2.5), 260 (9.3), 235 (100); in each cluster of Cl isotopes, only the relative intensity of the peak of lowest m/e is given. The molecular ion is found at m/e 470. The relative intensities are somewhat dependent on instrumental parameters. A direct probe was used for sample introduction.

Preparation of Pentachloroanisole (9).—To 6 g of sodium hydroxide in 400 ml of water was added 13 g of pentachlorophenol (Aldrich), followed by 9 ml of dimethyl sulfate. The solution was stirred and warmed; a white precipitate formed which was filtered and washed with small portions of 95% ethanol. The residue was dried and 1 g of 9 was obtained: mp 106–107° (lit.[9] 108–109°); mass spectrum (70 eV) m/e (rel intensity) 278 (61), 263 (45.5), 235 (29.5), and clusters corresponding to 5Cl, base peak, m/e 280 (100).

Pyrolyses.—The pyrolysis apparatus and procedure for use with a quartz tube heated by an electric furnace have been described in a previous article.[10] In the trapping experiments, the trapping agents were added at the point the stream enters the heated area.

In the alternate pyrolysis apparatus, a heated Nichrome coil is used. The flow of the carrier gas (N$_2$) is controlled by means of a needle valve, and the nitrogen is dried by passing it through a drying tower containing Drierite. The rate of gas flow is read from a rotometer calibrated in liters/minutes and adjusted by means of a needle valve. The carrier gas is passed through a heated chamber containing the material to be pyrolyzed placed on a porous glass disk. The carrier gas and reactant vapor are passed through a reactor which contains heated, coiled Nichrome wire bent back upon itself to form five or seven strands. The vapors leaving the reactor are led into a series of cooled traps. The

pressure of the system is obtained from a McLeod gauge or a manometer. A thermocouple is placed into the center of the coiled strands of wire; the temperature reported for the pyrolysis is obtained from a calibration curve of temperature *vs.* reading on the transformer dial.

Pyrolysis of Tetrachloro-*o*-benzoquinone (7). A. Wire.—In a typical experiment, compound 7 (1.21 g) was pyrolyzed over the Nichrome coils at 650°, at a system pressure of 17 mm, and a nitrogen flow rate of 0.50 l./min. A total of 784 mg of crude pyrolysate was obtained. Octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione (10) was obtained from the crude pyrolysate in 47% yield: mp 158–160° (lit.[11] 160–161°); ir, same as reported.[12]

B. Oven.—In a typical experiment, compound 7 (1.6 g) was pyrolyzed with the quartz tube heated to 710–720° at a nitrogen flow rate of 0.85 l./min. The products were separated by glpc on a 3 ft × 0.25 in., 5% Apiezon L on Chromosorb W, 60–80 mesh column programmed at 50–225°. Yields were determined by comparing (by weighing) areas of peaks produced by solutions of the pyrolysis products with those of standard solutions. Tetrachlorobut-1-en-3-yne (11), 60.2% yield, was identified by its ir spectrum[13] and mass spectrum (70 eV) m/e (rel intensity) 188 (76) [190 (100)], 153 (73), 118 (48). Dichloro-1,3-butadiyne (12) was obtained in less than 1% yield; it was identified by its ir spectrum[14] and mass spectrum (70 eV) m/e (rel intensity) 118 (100), 83 (22). Dimer 10 was obtained in 13.6% yield. A small quantity of a compound was isolated by column chromatography (silica gel) and identified as C$_8$Cl$_8$ by mass spectrometry. It is probably a dimer of tetrachlorobut-1-en-3-yne.[13]

When compound 7 (2.0 g) was pyrolyzed at 850° at a nitrogen flow rate of 0.7 l./min, the two major products were 11 and 12. By relative glpc peak areas, 12 was approximately twice as abundant as 11. No C$_{10}$Cl$_{10}$, C$_{10}$Cl$_8$, or C$_9$Cl$_8$ compounds have been isolated from pyrolysis of 7 when either the oven or the wire method was used.

Pyrolysis of Tetrachloro-*o*-phenylene Carbonate (6).—The conditions and results of two pyrolyses of 6 are given in Table I.

TABLE I

CONDITIONS AND RESULTS OF PYROLYSES OF
TETRACHLORO-*o*-PHENYLENE CARBONATE (6)

Amount of 6	Oven temp, °C	N$_2$ flow rate	% yields 11	12
0.985 g	750–760	0.8 l./min	4.6	12.3
0.970 g	700	0.8 l./min	2.8	14.9

None of dimer 10 was obtained. Compounds 11 and 12 were obtained from a trap cooled by 2-propanol–Dry Ice, and they were collected from glpc; yields are given in Table I. The first trap after the oven was air-cooled; a chloroform solution of the

(7) R. E. Stenseth, R. M. Schisla, and J. W. Baker, *J. Chem. Eng. Data*, **9**, 390 (1964).

(8) E. T. McBee, J. D. Idol, and C. W. Roberts, *J. Amer. Chem. Soc.*, **77**, 4375 (1955).

(9) T. van der Linden, *Recl. Trav. Chim. Pays-Bas*, **57**, 781 (1938).

(10) D. A. Brent, J. D. Hribar, and D. C. DeJongh, *J. Org. Chem.*, **35**, 135 (1970).

(11) M. R. Kamal and J. E. Wicklatz, *Can. J. Chem.*, **42**, 1500 (1964).

(12) "Sadtler Standard IR Spectra," Sadtler Research Laboratories, Philadelphia, Pa., Spectrum No. 23,569.

(13) A. Roedig and R. Kohlhaupt, *Tetrahedron Lett.*, 1107 (1964).

(14) F. Straus, L. Kollek, and H. Hauptmann, *Chem. Ber.*, **63**, 1886 (1930).

material in this trap was placed on a silica gel column. The column was eluted with hexane followed by ether. Nothing was obtained from the ether fractions. Upon evaporating the hexane fractions, a solid remained which moves as one spot on tlc (silica gel) developed with hexane.

The mass spectrum of the brownish-colored solid shows that it is a mixture of $C_{10}C_{10}$, $C_{10}Cl_8$, and C_9Cl_8 compounds: mass spectrum (70 eV) m/e (formula, rel intensity) 470 ($C_{10}Cl_{10}$, 3), 400 ($C_{10}Cl_8$, 21), 388 (C_9Cl_8, 0.6), 353 (C_9Cl_7, 6), 235 (C_5Cl_5, 100). The uv spectrum of this mixture is similar to the uv spectrum of octachloronaphthalene (13),[15] indicating that the $C_{10}Cl_8$ component is **13**. There are no absorption maxima at 386 or 590 nm in the uv spectrum of the mixture; hence $C_{10}Cl_8$ is not the blue compound octachlorofulvalene.[16]

The colors, uv spectra, and mass spectra of six known $C_{10}Cl_{10}$ isomers with bicyclopentyl carbon skeletons have been reported.[17] The data from our mixture were compared with the data reported for these six isomers and are most consistent with the assignment of the $C_{10}Cl_{10}$ component with the structure bis(pentachlorocyclopentadienyl) (8).[18] Attempts to separate the components from the small amount of mixture available were unsuccessful.

In order to get a rough estimation of yields, the $C_{10}Cl_{10}$ component was assumed to be **8** and the $C_{10}Cl_8$ component was assumed to be **13**. The mixture, **8**, and **13** have absorption maxima at 330 nm in their uv spectra. A λ_{max} 275 nm (log ϵ 4.67) has been reported for **13**,[15] and a λ_{max} 280 (log ϵ 3.32) has been reported for **8**;[17] the uv spectrum of the mixture has a maximum at 277 nm. Compounds **8** and **13** were assumed to follow Beer's Law and the method of continuous approximation was employed using the absorbances at 330 and 275 nm in the uv spectrum of the mixture. The yields for **8**, estimated on this basis, were 12.6 and 9.7% for the two pyrolyses, and the yields for **13** plus the C_9Cl_8 component were 9.0 and 7.1% for the two runs.

Trapping of Pyrolytic Intermediates from 6. A. Using Methanol.—Attempts were made to trap intermediates in the pyrolysis of **6** by introducing methanol into the stream before it enters the oven. No trapped intermediates were isolated; oven temperatures of 702–740 and 800–830° were used.

B. Using Dimethyl Acetylenedicarboxylate.—A furnace setting of 800° was used, with a system pressure of 22 mm and a flow rate of 0.9 l./min. The trapping agent required heating to 115–117° in order to volatilize it into the stream at the point it enters the oven area; 10 ml of agent and 1.5 g of **6** were used. No trapped intermediates were isolated, and no trapping agent was recovered.

C. Using Carbon Disulfide.—**6** (1 g) and 25 ml of CS_2 were pyrolyzed as described above: oven, 800–820°; nitrogen flow rate, 0.8 l./min; system pressure, 18 mm. The major product was **11**; minor products were hexachloro-1,3-butadiene (**14**), tetrachlorothiophene (**15**), hexachlorobenzene, and recovered **6**. The mass spectrum of **14** exhibits a molecular ion at m/e 258 (with a 6Cl isotope cluster); the ir spectrum of the isolated material agrees with the published spectrum.[19] Tetrachlorothiophene (**15**) was identified by ir[20] and mp 28° (lit.[21] 29°); mass spectrum (70 eV) m/e (rel intensity) 222 (100), 220 (M+, 75.6), 185 (27.2), 150 (9.5), 141 (25.2), and peaks due to Cl isotopes. Hexachlorobenzene and tetrachloro-*o*-phenylene carbonate (**6**) were identified by comparison of their retention times on glpc, ir spectra, and mass spectra with those of authentic samples.

Pyrolysis of Pentachloroanisole (9).—Pentachloroanisole (**9**) (0.5 g) was pyrolyzed with the oven set at 850–880°. No peaks due to $C_{10}Cl_{10} \cdot {}^+$ are evident in the mass spectra of crude mixtures of products; peaks due to $C_6Cl_6 \cdot {}^+$ and $C_6HCl_5 \cdot {}^+$ are present.

A crystalline product was sublimed from the brown mixture of products at room temperature and atmospheric pressure. The

mass spectrum of the compound shows it to be C_6HCl_5. The ir spectrum agrees with that published for pentachlorobenzene.[22]

Results

Mass Spectra of Tetrachloro-*o*-phenylene Carbonate (6) and Tetrachloro-*o*-benzoquinone (7).

—The 70-eV mass spectrum of **6** is given in Figure 1 and is summarized in Scheme I. The M − CO_2 path is favored

SCHEME I
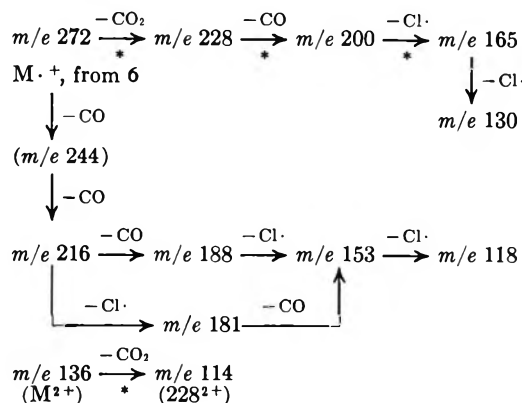
over the M − CO path, both in terms of relative intensities of peaks and the presence of metastables. The 70-eV spectrum of **7** is given in Figure 2 and is summarized in Scheme II. The losses of 2Cl in the schemes

SCHEME II
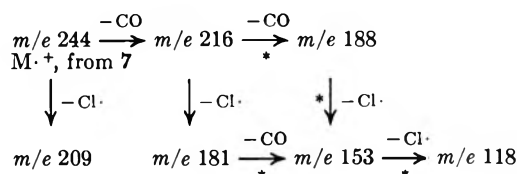
are shown as stepwise losses of Cl· rather than losses of Cl_2, because metastable peaks are found in the mass spectrum of **7** for the former type of elimination.

At lower voltages, the M − CO path in the mass spectrum of **6** becomes of increasingly less importance, whereas the M − CO_2 path remains prominent. For example, at 18 eV (uncorrected) the base peak is m/e 274; the prominent fragment ions are m/e 228 (27.8%), 200 (19.6%), and 165 (5.6%).

Examination of the two spectra shows that the peaks which are intense in the mass spectrum of **7**, *e.g.*, m/e 118, 153, 181, 188, and 216, and their isotope peaks, represent the minor path (M − CO) in the mass spectrum of **6**. Thus an ion corresponding to the molecular ion of **7** may be the intermediate in this minor fragmentation pathway of the molecular ion of **6**.

Pyrolysis of Tetrachloro-*o*-benzoquinone (7).—Tetrachloro-*o*-benzoquinone (**7**) was pyrolyzed in the gas phase. When the heated reactor consists of coiled Nichrome wire heated to 650°, octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione (**10**) is isolated (eq 4). The formation of **10** can be rationalized by the dimerization of tetrachlorocyclopentadienone, formed by the loss of CO from **7**.

(15) W. L. Mosby, *J. Amer. Chem. Soc.*, **77**, 758 (1955).

(16) V. Mark, *Tetrahedron Lett.*, 333 (1961).

(17) R. M. Smith and R. West, *J. Org. Chem.*, **35**, 2681 (1970).

(18) The mass spectrum of **8** has been reported.[17] The peak at m/e 470 for the molecular ion is given as <1% relative intensity. We find relatively intense peaks at m/e 470 and 235 in the mass spectrum of **8** as well as in the mass spectrum of the mixture. Our spectra were obtained using a direct-introduction probe, whereas the data from Smith and West may have been obtained using a heated-inlet system which increases the possibility of thermal degradation.

(19) Reference 12, Spectrum No. 3229.

(20) Reference 12, Spectrum No. 16,580.

(21) R. C. Weast, Ed., "Handbook of Chemistry of Physics," 49th ed., Chemical Rubber Co., Cleveland, Ohio, 1968.

(22) E. K. Plyer, H. C. Allen, and E. D. Tidwell, *J. Res. Nat. Bur. Stand.*, **58**, 255 (1957).

$$ (4) $$

10 (47%)
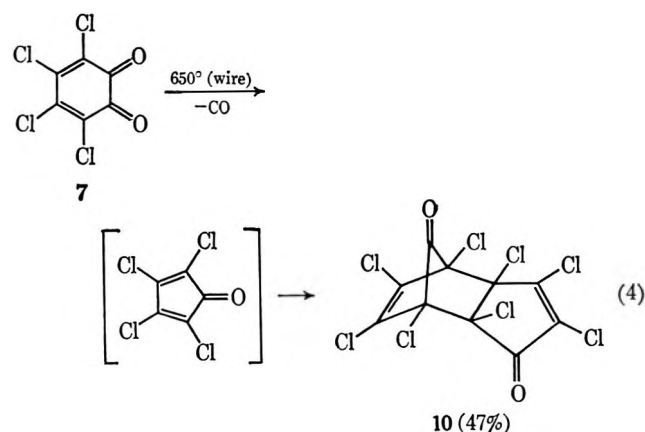
When the heated reactor consists of a quartz tube heated to 720°, the major product from **7** is tetrachlorobut-1-en-3-yne (**11**); **10** is also obtained. Minor quantities of dichloro-1,3-butadiyne (**12**) and of a C_8Cl_8 compound[13] are formed. These results are summarized in Scheme III.

Scheme III
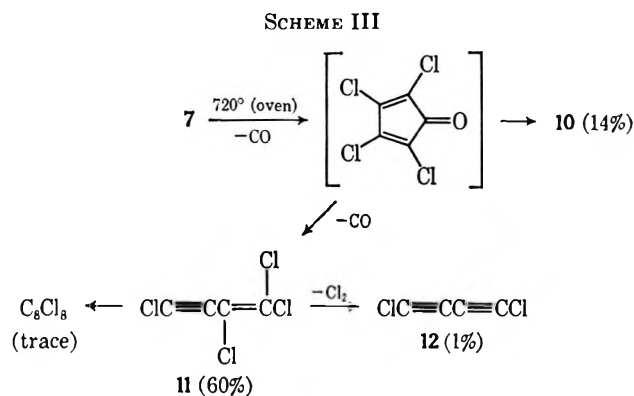
At 850°, **12** is obtained in approximately twice the quantity of **11** and dimer **10** is not formed; thus **11** is probably a precursor of **12**. It is possible that **11** arises *via* a tetrachlorocyclobutadiene intermediate (**16**) (eq 5), although the data do not provide information to confirm this.

$$ (5) $$
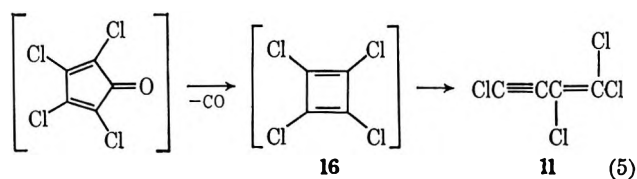
Pyrolysis of Tetrachloro-*o*-phenylene Carbonate (6). —When tetrachloro-*o*-phenylene carbonate (**6**) is pyrolyzed, tetrachlorobut-1-en-3-yne (**11**, 12%), dichloro-1,3-butadiyne (**12**, 5%), and a mixture (*ca.* 22%) of $C_{10}Cl_{10}$, $C_{10}Cl_8$, and C_9Cl_8 compounds are obtained. Products **11** and **12** most likely form after initial loss of CO from **6** through the intermediacy of **7** (*cf.* Scheme III). None of dimer **10** was isolated.

Mass spectral and uv data are most consistent with the assignments of bis(pentachlorocyclopentadienyl) (**8**) to the $C_{10}Cl_{10}$ component and octachloronaphthalene (**13**) to the $C_{10}Cl_8$ component. The C_9Cl_8 component in the mixture is, most likely, octachloroindene (**17**).[23]

(23) P. Eaton, E. Carlson, P. Lombardo, and P. Yates, *J. Org. Chem.*, **25**, 1225 (1960).

Scheme IV
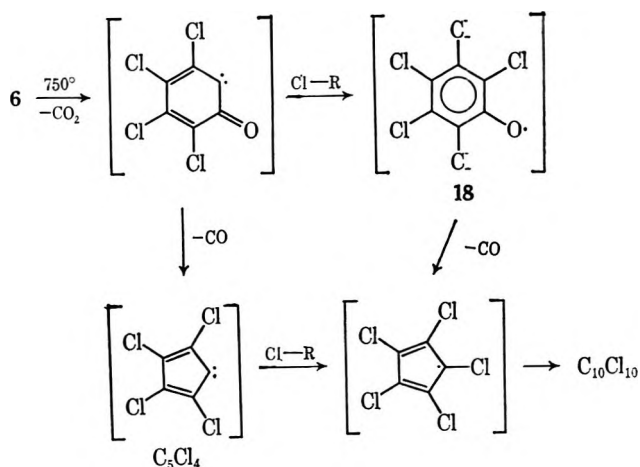
A possible route to $C_{10}Cl_{10}$ is proposed in Scheme IV, in which CO_2 is initially eliminated to form a ketocarbene. The ketocarbene then abstracts a chlorine atom to form intermediate **18** which loses CO; $C_5Cl_5\cdot$ then dimerizes. An alternate route could be formation of a C_5Cl_4 carbene which could abstract a chlorine atom, as shown in Scheme IV also.

Hexachlorocyclopentadiene has been reported to form **8** and **13** upon pyrolysis (eq 6).[24] Thus, it is likely that

$$ (6) $$
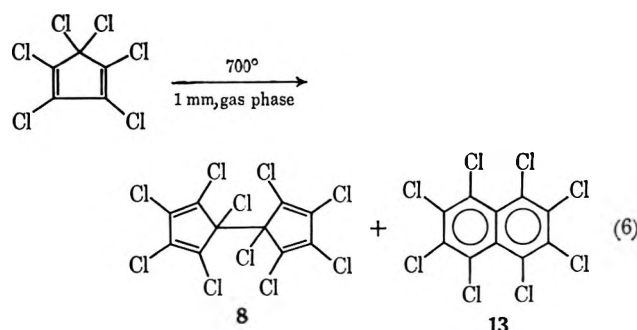
8 and **13** arise, at least in part, from an intermediate which is common to the pyrolyses of **6** and of hexachlorocyclopentadiene.

Pentachloroanisole (**9**) was pyrolyzed under the same conditions that **6** was (eq 7), in an attempt to generate

$$ (7) $$
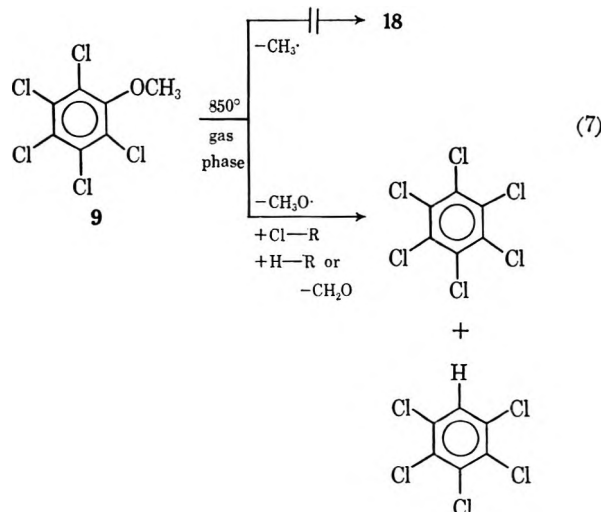
(24) A. E. Ginsberg, R. Paatz, and F. Korte, *Tetrahedron Lett.*, 779 (1962).

intermediate **18** in order to see if it is a precursor to **8**. However, we find that pentachloroanisole cleaves the phenyl–oxygen bond pyrolytically and not the oxygen–methyl bond, and hexa- and pentachlorobenzene are formed. On the other hand, phenyl ethers, including anisole, yield products arising from demethylation as well as demethoxylation.[25-27]

Methanol, CS_2, and dimethyl acetylenedicarboxylate were used in attempts to trap intermediates in the pyrolysis of **6**. No adducts were isolated when methanol and dimethyl acetylenedicarboxylate were used. With CS_2, tetrachlorothiophene (**15**) was isolated. A possible route to its formation from tetrachlorocyclopentadienone is given in Scheme V. It is also possible that CS_2 has trapped **16** or another C_4Cl_4 intermediate.

Scheme V
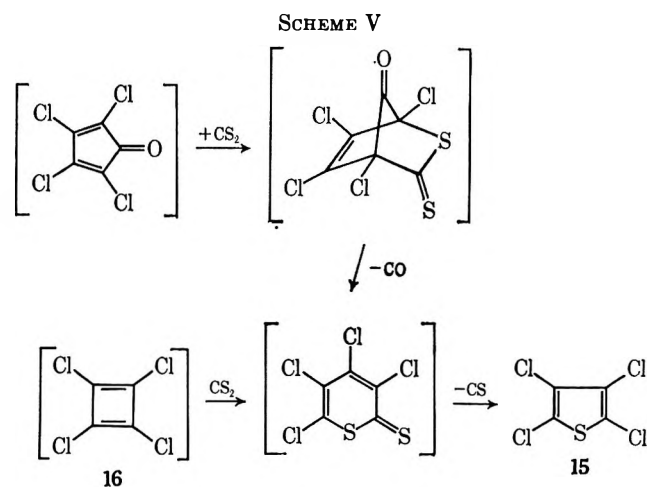
Discussion

The gas phase pyrolysis of tetrachloro-*o*-phenylene carbonate (**6**) can be rationalized by two competing paths, initial loss of CO_2 and initial loss of CO (eq 8). We pyrolyzed tetrachloro-*o*-benzoquinone (**7**) in order to establish that it is an intermediate in the pyrolysis of

(8)
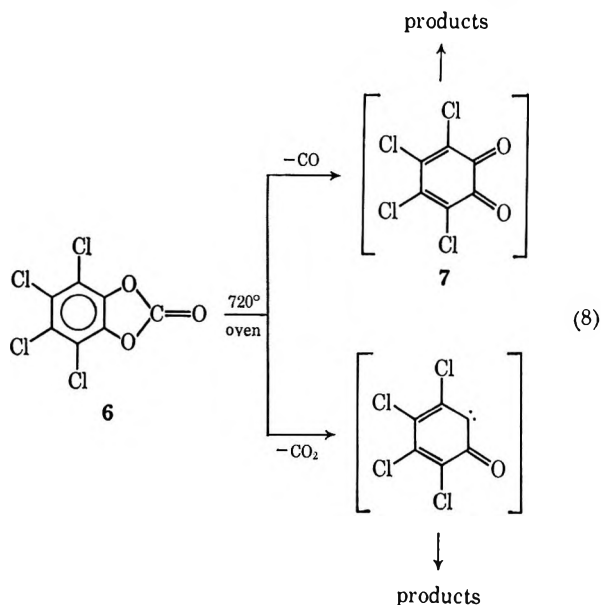
6. The liquid phase pyrolysis of 3,4,5,6-tetrachloro-benzo-2-diazo-1-oxide (**19**) has been reported,[28] and the intermediate suggested in this pyrolysis is the same as that we propose for the loss of CO_2 from **6** (eq 9).

(9)
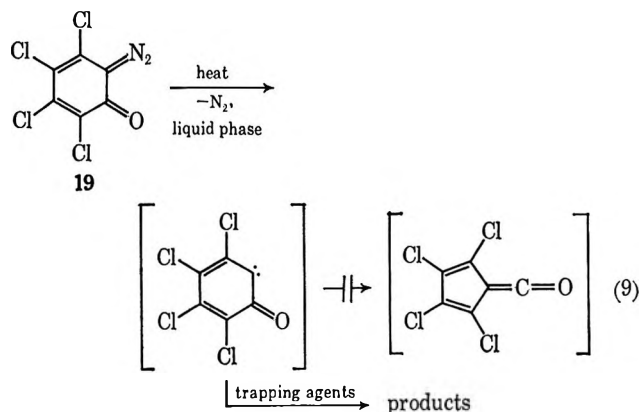
The intermediate ketocarbene which forms on the liquid phase pyrolysis and photolysis of **19** does not undergo the Wolff rearrangement to a ketene. It can be trapped with various reagents; for example, trapping with CS_2 yields **20** and with CH_3OH, **21**.[28] However,
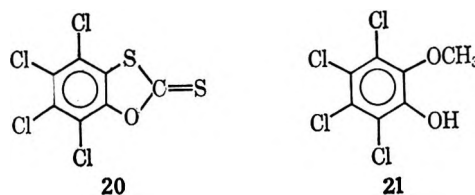
our gas phase pyrolyses with CS_2, CH_3OH, and dimethyl acetylenedicarboxylate in the stream with **6** did not result in products from trapping, except for a small amount of tetrachlorothiophene (**15**) when CS_2 was used. In the case of dimethyl acetylenedicarboxylate, the trapping agent may have decomposed pyrolytically before it had a chance to react.

The $C_{10}Cl_{10}$, $C_{10}Cl_8$, and C_9Cl_8 products, which may be **8**, **13**, and **17**, respectively, can be rationalized most readily in terms of a path involving initial loss of CO_2. On the other hand, formation of tetrachlorobut-1-en-3-yne (**11**) and dichloro-1,3-butadiyne (**12**) can be more readily explained by the route of initial loss of CO from **6**. We pyrolyzed **7** under the same conditions that we had used to pyrolyze **6**; we obtained compounds **11** and **12**. The dimer (**10**) of tetrachlorocyclopentadienone was obtained also, showing that this dienone is also an intermediate in the pyrolysis and has been trapped by dimerization.

A rough estimation of the importance of the M − CO_2 path *vs.* the M − CO in the 70-eV mass spectrum of tetrachloro-*o*-phenylene carbonate can be obtained by summing the relative intensities of peaks associated with each path. Using this approach, the M − CO_2 path is favored over the M − CO path by a factor of 5. By summing the yields of products isolated from the pyrolytic paths associated with the initial loss of CO_2 and with the initial loss of CO, the factor 1.3 is obtained, favoring the M − CO_2 path. Thus, while it is difficult to get accurate quantitative data on the extent to

(25) R. F. Pottie and F. P. Lossing, *J. Amer. Chem. Soc.*, **85**, 269 (1963).
(26) E. Hedaya and D. McNeil, *ibid.*, **89**, 4213 (1967).
(27) Yu. K. Shaposhnikcv and L. V. Kosyukova, *Khim. Pererab. Drev.*, 6 (1965); *Chem. Abstr.*, **66**, 37557a (1967).

(28) R. Huisgen, G. Binsch, and H. Koenig, *Chem. Ber.*, **97**, 2868, 2884 (1964).

which the molecule fragments *via* initial losses of CO_2 and of CO, the electron-impact and pyrolytic fragmentations of **6** appear to be qualitatively similar; the same is true of **7**. We are studying the mass spectra and pyrolyses of various aromatic molecules in order to explore the similarities between the two processes.

We hope to develop this technique into a means of predicting a molecule's pyrolysis pathway from its mass spectrum and to elucidate possible electronic relationships between the two processes.

Registry No.—**6**, 711-62-6; **7**, 2435-53-2.

The Pyrolysis of 1,1-Dihexyl-1-methylamine-2-acylimides

S. WAWZONEK*[1] AND E. E. PASCHKE[2]

Department of Chemistry, University of Iowa, Iowa City, Iowa 52240

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Pyrolysis of 1,1-dihexyl-1-methylamine-2-acetylimide gave 1-hexene, methyl isocyanate, 1-hexyl-1-methyl-2-acetylhydrazine, and dihexylmethylamine. The corresponding benzoyl derivative gave 1-hexene, dihexylmethylamine, diphenylurea, 2-phenylbenzimidazole, benzanilide, and 1-phenyl-3-methylurazole. The abnormal products isolated result from the reaction of phenyl isocyanate with moisture, the aminimide, and 1-hexyl-1-methyl-2-benzoylhydrazine.

Studies of the pyrolysis of open-chain aminimides have been limited to examples containing three methyl groups,[3] two methyls and a 2-acetoxypropyl group,[4] benzyl and two methyls,[5] and recently two methyls and a cyclooctyl or 2-phenylpropyl group.[6] The first two form the tertiary amine and isocyanate and the third type proceeds with rearrangement of the benzyl group. The last two are reported to proceed solely with elimination.

The present work describes the pyrolysis of 1,1-dihexyl-1-methylamine-2-acetylimide (**1a**) and 1,1-dihexyl-1-methylamine-2-benzoylimide (**1b**) and finds that the products formed depend upon the acyl group present.

$$\overset{-\ +}{RCONN}(C_6H_{13})_2$$
$$|$$
$$CH_3$$

1a, R = CH₃
b, R = C₆H₅
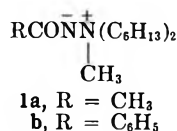
1,1-Dihexyl-1-methylamine-2-acetylimide (**1a**) upon pyrolysis at 140° gave 1-hexene, methyl isocyanate, 1-hexyl-1-methyl-2-acetylhydrazine, and dihexylmethylamine. Based on the ratio of the last two compounds, the elimination reaction occurred to the extent of 64.5%.

The 2-benzoyl derivative **1b**, when heated at its decomposition point of 175–185°, gave a more complicated mixture consisting of 1-hexene, dihexylmethylamine, benzanilide, diphenylurea, 2-phenylbenzimidazole, and 1-phenyl-3-methylurazole (**2**). The last compound
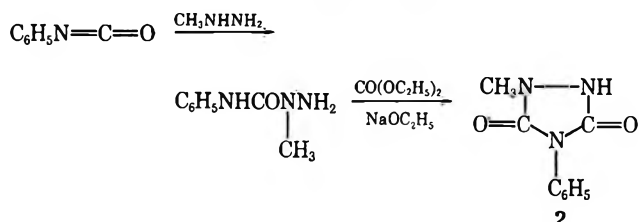
was identified by comparison with a sample synthesized by the following series of reactions.

The formation of these products can be rationalized upon the basis of a similar decomposition of the benzoyl derivative **1b** to that found with the acetyl compound **1a**. The absence of phenyl isocyanate or its trimer and 1-hexyl-1-methyl-2-benzoylhydrazine suggests that these compounds are involved in the formation of benzanilide, diphenylurea, 2-phenylbenzimidazole, and 1-phenyl-3-methylurazole (**2**).

2-Phenylbenzimidazole has been isolated previously in the decomposition of 1,1,1-trimethylamine-2-benzoylimide and is considered to be formed from the reaction of phenyl isocyanate with the aminimide.[7]

Diphenylurea is probably formed from phenyl isocyanate and traces of water; no precautions were taken to exclude moisture from the pyrolysis.

Benzanilide and 1-phenyl-3-methylurazole (**2**) result from a reaction of phenyl isocyanate and 1-hexyl-1-methyl-2-benzoylhydrazine. This reaction was verified by heating these two compounds at 170°; 1-hexene, benzanilide, diphenylurea, and 1-phenyl-3-methylurazole were formed.

The initial step in this reaction parallels that observed between phenyl isocyanate and *N*-alkylamides.[8]

$$C_6H_5CONHNC_6H_{13} \xrightarrow{C_6H_5N=C=O} C_6H_5NHC=O \longrightarrow$$
$$| \qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$CH_3 \qquad\qquad\qquad\qquad\qquad C_6H_5CONNC_6H_{13}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_3$$
$$\mathbf{3}$$

$$C_6H_5N=C=O \xrightarrow{CH_3NHNH_2}$$

$$C_6H_5NHCONNH_2 \xrightarrow[NaOC_2H_5]{CO(OC_2H_5)_2}$$
$$|$$
$$CH_3$$

structure **2**

structure **4**
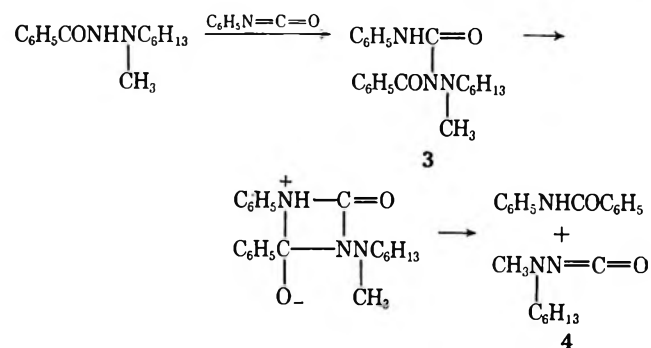
The intermediate urea **3** at the temperature used would decompose into benzanilide and methylhexylaminoisocyanate (**4**). The last species (**4**) is not isolated but reacts with phenyl isocyanate and forms a cyclic amini-

(1) To whom inquiries should be addressed.
(2) Abstracted in part from the Ph.D. thesis of E. E. Paschke, May 1971.
(3) S. Wawzonek and R. C. Gueldner, *J. Org. Chem.*, **30**, 3031 (1965); M. S. Gibson and A. W. Murray, *J. Chem. Soc.*, 880 (1965); R. F. Smith and P. C. Briggs, *Chem. Commun.*, 120 (1965).
(4) R. C. Slagel, *J. Org. Chem.*, **33**, 1374 (1968).
(5) S. Wawzonek and E. Yeakey, *J. Amer. Chem. Soc.*, **82**, 5718 (1960).
(6) D. G. Morris, B. W. Smith, and R. J. Wood, *Chem. Commun.*, 1134 (1968). This work appeared during the course of our investigation.

(7) M. S. Gibson, P. D. Callaghan, R. F. Smith, A. C. Bates, J. R. Davidson, and A. J. Battisti, *J. Chem. Soc. C*, 2577 (1967).
(8) P. F. Wiley, *J. Amer. Chem. Soc.*, **71**, 3746 (1949).

mide **5**. This compound can undergo β elimination and form the urazole **2** and 1-hexene.
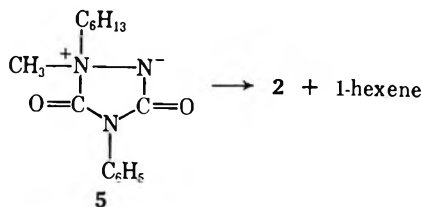
The reactions proposed have precedent in the literature. Dimethylaminoisocyanate has been trapped with another isocyanate and forms a cyclic aminimide.[9] The triethyl analog of **5** is reported to undergo β elimination and to form ethylene.[10]

Further verification of this reaction was the trapping of methylhexylaminoisocyanate, prepared from methylhexylhydrazine and phosgene, with phenyl isocyanate; 1-phenyl-3-methylurazole (**2**) and diphenylurea were obtained as products.

The series of reactions proposed is consistent with the yield of the compounds obtained. The yields of benzanilide (20.5%) and 1-phenyl-3-methylurazole (**2**) (20.2%) were the same since they are formed from a common intermediate. The yield of 1-hexene (35.6%) was approximately twice that of the benzanilide (30.5%) as expected.

The ratio of rearrangement to elimination was 4:1 for the benzoyl derivative **1b** and is higher than that (1:2) observed for the acetyl derivative **1a**. Since the decomposition of the former **1b** was carried out at 175° and that for the acetyl at 140°, the effect of temperature on the ratio of products from the acetyl derivative was studied. Pyrolysis at 175° gave 67.6% elimination and indicated that the temperature dependence of the reaction was small.

The difference in behavior of the two aminimides (**1**) can be ascribed to the greater nucleophilic properties of the imide nitrogen in the acetyl derivative **1a**. Less delocalization of this charge is involved in this compound (**1a**) than in the benzoyl derivative **1b**. This difference is in agreement with the infrared spectra for the two compounds; the carbonyl absorption for the carbonyl group is at 1560 cm^{-1} for **1b** and 1580 cm^{-1} for **1a**.

Experimental Section[11]

1,1-Dihexyl-2-benzoylhydrazine.—A solution of 1,1-dihexylhydrazine[12] (50.0 g, 0.25 mol) and triethylamine (52.2 g, 0.517 mol) in benzene (400 ml) was treated dropwise with a solution of benzoyl chloride (35.3 g, 0.251 mol) in benzene (100 ml) and the resulting solution was refluxed for 1 hr. Addition of water and sodium hydroxide (20 g, 0.5 mol) was followed by separation of the aqueous layer. The aqueous layer was extracted with benzene, the benzene extracts were combined, and the solvent was removed under reduced pressure. The white crystals (62.3 g, 0.205 mol, 82%) obtained were recrystallized from absolute ethanol: mp 75–76°; ir (Nujol) 3280 (NH), 1640 cm^{-1} (CO); nmr (DCCl$_3$) δ 7.50 (m, 5, C$_6$H$_5$), 7.12 (s, 1, NH), 2.81 (t, 4, N(CH$_2$)$_2$), 1.10 (m, 22, [CH$_3$(CH$_2$)$_4$]$_2$).

Anal. Calcd for C$_{19}$H$_{32}$N$_2$O: C, 74.95; H, 10.59; N, 9.20. Found: C, 75.14; H, 10.53; N, 8.99.

1,1-Dihexyl-1-methyl-2-benzoylhydrazonium p-Toluenesulfonate.—A solution of 1,1-dihexyl-2-benzoylhydrazine (51.9 g,

0.171 mol) and methyl p-toluenesulfonate (36.9 g, 0.198 mol) in acetonitrile (500 ml) was refluxed for 17 hr. Removal of the acetonitrile and excess methyl p-toluenesulfonate under reduced pressure gave 65.4 g of an oil which was purified by chromatography on silica gel. Elution with ethyl acetate gave three fractions. The first fraction (8.1 g) consisted of methyl p-toluenesulfonate and 1,1-di-n-hexyl-2-benzoylhydrazine. Fraction 2 (41.7 g, 0.085 mol, 49.7%) consisted of 1,1-dihexyl-1-methyl-2-benzoylhydrazonium p-toluenesulfonate. This compound was first isolated as an oil which crystallized on standing for several days: mp 69–71°; ir (Nujol) 3490 and 3220 (NH), 1680 (CO), 1180 cm^{-1} (SO$_3$$^-$); nmr (DCCl$_3$) δ 10.50 (broad singlet, 1, NH), 7.45 (m, 9 aromatic hydrogens), 3.90 (t, 4, N(CH$_2$)$_2$), 3.57 (s, 3, NCH$_3$), 2.19 (s, 3, CH$_3$C$_6$H$_4$), 1.11 (m, 22, (C$_5$H$_{11}$)$_2$).

Anal. Calcd for C$_{27}$H$_{42}$N$_2$O$_4$S: C, 66.08; H, 8.63; N, 5.71. Found: C, 66.09; H, 8.94; N, 5.81.

Fraction 3 was a brown oil (8.07 g, 0.0253 mol, 14.8%) and proved to be 1,1-dihexyl-1-methylamine-2-benzoylimide.

1,1-Dihexyl-1-methylamine-2-benzoylimide.—A solution of 1,1-dihexyl-1-methyl-2-benzoylhydrazonium p-toluenesulfonate (37.48 g, 0.0764 mol) in dry methanol (100 ml) was treated with a solution of sodium methoxide (5.05 g, 0.0935 mol) in dry methanol (50 ml), and the resulting solution was heated to boiling. Removal of the methanol gave a viscous oil which was purified by dissolving in water and extracting with chloroform. The oil obtained after removing the chloroform was treated with dry benzene and filtering the traces of sodium p-toluenesulfonate which precipitated. Removal of the benzene gave the aminimide (23.66 g, 0.0764 mol, 97.2%) as an oil: ir (neat) 1560 cm^{-1} (CO); nmr (CDCl$_3$) δ 7.55 (m, 5, C$_6$H$_5$), 3.52 (t, 4, N(CH$_2$)$_2$), 3.15 (s, 3, NCH$_3$), 1.13 (m, 22, [CH$_3$(CH$_2$)$_4$]$_2$).

Anal. Calcd for C$_{20}$H$_{34}$N$_2$O: C, 75.42; H, 10.76; N, 8.80. Found: C, 75.24; H, 10.75; N, 8.62.

Pyrolysis of 1,1-Dihexyl-1-methyl-2-benzoylimide.—The aminimide **1b** (12.76 g, 0.040 mol) was heated at 175–185° for 2.3 hr, and volatile products were collected in a receiver cooled with a Dry Ice–acetone mixture. In this manner 1-hexene (1.20 g, 0.0143 mol, 17.8%) was isolated, bp 62–63°. The ir and nmr spectra were identical with those of an authentic sample.

The residue from the pyrolysis upon extraction with hexane gave dihexylmethylamine (6.08 g, 0.0305 mol, 76%): bp 58–59° (0.9 mm); n^{20}D 1.4337 (lit.[13] bp 118° (12 mm); n^{20}D 1.434); nmr (neat) δ 2.27 (t, 4, N (CH$_2$)$_2$), 2.11 (s, 3, NCH$_3$), and 1.13 (m, 22, [CH$_3$(CH$_2$)$_4$]$_2$).

The hexane-insoluble residue (4.94 g) was chromatographed on silica gel using benzene with increasing amounts of ethyl acetate as solvent. The first fraction contained benzanilide (1.62 g, 8.22 mmol, 20.5%), mp 162–163°. The second compound isolated was 1,3-diphenylurea (0.76 g, 3.58 mmol, 8.9%), mp 241–242°. Fraction 3 contained 2-phenylbenzimidazole (0.75 g, 3.86 mmol, 9.6%), mp 293–294° dec (lit.[14] 299–301°). The ir and nmr spectra were identical with the spectra of an authentic sample.

The fourth compound isolated was 1-phenyl-3-methylurazole (**2**) (1.55 g, 8.1 mmol, 20.2%), mp 187–188°.

1-Phenyl-3-methylurazole (2).—A solution of 2-methyl-4-phenylsemicarbazide[15] (6.64 g, 0.04 mol), diethyl carbonate (15.77 g, 0.134 mol), and sodium ethoxide (5.68 g, 0.0835 mol) in ethanol (80 ml) was refluxed for 8.5 hr. Removal of the ethanol was followed by treatment with water and neutralization with hydrochloric acid. Extraction with chloroform gave white crystals which were recrystallized from a mixture of acetone and hexane, yield 3.00 g (39.0%). Sublimation at 80° at a pressure of 0.08 mm gave a sample melting at 186–187°: ir (Nujol) 3225 (NH), 1775 and 1685 cm^{-1} (C=O); nmr (DMSO-d_6) δ 8.40 (s, 1, NH), 7.50 (m, 5, C$_6$H$_5$), 3.15 (s, 3, CH$_3$).

Anal. Calcd for C$_9$H$_9$N$_3$O$_2$: C, 56.54; H, 4.74; N, 21.98; mol wt 191. Found: C, 56.27; H, 4.92; N, 21.75; mol wt (mass spectrum), 191.

N-Nitroso-n-hexylmethylamine.—A solution of hexylmethylamine[16] (94.4 g, 0.819 mol) in acetic acid (128 ml) and water (425 ml) was treated simultaneously dropwise with a solution of sodium nitrite (176.0 g, 2.55 mol) in water (425 ml) and a solution of acetic acid (93.5 ml) in water (255 ml). The resulting

(9) W. S. Wadsworth and W. D. Emmons, *J. Org. Chem.*, **32**, 1279 (1967).

(10) W. Lwowski, R. A. de Mauriac, R. A. Murray, and L. Lunow, *Tetrahedron Lett.*, 425 (1971).

(11) Melting points are corrected; boiling points are not.

(12) O. Westphal, *Ber. Deut. Chem. Ges. B.*, **74**, 759 (1941).

(13) O. Westphal and D. Jerehel, *ibid.*, **73**, 3, 1002 (1940).

(14) F. C. Cooper and M. W. Partridge, *J. Chem. Soc.*, 255 (1953).

(15) M. Busch, E. Opermann, and H. Walther, *Ber.*, **37**, 2318 (1904).

(16) S. Wawzonek and J. P. Culbertson, *J. Amer. Chem. Soc.*, **82**, 441 (1960).

solution was stirred for 2 hr at 55–65° and then extracted with three 200-ml portions of ether. Removal of the ether gave an oil which was purified by distillation: yield 105.4 g (89.2%); bp 108–110° (8 mm); n^{21}D 1.4524; nmr (neat) δ 4.11, 3.53 (two t, 2, NCH_2), 3.70, 2.96 (two s, 3, NCH_3), 1.11 (m, 11, C_5H_{11}).

Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.19; N, 19.42. Found: C, 58.58; H, 10.98; N, 19.81.

1-Hexyl-1-methylhydrazine.—A solution of *N*-nitrosohexylmethylamine (104.8 g, 0.727 mol) in anhydrous ether (500 ml) was added dropwise to a solution of lithium aluminum hydride (44.9 g, 1.18 mol) in anhydrous ether (1000 ml). The resulting mixture was refluxed for 1 hr and the excess lithium aluminum hydride was decomposed with water. Filtration of the mixture, followed by removal of the ether, gave an oil which was purified by distillation: yield 71.5 g (75.5%); bp 68–69° (15 mm); n^{20}D 1.4562; ir (neat) 3380, 3250 cm^{-1} (NH_2); nmr (neat) δ 3.02 (s, 2, NH_2), 2.45 (t, 2, NCH_2), 2.33 (s, 3, NCH_3), 1.13 (m, 11, C_5H_{11}).

Anal. Calcd for $C_7H_{18}N_2$: C, 64.56; H, 13.94; N, 21.51. Found: C, 64.91; H, 13.91; N, 21.65.

1-Hexyl-1-methyl-2-benzoylhydrazine.—A well-stirred solution of 1-hexyl-1-methylhydrazine (20.0 g, 0.154 mol) and triethylamine (17.3 g, 0.171 mol) in dry benzene (100 ml) was treated with benzoyl chloride (23.4 g, 0.166 mol) in dry benzene (100 ml), and the resulting mixture was refluxed for 1 hr. The mixture was cooled and treated with sodium hydroxide (14.9 g, 0.373 mol) in water (100 ml). Separation of the layers was followed by a further extraction of the aqueous layer with benzene. Removal of the benzene from the combined extracts gave white crystals (20.4 g, 0.087 mol, 56.5%) which upon recrystallization from ethanol–hexane melted at 81–82°: ir (Nujol) 3290 (NH), 1640 cm^{-1} (CO); nmr (DCCl$_3$) δ 8.21 (s, 1, NH), 7.55 (m, 5, C_6H_5), 2.75 (t, 2, NCH_2), 2.63 (s, 3, NCH_3), 1.08 (m, 11, C_5H_{11}).

Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.75; H, 9.46; N, 11.96. Found: C, 71.87; H, 9.28; N, 11.99.

Reaction of Phenyl Isocyanate with 1-Hexyl-1-methyl-2-benzoylhydrazine.—A mixture of 1-hexyl-1-methyl-2-benzoylhydrazine (5.80 g, 0.0248 mol) and phenyl isocyanate (3.09 g, 0.0259 mol) was heated to 170° for 3 hr, and the 1-hexene formed was collected in a receiver cooled with Dry Ice in acetone, yield 0.65 g (31.2%).

The pyrolysis residue (7.97 g) was chromatographed on silica gel in the same manner as was described under the pyrolysis of the aminimide. Products isolated in the order listed were benzanilide (1.65 g, 8.37 mmol, 33.8%), 1,3-diphenylurea (0.97 g, 4.57 mmol, 18.5%), 1-hexyl-1-methyl-2-benzoylhydrazine (3.65 g, 15.6 mmol, 62.9%), and 1-phenyl-3-methylurazole (1.56 g, 8.16 mmol, 33%).

Reaction of Hexylmethylaminoisocyanate with Phenyl Isocyanate.—A well-stirred cold solution of phosgene (11.4 g, 0.116 mol) in benzene (90 ml) was treated dropwise with a solution of 1-hexyl-1-methylhydrazine (10.0 g, 0.0773 mol) and quinoline (20.8 g, 0.161 mol) in benzene (50 ml), and the resulting mixture was stirred at room temperature for 1 hr. Removal of quinoline hydrochloride by filtration and benzene and excess phosgene by distillation under reduced pressure gave a viscous oil (17.8 g). The resulting oil was heated at 230–240° and the distillate was added to a solution of phenyl isocyanate (14.9 g, 0.118 mol) in benzene (20 ml). The resulting solution was refluxed for 1 hr, and the excess phenyl isocyanate and benzene were removed under reduced pressure. The white solid (1.86 g) obtained when chromatographed on silica gel using a mixture of benzene and ethyl acetate (1:1) as a solvent gave 1,3-diphenylurea (0.91 g, 4.3 mmol, 7.3%) and 1-phenyl-3-methylurazole (2) (0.61 g, 3.19 mmol, 4.1%).

1,1-Dihexyl-2-acetylhydrazine.—A well-stirred solution of 1,1-dihexylhydrazine (32.65 g, 0.163 mol) in benzene (100 ml) was treated with acetic anhydride (24.8 g, 0.243 mol) in benzene (100 ml). The resulting solution was cooled and treated with a slight excess of aqueous sodium hydroxide. The benzene layer upon removal of the solvent gave an oil which, upon purification by distillation, solidified: yield 35.1 g (0.145 mol, 88.8%); bp 118–120° (0.07 mm); mp 56–58°; ir (Nujol) 3300, 3125 (NH),

1685 cm^{-1} (C=O); nmr (DCCl$_3$) δ 7.76 (s, 1, NH), 2.64 (t, 4, N(CH$_2$)$_2$), 2.08, 1.91 (2 s, 3, CH_3CO), 1.23 (m, 22, (C$_5$H$_{11}$)$_2$).

Anal. Calcd for $C_{14}H_{30}N_2O$: C, 69.36; H, 12.48; N, 11.56. Found: C, 69.48; H, 12.53; N, 11.44.

1,1-Dihexyl-1-methyl-2-acetylhydrazonium *p*-Toluenesulfonate.—A solution of 1,1-dihexyl-2-acetylhydrazine (39.9 g, 0.165 mol) and methyl *p*-toluenesulfonate (46.0 g, 0.247 mol) in acetonitrile (100 ml) was refluxed for 29 hr. Removal of the solvent and excess methyl *p*-toluenesulfonate gave a dark brown oil (66.9 g) which was purified by chromatography on silica gel. Elution with ethyl acetate gave an initial fraction of methyl *p*-toluenesulfonate and 1,1-dihexyl-2-acetylhydrazine. The second fraction gave an oil (61.2 g, 0.143 mol, 86.7%) which on the basis of spectra was 1,1-dihexyl-1-methyl-2-acetylhydrazonium *p*-toluenesulfonate: ir (neat) 3480, 3250 (NH), 1710 (CO), 1190 cm^{-1} (SO$_3$$^-$); nmr (DCCl$_3$) δ 10.45 (s, 1, NH), 7.45 (q, 4, C_6H_4), 3.85 (t, 4, N(CH$_2$)$_2$), 3.39 (s, 3, NCH_3), 2.21 (s, 3, $CH_3C_6H_4$), 1.95 (s, 3, CH_3CO), 1.15 (m, 22, (C$_5$H$_{11}$)$_2$).

Anal. Calcd for $C_{22}H_{40}N_2O_4S$: C, 61.64; H, 9.41; N, 6.54. Found: C, 61.43; H, 9.65; N, 6.59.

1,1-Dihexyl-1-methylamine-2-acetylimide (1a).—1,1-Dihexyl-1-methyl-2-acetylhydrazonium *p*-toluenesulfonate (56.6 g, 0.132 mol), in chloroform (100 ml) was stirred with excess aqueous sodium hydroxide until the aqueous layer remained alkaline. The chloroform layer was separated and the solvent was removed under reduced pressure. The oil obtained was dried by adding dry benzene and distilling off the benzene. The product was a brown oil (26.4 g, 0.103 mol, 78%) which was homogeneous according to tlc analysis on silica gel using ethyl acetate as a solvent: ir (neat) 1580 cm^{-1} (CO); nmr (DCCl$_3$) δ 3.63 (t, 4, N(CH$_2$)$_2$), 3.18 (s, 3, NCH_3), 1.79 (s, 3, CH_3CO), 1.25 (m, 22, (C$_5$H$_{11}$)$_2$).

Anal. Calcd for $C_{15}H_{32}N_2O$: C, 70.25; H, 12.58; N, 10.93. Found: C, 70.34; H, 12.45; N, 11.11.

Pyrolysis of 1,1-Dihexyl-1-methylamine-2-acetylimide.—The aminimide (11.14 g, 0.0434 mol) was heated at 140° for 2 hr and the volatile products were trapped in a solution of aniline in dry toluene. The white solid formed in this solution was filtered and proved to be 1-methyl-3-phenylurea (1.98 g, 0.0131 mol, 32%), mp 149–150°. The filtrate upon distillation gave 1-hexene (2.33 g, 0.0277 mol 68%), bp 62–63°.

The residue (7.67 g) from the pyrolysis was analyzed by gas chromatography on a silicon rubber W98 column at 180° and found to consist of a mixture of dihexylmethylamine and 1-hexyl-1-methyl-2-acetylhydrazine in a ratio of 35.5:64.5. Identification was made by fractional distillation and comparison with authentic samples. Pyrolysis gave similar results at 175°.

1-Hexyl-1-methyl-2-acetylhydrazine.—A solution of 1-hexyl-1-methylhydrazine (20.45 g, 0.157 mol) in benzene (100 ml) was treated dropwise with acetic anhydride (16.0 g, 0.157 mol) in benzene (40 ml). The resulting solution was allowed to cool and then was treated with a slight excess of aqueous sodium hydroxide. The benzene layer upon removal of the solvent gave an oil which was purified by distillation: yield 21.3 g (78.7%); bp 85–87° (0.2 mm); n^{20}D 1.4568; ir (neat) 3300, 3110 (NH), 1670 cm^{-1} (C=O); nmr (DCCl$_3$) δ 8.80, 8.22 (2 s, 1, NH), 2.68 (m, 2, NCH_2), 2.59, 2.52 (2 s, 3, NCH_3), 2.03, 1.89 (2 s, 3, CH_3CO), 1.15 (m, 11, C_5H_{11}).

Anal. Calcd for $C_9H_{20}N_2O$: C, 62.74; H, 11.70; N, 16.27. Found: C, 62.68; H, 11.90; N, 16.38.

Registry No.—**1a,** 28538-65-0; **1b,** 28538-66-1; **2,** 28538-67-2; 1,1-dihexyl-2-benzylhydrazine, 28538-68-3; 1,1-dihexyl-1-methyl-2-benzoylhydrazonium *p*-toluenesulfonate, 28538-69-4; *N*-nitroso-*n*-hexylmethylamine, 28538-70-7; 1-hexyl-1-methylhydrazine, 28538-71-8; 1-hexyl-1-methyl-2-benzoylhydrazine, 28538-72-9; 1,1-dihexyl-2-acetylhydrazine, 28538-73-0; 1,1-dihexyl-1-methyl-2-acetylhydrazonium *p*-toluenesulfonate, 28538-74-1; 1-hexyl-1-methyl-2-acetylhydrazine, 28538-75-2.

Reaction of 2-Acyl-1,3-indandiones with 1,8-Naphthalenediamine. A New Route to 2-Substituted Perimidines

William A. Mosher* and Thurston E. Banks

Department of Chemistry, University of Delaware, Newark, Delaware 19711

A number of 2-acyl-1,3-indandiones reacted with 1,8-naphthalenediamine to give 2-substituted perimidines and 1,3-indandione. Under essentially the same conditions 2-diphenylacetyl-1,3-indandione gave 2-methyl-perimidine, 2,2'-o-phenylenediperimidine, and diphenylmethane. Mechanisms for these different reactions are presented. A number of new perimidines are described.

The reactions of 2-acyl-1,3-indandiones with diamines have been shown to give noncyclic or cyclic condensation products, depending upon the structure of the acyl group and the reaction conditions.[1-4] Among the cyclic compounds, indenopyrazolones and diazepinones have been reported from this laboratory.[2,4]

The specific reaction of 2-acyl-1,3-indandiones (1) with 1,8-naphthalenediamine (2) has now been investigated as a possible route to eight-membered heterocyclic compounds. We have found, however, that this reaction proceeds similarly to that reported by Sachs[5] between β-keto esters and 1,8-naphthalenediamine. In fact, 2-substituted perimidines[6a] (5a-j, Scheme I) and 1,3-indandione were obtained, instead of the expected 8-substituted benzo[3,4]cyclopenta[2,1-f]naphtho[1,8-b,c][1,5]diazocin-9(14H)-one[6b] (3).

The mechanism proposed for this reaction is shown in Scheme II and contains a series of nonisolable intermediates.

The absence of even small amounts of a noncyclized condensation compound among the reaction products indicates that ring closure of 6 occurs rapidly. The cleavage of 7 can be considered formally analogous to the cleavage of β diketones in the presence of bases.[7] The carbanion resulting from cleavage of a β diketone is stabilized through resonance with the remaining carbonyl group. In structure 7 the cleavage is even more favorable due to the presence of two carbonyl groups, either of which could stabilize the pair of electrons remaining with the indandione molecule.

The condensation of the 2-acyl-1,3-indandiones 1a-j with diamine 2 was run in ethanol, using a stoichiometric amount of p-toluenesulfonic acid as the catalyst. The perimidines were separated as the p-toluenesulfonic acid salts (4a-j) in yields of 50% or better. The other product of the reaction, 1,3-indandione, was isolated through column chromatography of the reaction residue and identified by comparison with an authentic sample.

The perimidine salts bearing an alkyl group in the 2 position are green, whereas those with an aryl group in

(1) R. A. Braun and W. A. Mosher, *J. Amer. Chem. Soc.*, **80**, 2749 (1958).

(2) R. A. Braun and W. A. Mosher, *J. Org. Chem.*, **24**, 648 (1959).

(3) W. A. Mosher and S. Piesch, *ibid.*, **35**, 1026 (1970).

(4) W. A. Mosher and S. Piesch, *ibid.*, **35**, 2109 (1970).

(5) F. Sachs, *Justus Liebigs Ann. Chem.*, **365**, 72, 156 (1909).

(6) (a) The possibility of the formation of 2-substituted perimidines from 1,8-naphthalenediamine and the acid-cleaved products (esters) of 2-acyl-1,3-indandiones, as suggested by the referee, is eliminated by the fact that 2-acyl-1,3-indandiones are not cleaved by acids. (b) The referee has suggested that the use of a weak acid and a nonalcoholic solvent in the reaction of 2-acyl-1,3-indandiones and 1,8-naphthalenediamine would favor the formation of the diazocinone 3. Unpublished work by W. A. Mosher and S. Piesch showed that the diazocinone 3 was not formed when this reaction was run in ethanol or in chlorobenzene in the presence of acetic acid as the catalyst.

(7) E. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinhart and Winston, New York, N. Y., 1959, pp 337–339.

SCHEME I

1a, R = CH$_3$
b, R = C$_2$H$_5$
c, R = CH(CH$_3$)$_2$
d, R = CH$_2$CH(CH$_3$)$_2$
e, R = C(CH$_3$)$_3$
f, R = CH$_2$C$_6$H$_5$
g, R = C$_6$H$_5$
h, R = p-CH$_3$C$_6$H$_4$
i, R = p-CH$_3$OC$_6$H$_4$
j, R = p-ClC$_6$H$_4$

this position are yellow-orange. The elemental analyses of these salts were found to agree with their molecular formulas.

Salts 4a-j were converted to the free bases (5a-j) by neutralization with dilute ammonium hydroxide. Several of these perimidines had previously been synthesized and in these cases the melting points were in agreement with those reported in the literature.

Unlike the acylindandiones 1a-j, 2-diphenylacetyl-1,3-indandione reacts with diamine 2 to give 2-methyl-perimidine (5a), 2,2'-o-phenylenediperimidine (11), and diphenylmethane. This different behavior is not completely unexpected, considering that 2-diphenyl-acetyl-1,3-indandione was found to be the only 2-acyl-1,3-indandione investigated to give with hydrazine a derivative with the hydrazono group in the indan ring.[1] A reasonable mechanism for the formation of compounds 11 and 5a is shown in Scheme III.

SCHEME II

SCHEME III

The assumption that diamine 2 attacks the indan carbonyl with subsequent ring opening (step 8 to 9) is supported by the results of a separate experiment where 1,3-indandione was allowed to react with 2. The only product isolated was 10-methyl-10-phthaloperinol (14) indicating that ring opening must have occurred along the following path.
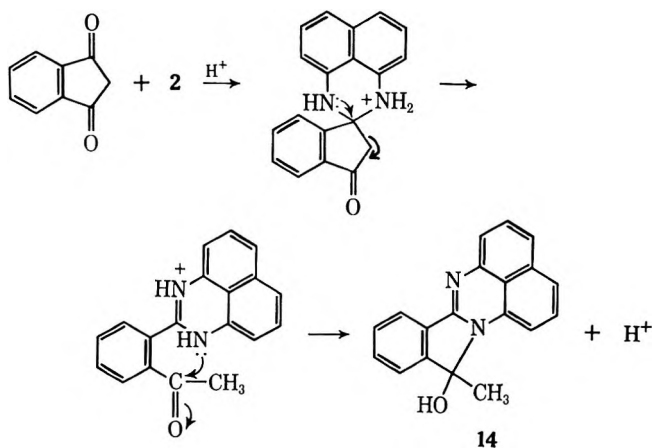
Once the ring opening has taken place, it is apparent that two subsequent cleavage reactions would account for the presence of 2-methylperimidine. The first of these cleavages (step 10 to 11) is formally analogous to that shown by β diketones and previously mentioned. That the second cleavage (step 12 to 5a) occurred is supported by the results of a separate experiment where
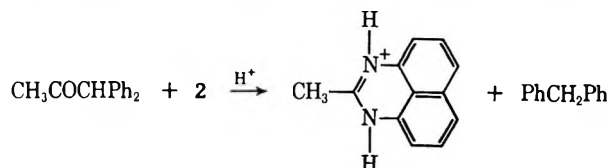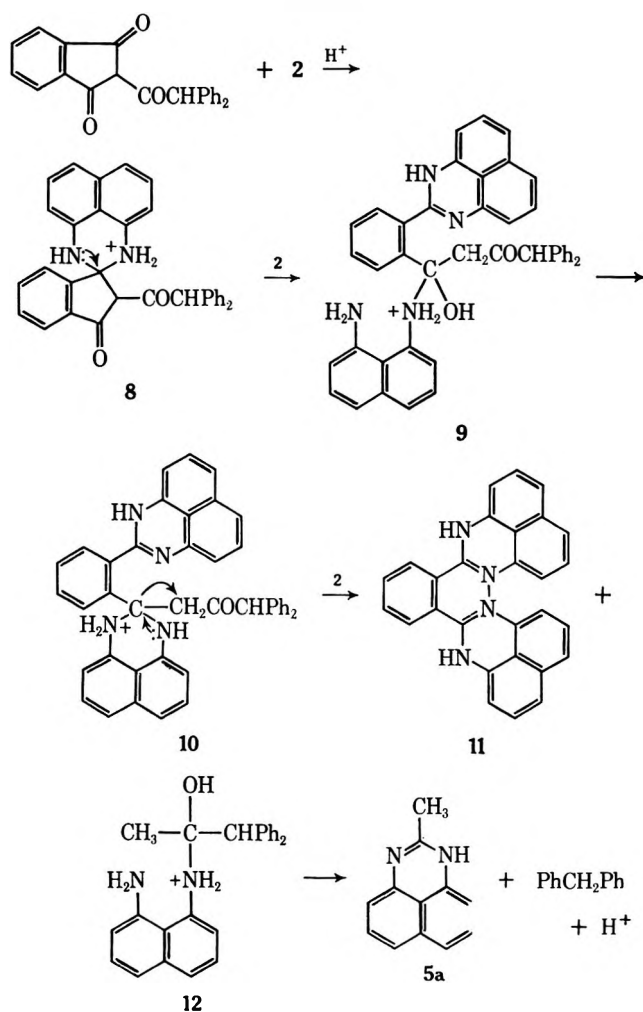
2-methylperimidine and diphenylmethane were obtained from the reaction of 1,1-diphenylacetone and diamine 2 in the presence of p-toluenesulfonic acid.

The identity of 5a, 11, and diphenylmethane was established by comparing the properties of these compounds with those of authentic samples prepared by independent routes.

In the condensation of 2-acyl-1,3-indandiones with diamines, such as hydrazines and o-phenylenediamines, to form noncyclic 1,1 adducts, several tests have been used thus far to indicate which of the available carbonyl groups participate in the reaction.[1,4,8] The results of this investigation show that formation of 1,3-indandione from the reaction of 2-acyl-1,3-indandiones with 1,8-naphthalenediamine may be used as another, more reliable, test to indicate that the side chain carbonyl is the reacting group.

Experimental Section[9]

2-Substituted Perimidine p-Toluenesulfonates (4a–j).—To a refluxing solution of diamine 2 (0.013 mol) and p-toluenesulfonic

(8) W. A. Mosher and I. S. Bechara, *J. Heterocycl. Chem.*, **7**, 843 (1970).

(9) Melting points were taken on a Fisher–Johns melting point apparatus between circular cover plates and are uncorrected. The infrared spectra were determined in potassium bromide pellets with a Perkin–Elmer Model 137 spectrophotometer. The ultraviolet spectra were taken on a Perkin-Elmer spectrophotometer, Model 202. The nuclear magnetic resonance spectra were obtained on a Varian Associates spectrometer, Model A-60A. Elemental analyses were performed by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, Max Planck Institute fur Kohlenforschung, Mülheim (Ruhr), West Germany; by the Micro Analysis, Inc., Marshallton, Del.; and by the M-H-W Laboratories, Garden City, Mich.

Table I
2-Substituted Perimidine p-Toluenesulfonates (4a-j)

Compd	R	Mp, °C[a]	Yield, %	Formula	Calcd, %			Found, %		
					C	H	N	C	H	N
4a	CH_3	285–287	72	$C_{19}H_{18}N_2O_3S$	64.39	5.12	7.91	64.70	5.36	7.77
4b	C_2H_5	281–283	63	$C_{20}H_{20}N_2O_3S$	65.19	5.47	7.60	65.20	5.33	7.68
4c	$CH(CH_3)_2$	280–282	50	$C_{21}H_{22}N_2O_3S$	65.94	5.80	7.33	65.78	5.60	7.25
4d	$CH_2CH(CH_3)_2$	258–260	55	$C_{22}H_{24}N_2O_3S$	66.64	6.10	7.07	66.51	5.93	6.93
4e	$C(CH_3)_3$	257–259	54	$C_{22}H_{24}N_2O_3S$	66.64	6.10	7.07	66.83	6.26	6.93
4f	$CH_2C_6H_5$	255–256	54	$C_{25}H_{22}N_2O_3S$	69.74	5.15	6.51	69.60	5.30	6.32
4g	C_6H_5	245–246	70	$C_{24}H_{20}N_2O_3S$	69.21	4.84	6.72	69.68	5.00	7.03
4h	$p\text{-}CH_3C_6H_4$	246–247	56	$C_{25}H_{22}N_2O_3S$	69.74	5.15	6.51	69.52	5.00	6.55
4i	$p\text{-}CH_3OC_6H_4$	287–288	50	$C_{25}H_{22}N_2O_4S$	67.24	4.97	6.27	67.06	5.18	6.39
4j	$p\text{-}ClC_6H_4$	310–312	62	$C_{24}H_{19}N_2O_3SCl$	63.92	4.25	6.21	63.79	4.34	6.05

[a] All compounds decompose at the melting point.

Table II
2-Substituted Perimidines (5a-j)

Compd	R	Mp, °C		Infrared spectrum, cm⁻¹		Chemical shift,
		Found	Lit.	NH	C=N and C=C	NH, δ (broad)[a]
5a	CH_3	210 dec	210[b]	3140	1645, 1610–1595[c]	9.41
5b	C_2H_5	182 dec	161[b]	3145	1645, 1605–1590[c]	7.00
5c	$CH(CH_3)_2$	146–147	143[d]	3150	1640, 1600	7.00
5d	$CH_2CH(CH_3)_2$	169–170		3160	1645, 1605–1595[c]	6.83
5e	$C(CH_3)_3$	162		3200	1640, 1595	7.00
5f	$CH_2C_6H_5$	197–198 dec	194[b]	3140	1645, 1605–1595[c]	7.00
5g	C_6H_5	188	187[b]	3150	1640, 1600	7.66
5h	$p\text{-}CH_3C_6H_4$	141–142		3160	1645, 1601	7.16
5i	$p\text{-}CH_3OC_6H_4$	210–211 dec	212[d]	3140	1640, 1595	7.00
5j	$p\text{-}ClC_6H_4$	172–173		3200	1640, 1600	7.16

[a] The NH proton in each case exchanged on addition of deuterium oxide and integrated after exchange for one proton. [b] See ref 5. [c] Doublet. [d] N. Buu-Hoi, P. Jacquignon, and M. Marty, *Bull. Soc. Chim. Fr.*, 461 (1960).

acid monohydrate (0.011 mol) in anhydrous ethanol (200–250 ml) was added dropwise over a 0.5–1-hr period a solution of the appropriate 2-acyl-1,3-indandione[10,11] (0.010 mol) in 65 ml of ethanol (except in 4j where the ethanolic solution of 1j was added in one portion). The mixture was refluxed for an additional 24 hr, concentrated to half-volume under reduced pressure, and cooled. The precipitate was collected by filtration, washed with ether, dried, and recrystallized from ethanol to give 4a–j, as green or yellow-orange crystals. Partial evaporation of the filtrate gave an additional amount of product. (The mother liquor A was saved and chromatographed as described below.) Yields, melting points, and analyses of compounds 4a–j are listed in Table I. These compounds show ir absorption bands in the 2700–2800-cm⁻¹ region (N⁺H₂), at 1650 (C=N or C=C) and 1150–1200 cm⁻¹ (asymmetric SO₂), and doublets at 1010–1050 cm⁻¹ (symmetric SO₂).

In the special case of compound 4a, the above quantities of reactants were changed to acylindandione 1a (0.026 mol), diamine 2 (0.036 mol), p-toluenesulfonic acid (0.027 mol), and ethanol (450 ml). For compound 4j, 600 ml of ethanol was used.

The mother liquor A was evaporated to dryness and the residue dissolved in chloroform (4 ml) and chromatographed on activated alumina (elution with chloroform). The compounds isolated from the column in order of elution were diamine 2, 1,3-indandione, and unreacted 2-acyl-1,3-indandione.

Most of the 1,3-indandione dimerized on the alumina, as indicated by the appearance of a bright purple band at the head of the column, which did not elute with chloroform. This band was removed from the alumina by extraction with water. The resulting purple solution was acidified with 6 N hydrochloric acid and the precipitate was crystallized from dioxane to give bright yellow crystals of [Δ¹,²'-biindan]-1',3,3'-trione (bindone), mp 210–211° (lit.[12,13] 208–211°). Mixture melting point showed no depression. An authentic sample of 1,3-indandione chromatographed and extracted following the above procedure gave an identical product (mixture melting point showed no depression).

2-Substituted Perimidines (5a–j).—The general procedure used to prepare these compounds is illustrated by the preparation of 5g. To a stirred slurry of finely pulverized 4g (1 g, 0.0024 mol) in water (100 ml) was added concentrated ammonium hydroxide (4 ml). After standing for 4 hr, the precipitate was collected by filtration, washed with water until the washings were neutral, and dried at 60° *in vacuo* to yield 0.59 g (100%) of 5g. The melting points, ir absorption frequencies, and NH chemical shifts of perimidines 5a–j are listed in Table II.

Reaction of 2-Diphenylacetyl-1,3-indandione with Diamine 2. —A solution of 2-diphenylacetyl-1,3-indandione (17 g, 0.05 mol) in ethanol (1000 ml) was added in one portion to a refluxing solution of compound 2 (10 g, 0.065 mol) and p-toluenesulfonic acid monohydrate (10 g, 0.053 mol) in ethanol (500 ml), and the mixture refluxed as described in the method for preparing compounds 4. Upon cooling in ice unreacted 2-diphenylacetyl-1,3-indandione (13.2 g) was recovered by filtration. Successive evaporation and cooling of the filtrate gave a precipitate, which through fractional crystallization from ethanol yielded 1.9 g (27% based on diamine 2 available) of 4a as green platelets, mp 285–287° (this salt neutralized with ammonium hydroxide gave 5a as shown by mixture melting point with an authentic sample prepared from 2-acetyl-1,3-indandione as described above), and 2.5 g (20% based on diamine 2 available) of the p-toluenesulfonic acid salt of 2,2'-o-phenylenediperimidine as bright yellow needles, mp >300°.

Anal. Calcd for $C_{42}H_{34}N_4O_6S_2$: C, 66.83; H, 4.54; N, 7.42. Found: C, 66.77; H, 4.62; N, 7.31.

The above salt, neutralized with ammonium hydroxide, gave a product which was found identical (ir and nmr spectra) with an authentic sample of 11 prepared by a different route (see below).

The mother liquor, after separation of 4a and of the p-toluenesulfonic acid salt of 11, was taken up in chloroform, concentrated to approximately 20 ml, and chromatographed on activated alumina (elution with chloroform). Evaporation of the first fraction gave 0.25 g of diphenylmethane, identified by spectral comparison with an authentic sample.

2,2'-o-Phenylenediperimidine (11).—A solution of 2-(2-perimidyl)benzoic acid[14] (2 g, 0.007 mol) and p-toluenesulfonic

(10) L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

(11) R. L. Horton and K. C. Murdock, *J. Org. Chem.*, **25**, 938 (1960).

(12) W. Wislicenus and A. Kötzle, *Justus Liebigs Ann. Chem.*, **252**, 72 (1889).

(13) K. C. Murdock, *J. Org. Chem.*, **24**, 845 (1959).

(14) F. Sachs, *Justus Liebigs Ann. Chem.*, **365**, 60 (1909).

acid (1.32 g, 0.007 mol) in ethanol (250 ml) was added dropwise over a 1-hr period to a refluxing solution of compound 2 (2.2 g, 0.014 mol) and *p*-toluenesulfonic acid (1.32 g, 0.007 mol) in ethanol (100 ml). The mixture was refluxed for 24 hr and cooled in ice. A small amount of the *p*-toluenesulfonic acid of 2 was separated by filtration and the filtrate was concentrated *in vacuo* to approximately 150 ml and cooled in ice. The precipitate was collected by filtration and washed with ether until all the formed 10-phthaloperinone was removed. Recrystallization of the residue from ethanol yielded 1.6 g (30%) of the *p*-toluenesulfonic acid salt of 11 as bright yellow needles, mp >300°. This salt was neutralized with ammonium hydroxide. Chromatography on alumina of the resulting red solid and recrystallization from dimethylformamide–water gave 11, mp >300°.

Anal. Calcd for $C_{28}H_{18}N_4$: C, 81.93; H, 4.42; N, 13.65. Found: C, 81.84; H, 4.88; N, 13.47.

Reaction of 1,3-Indandione with Diamine 2. 10-Methyl-10-phthaloperinol (14).—To a refluxing solution of 2 (1.58 g, 0.01 mol) and *p*-toluenesulfonic acid monohydrate (1.9 g, 0.01 mol) in ethanol (100 ml) was added dropwise over 0.5 hr a solution of 1,3-indandione (1.46 g, 0.01 mol) in ethanol (100 ml). The mixture was refluxed for an additional 24 hr, concentrated to *ca.* 50 ml under reduced pressure, and cooled in ice to give 2.7 g (54%) of the *p*-toluenesulfonic acid salt of 14 with ethanol of crystallization as bright red-orange needles, mp 114–124°, with softening and evolution of ethanol. Removal of the ethanol of crystallization was carried out by refluxing a mixture of the above salt (2.7 g) with acetone (250 ml) for 24 hr, collecting the solid by filtration, and washing with acetone. A 62% yield was obtained.

To a slurry of the above *p*-toluenesulfonic acid salt (1.6 g, 0.0035 mol) in water (50 ml) was added concentrated ammonium hydroxide (2 ml); the mixture was allowed to stand for 4 hr.

The yellow precipitate collected by filtration, washed with water until free of ammonia, and dried at 60° *in vacuo* gave 1.0 g (100%) of a product which was found identical (mixture melting point, ir, and nmr) with an authentic sample of 14, prepared from phthalic acid and diamine 2 following the method of Sachs.[15]

Reaction of 1,1-Diphenylacetone with Diamine 2.—A solution of 1,1-diphenylacetone (4.2 g, 0.02 mol) in ethanol (75 ml) was treated with a solution of diamine 2 (3.2 g, 0.02 mol) and *p*-toluenesulfonic acid monohydrate (3.8 g, 0.02 mol) in ethanol (200 ml), following the procedure described above for compound 14. Upon cooling, 5.7 g (80%) of green platelets was separated and identified as 4a. The filtrate was evaporated and the dark gummy residue taken up in chloroform and chromatographed on alumina gave diphenylmethane, identified by spectral comparison with an authentic sample.

(15) F. Sachs, *Justus Liebigs Ann. Chem.*, **365**, 117, 120 (1909).

Tetrahydroindan Derivatives. Products from the Diels–Alder Condensation of 1-Vinylcyclopentene and *trans-o*-Methyl-β-nitrostyrene

BARTLETT D. WHELTON[1] AND ALAIN C. HUITRIC*

College of Pharmacy, University of Washington, Seattle, Washington 98105

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Three isomeric 5-*o*-tolyl-4-nitro- and 4-*o*-tolyl-5-nitro-3a,4,5,6-tetrahydroindans (compounds 1, 2, and 3) were obtained from the Diels–Alder condensation of 1-vinylcyclopentene and *trans-o*-methyl-β-nitrostyrene. The presence of the fourth isomer was not detected. Structure assignment was done by nmr.

Vapor phase chromatography (vpc) of the product of the Diels–Alder condensation of *trans-o*-methyl-β-nitrostyrene and 1-vinylcyclopentene indicated three components which were designated 1, 2, and 3 according to the order of emergence from a QF-1 column. The integrated peaks were in the approximate ratio of 2:1:1, respectively. The products were separated by descending dry column chromatography[2] on silica gel. The presence of the fourth isomer was not detected. The isolated isomers were characterized by nmr to be *trans*-4-nitro-*cis*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (1), *cis*-4-*o*-tolyl-*trans*-5-nitro-3a,4,5,6-tetrahydroindan (2), and *cis*-4-nitro-*trans*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (3).[3] Compound 1 was isomerized to 5 when chromatographed on acid-washed alumina or by treating with base. Compounds 2, 3, and 5 were desired as possible intermediates for the preparation of certain cyclopentanohexahydrophenanthridines.

Characterization by nmr was done from the signals of the hydrogens at C-4 and C-5, which are isolated

from those of the other alicyclic hydrogens. The signal of the hydrogen on the nitro-bearing carbon is readily recognized because of the large deshielding resulting from the electronegativity and magnetic anisotropy of the nitro group.[4] The signal of the hydrogen on the *o*-tolyl-bearing carbon is also recognizable from other signals, as shown for *trans*-4-nitro-5-*o*-tolycyclohexene-3,3,6,6-d_4 (6)[5] (see Table I for chemical shift data). The positions of the substituents, C-4 *vs.* C-5, are readily determined from the multiplicity of the signals. H-4 is adjacent to only two hydrogens and its signal will be either a triplet or a quartet (doublet of doublets), while the signals of H-5 will be more complex because of spin–spin splitting by three adjacent hydrogens. Thus, structures 1 and 3 can be differentiated from their positional isomers 2 and 4. Differentiation between diastereomers is readily done from the widths of the signals of H-4 and H-5; for example, in isomer 3, in its most probably conformation, H-4 is axial and coupled with axial H-5 and pseudoaxial H-4a, while in the diastereo-

(1) (a) Public Health Service Predoctoral Fellow 5-F01-GM-34,830; (b) abstracted in part from the Ph.D. dissertation of B. D. Whelton, University of Washington, 1970.

(2) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

(3) In the nomenclature adopted the configuration of the substituents (cis or trans) is related to the axial bridgehead hydrogen on C-3a.

(4) (a) A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962); (b) W. F. Trager, F. F. Vincenzi, and A. C. Huitric, *ibid.*, **27**, 3006 (1962); (c) D. B. Roll, B. J. Nist, and A. C. Huitric, *Tetrahedron*, **20**, 2851 (1964).

(5) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *ibid.*, **19**, 2145 (1963).
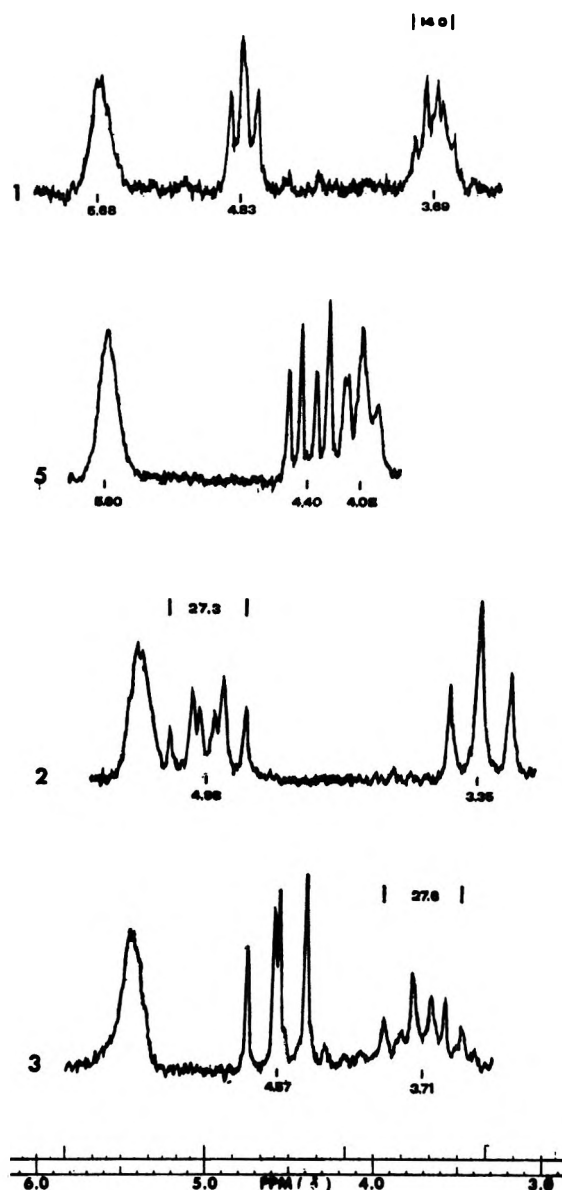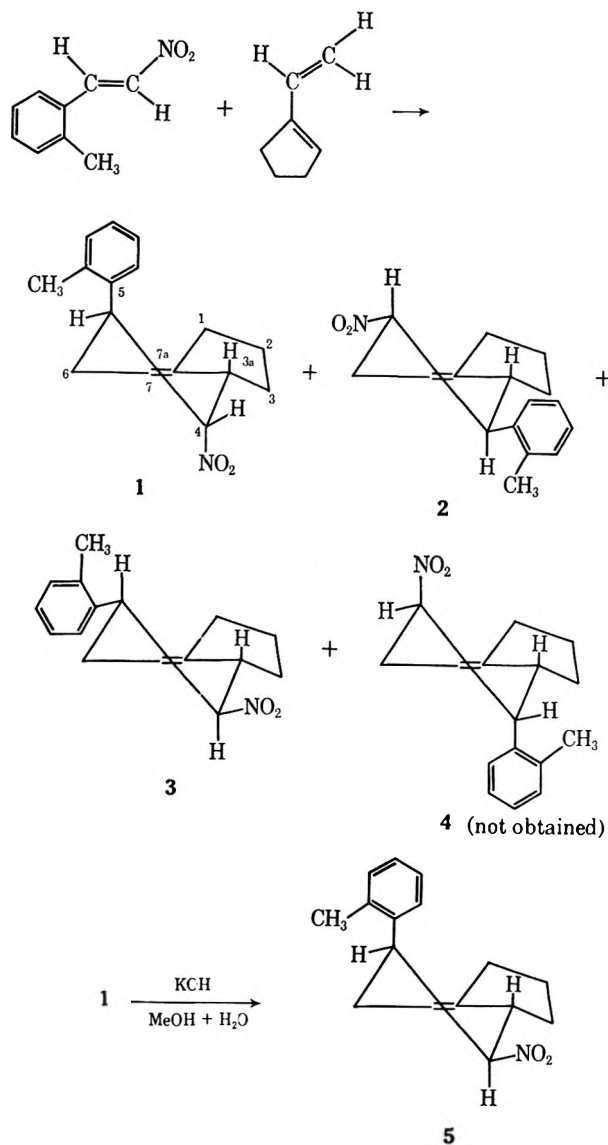
Figure 1.—Portions of 60-MHz nmr spectra of **1**, **5**, **2**, and **3** in carbon tetrachloride. Chemical shifts are in δ units with TMS as internal reference.

TABLE I

CHEMICAL SHIFT DATA FOR THE 4,5-DISUBSTITUTED 3a,4,5,6-TETRAHYDROINDANS AND RELATED COMPOUNDS[a]

Compd	Solvent	HCNO₂	HCPh	Tolyl arom	Tolyl CH₃	Vinylic
1	CCl₄	4.83	3.69	7.05	2.39	5.68
2	CCl₄	4.98	3.35	7.09	2.35	5.39
	Pyridine	≃ 5.38	3.43	...	2.38	≃ 5.38
3	CCl₄	4.57	3.71	7.07	2.34	5.45
5	CCl₄	4.40	4.08	7.02	2.15	5.60
6[b]	CCl₄	4.93	3.69	7.10	2.36	5.41
7[c]	CCl₄	4.71	3.40	7.09	2.33	...

[a] Expressed in δ units; TMS used as internal reference. [b] *trans*-4-Nitro-5-o-tolylcyclohexene-3,3,6,6-d_4.[5] [c] *trans*-2-o-Tolylnitrocyclohexane-3,3,6,6-d_4.[5]

mer **1** H-4 is cis to the bridgehead axial H-3a and can never assume an axial orientation. The sum of J_{43a} and J_{45} will be smaller in **1** than in **3** regardless of the conformation of **1**. Likewise, the sum of the coupling constants of H-5 with the three adjacent hydrogens is larger for **3** than for **1**. Only one half-chair conformation is possible because of the fixed orientation of bridgehead H-3a, but other flexible conformations are not excluded. The same reasoning applies to the relative widths of the signals of H-5 in **1** and **3**. Differentiation

between diastereomers **2** and **4** is done in the same manner.

Figure 1 gives the spectra of the signals of H-4, H-5, and H-7 for compounds **1**, **2**, **3**, and **5**. Compound **1** gives spectrum 1. The signal of the hydrogen on the nitro-bearing carbon is at δ 4.83 and that on the tolyl-bearing carbon is at δ 3.69. The relative multiplicity of the two signals establishes that the nitro group is on C-4 and the tolyl group on C-5. The widths of the signals, 9.6 Hz for H-4 and 14.0 Hz for H-5, establish the configuration shown in structure **1**. Analysis of the apparent triplet of H-4 at δ 4.83 shows unequal spacing between peaks and indicates coupling constants of 5.2 and 4.4 Hz for H-4 with H-3a and H-5. Skewness of the signal toward the upfield direction prevents complete resolution of the expected doublet of doublets. A dynamic equilibrium between several conformations is expected but the widths of the signals of H-4 and H-5 suggest that on a time average there is a considerable population of the half-chair conformation depicted in structure **1** with both substituents having essentially

axial orientations. The spectrum of 5, the compound resulting from epimerization of 1 at C-4, is also very relevant in the characterization of 1. The signal of H-4 at δ 4.40 is a four-peak multiplet, J_{43a} = 9.8 and J_{45} = 4.4 Hz, and is consistent with H-4 having essentially an axial orientation and being coupled with one axial and one equatorial hydrogen. The signal of H-5 at δ 4.08 has a width of 12.3 Hz and is slightly narrower than in 1. On the basis of the known J_{54} of 4.4 Hz from the signal of H-4, the splitting pattern of H-5 indicates that H-5 is coupled unequally with the hydrogens on C-6 ($J_{56(axial)}$ = 6.7 and $J_{56(eq)}$ $\simeq$ 1.2 Hz). This indicates that the time average dihedral angle between H-5 and equatorial H-6 is different from that between H-5 and axial H-6. The widths of the signals of H-4 and H-5 indicate that on a time average there is a considerable population of the conformation depicted by structure 5.

Compound 3 gives spectrum 3. The relative multiplicity of the signals at δ 4.57 and 3.71 establishes that the nitro group is on C-4 and the tolyl group on C-5. The signal of H-4 (doublet of doublets) yields coupling constants of J_{45} = 11.3 and J_{43a} = 9.6 Hz and clearly indicates that H-4 is axial and coupled with two axial hydrogens.[5] The width of the signal of H-5 (δ 3.71) of approximately 27.6 Hz is consistent with H-5 being axial and coupled with two axial and one equatorial hydrogens. The complexity of the signal of H-5 indicates that there is averaging of coupling constants of $J_{56(eq)}$ and $J_{56(axial)}$. Spectrum 3 definitely establishes that 3 is the diastereomer of 1 and that it has the configuration and conformation depicted by structure 3.

Spectrum 2 establishes that compound 2 has the nitro group on C-5 and the tolyl group on C-4 and that both substituents have the equatorial orientation as depicted in structure 2. The signal of H-4 at δ 3.35 gives an apparent triplet with slightly unequal spacings, 11.3 and 10.3 Hz. This establishes that H-4 is axial and coupled with two axial hydrogens. The slight difference in spacings indicates a small difference in coupling constants between J_{45} and J_{43a}. The former is probably the largest. Skewness to the right (toward the signal of H-3a) of the expected four-peak multiplet prevents the resolution of the inner components into discrete peaks. The width of the signal of H-5 (27.3 Hz) clearly indicates that H-5 has the axial orientation and is coupled with two axial and one equatorial hydrogens. The complexity of the signal indicates that there is averaging of coupling constants of $J_{56(eq)}$ and $J_{56(axial)}$ resulting from the closeness of chemical shifts of the axial and equatorial hydrogens on C-6. This averaging of coupling constants precludes the determination of coupling constants between H-5 and C-6 hydrogens by first-order approximation, but it does not change the width of the signal of H-5. The sum of the coupling constants is not affected.[6] The observed multiplet is consistent with J_{54} = 11.2 Hz and averaging of coupling constants of axial and equatorial C-6 hydrogens with H-5 to give apparent constants of 8.2 and 8.0. A sum of 16.2 Hz is not unreasonable for the two coupling constants since it has been observed that geminal and vicinal coupling constants of hydrogens on carbons in proximity to an sp^2

hybridized carbon are often increased.[7] The spectrum of 2 was also determined in pyridine, in which case the signal of H-5 overlapped the signal of the vinylic hydrogen at about δ 5.38. The width of the signal was unchanged and the separation of the two outer components was again 8.0 Hz, indicating that the difference in chemical shifts of the two hydrogens on C-6 is still small. The position of the signals of the C-6 hydrogens cannot be determined with certainty. In pyridine the signal of H-4 is shifted to δ 3.43 but is otherwise identical with that in spectrum 2.

Experimental Section

All nmr spectra were recorded on a Varian A-60 spectrometer at *ca.* 37° utilizing ~20% w/v solutions with tetramethylsilane (TMS) as the internal reference. Infrared spectra were determined using a Beckman IR-5-A infrared spectrophotometer. Melting points were determined on the Kofler micro hot stage and are uncorrected. The Aerograph 204 gas chromatograph was employed for all vpc analyses. Elemental analyses were conducted by the Huffman Laboratories, Wheatridge, Colo. The silica gel used was Brinkmann 0.05–0.2 mm (70–325 mesh). For the sake of uniformity and reproducibility, the silica gel was always heated at 120° for 48 hr prior to deactivation. The hexane used for chromatography was purified by shaking with concentrated sulfuric acid and distillation over calcium hydride as the final purification step. Reagent grade carbon tetrachloride was used without purification.

1-Vinylcyclopentene.[8]—1-Ethynylcyclopentanol[9] was reduced to 1-vinylcyclopentanol by the general method of acetylene reduction described by Augustine[10] using 5% palladium on barium sulfate. The product, fractionated with a spinning band column, was found by vpc on QF-1 to contain less than 10% of the saturated alcohol. Dehydration by potassium bisulfate[11] gave 1-vinylcyclopentene of about 90% purity.

trans-4-Nitro-*cis*-2-*o*-tolyl-3a,4,5,6-tetrahydroindan (1), *cis*-4-*o*-Tolyl-*trans*-5-nitro-3a,4,5,6-tetrahydroindan (2), *cis*-4-Nitro-*trans*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (3), and *cis*-4-Nitro-*cis*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (5).—Compounds 1, 2, and 3 were synthesized essentially by the methods known for the Diels-Alder condensation of β-nitrostyrenes and butadiene.[4b] A solution of 28.6 g of a mixture of olefins containing at least 90% 1-vinylcyclopentane, 18.37 g (0.112 mol) of *trans*-*o*-methyl-β-nitrostyrene,[4b] 15 ml of toluene, and 50 mg of hydroquinone was heated under nitrogen at 90–95° in a small stainless steel Parr bomb for 4 days. Periodic vpc analysis on a QF-1 column showed the formation of three products which remained in the same ratio of about 2:1:1 throughout the progress of the reaction. Removal of the volatile material yielded an orange-brown oil from which isomers 1, 2, and 3 were obtained by a sequence of dry column[2] chromatography procedures. The initial purification was done by placing the content of the reaction mixture (impregnated on some silica gel) on a 4-ft column containing 2000 g of silica gel deactivated with 15% of water (Brockmann Activity III[2]). Elution with 3 l. of 1:19 carbon tetrachloride-hexane solution removed the hydrocarbon materials. The column was next eluted with 3 l. of carbon tetrachloride to give 18.4 g of yellow oil containing 1 in greater amount and 3 in lesser amount. A final elution, with 3 l. of carbon tetrachloride, gave 7.9 g of yellow oil containing 2 in greater amount, some 3, and small amounts of 1 and of the starting styrene. The final sepration of these mixtures was done by the dry column technique using a 3:2 (by volume) carbon tetrachloride-hexane mixture and 15% water-deactivated silica gel equilibrated with 10% (by weight) of the solvent mixture. Optimal results were achieved when a 4 ft by 46 mm column was used for 3 g of mixture. The separated isomers were treated with decolorizing carbon in hexane.

(6) (a) W. F. Trager, B. J. Nist, and A. C. Huitric, *Tetrahedron Lett.*, 2931 (1965); (b) W. F. Trager, B. J. Nist, and A. C. Huitric, *J. Pharm. Sci.*, 56, 698 (1967), and references therein.

(7) W. F. Trager and A. C. Huitric, *ibid.*, 56, 1111 (1967), and references therein.

(8) V. F. Kucherov and E. P. Serebryakov, *Izv. Akad. Nauk SSSR., Otd. Khim. Nauk*, 1057 (1960); *Chem. Abstr.*, 55, 475 (1961).

(9) O. F. Beumel and R. F. Harris, *J. Org. Chem.*, 29, 1872 (1964).

(10) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, p 69.

(11) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, 20, 1178 (1955).

Compound 1 failed to crystallize and elemental analysis was obtained on its solid epimer 5 which was obtained by dry column chromatography of 1 on Merck acid-washed alumina (activity II[2]) and carbon tetrachloride or by isomerization of 1 under basic conditions (0.37 equiv KOH) in a 12:1 methanol-water solution. Neutralization of the basic solution with aqueous ammonium chloride solution yielded a mixture of 5 and 1 in a ratio of 7:3 (vpc on QF-1) from which 5 crystallized out in methanol. The isomerization was repeated on the residue.

Compound 2 gave colorless crystals from 2-propanol: mp 95.5-97°; ir (KBr) 1372 and 1540 (NO₂). Compound 3 gave colorless crystals from methanol: mp 91.8-92.2°; ir (KBr) 1378 and 1537 (NO₂). Compound 5 gave colorless crystals from methanol: mp 103.5-104°; ir (KBr) 1355 and 1520 (NO₂).

Anal. Calcd for $C_{16}H_{19}NO_2$: 74.68; H, 7.44; N, 5.44. Found for 2: C, 74.42; H, 7.63; N, 5.27. Found for 3: C, 74.29, H, 7.48; N, 5.37. Found for 5: C, 74.47; H, 7.39; N, 5.21.

Registry No.—1, 28638-60-0; 2, 28638-61-1; 3, 28638-62-2; 5, 28638-63-3; 1-vinylcyclopentene, 28638-58-6; *trans-o*-methyl-β-nitrostyrene, 28638-59-7.

Unique Formation of a Benzocyclobutene Derivative.
The Diazotization of 3-Amino-4-*tert*-butyl-5-nitrobenzoic Acid[1]

MICHAEL H. KNIGHT, THOMAS PUTKEY, AND HARRY S. MOSHER*

Department of Chemistry, Stanford University, Stanford, California 94305

We have observed an unusual ring closure reaction leading to the formation of 1,1-dimethyl-4-carboxyl-6-nitrobenzocyclobutene (4a, the major isolated product, 41% crude yield) during the decomposition of the diazonium salt from 3-amino-4-*tert*-butyl-5-nitrobenzoic acid (3a). The methyl ester 3b gave comparable results. This benzocyclobutene derivative was formed in approximately the same yield when the dilute sulfuric acid solution of the diazonium salt was heated (65°), was photolyzed (0°) with ultraviolet light, or was heated (65°) with copper bronze. However, treatment with cuprous bromide in hydrobromic acid gave the normal bromo derivative (47% yield with 44% recovered starting amine); no benzocyclobutene was observed under these conditions. The 1,1-dimethyl-4-carboxyl-6-nitrobenzoic acid was reduced to the corresponding amine which underwent normal diazotization and decomposition of the diazonium compound to give the corresponding phenol.

A recent report by Martinson[2] concerning a reaction leading to the closure of a five-membered ring to give indans (2) during deamination of certain *o*-alkylanilines (1) has prompted us to publish the following observation encountered during an attempt to synthesize 3-hydroxy-4-*tert*-butyl-5-nitrobenzoic acid.

Martinson found indan (2, R, R' = H; 13%), 2-methylindan (2, R = H; R' = Me; 35%), and 2,2-dimethylindan (2, R, R' = Me; 88%) to be formed along with the expected phenol from the diazotization of *o*-propyl-, *o*-isobutyl-, and *o*-neopentylanilines, respectively.
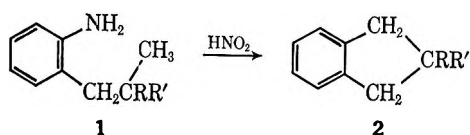
We have found that deamination of the *o-tert*-butylaniline derivative 3a failed to give any appreciable amount of the expected 3-hydroxy-4-*tert*-butyl-5-nitrobenzoic acid; instead, the major product was identified as 1,1-dimethyl-4-carboxy-6-nitrobenzocyclobutene 4a (41% crude yield, 27% purified yield, isolated as its methyl ester) by its analysis and spectral properties. The deamination of the methyl ester 3b followed a parallel course. The diazotization was carried out with sodium nitrite in sulfuric acid (nitrosoylsulfuric acid). The decomposition was either done by heating to 65°, by heating to 65° in the presence of copper bronze, or by irradiating at 0° with ultraviolet light (2537 Å, quartz vessel) with no significant change in the yield of the benzocyclobutene 4a.

The benzocyclobutene structure of this product is derived from the following evidence. The acid 4a no
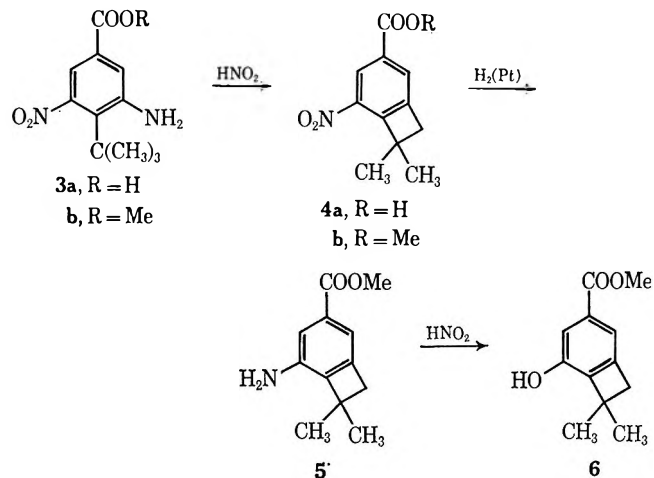
longer shows an nmr signal for a *tert*-butyl group but instead has a singlet δ 1.58 (6 H) assigned to the *gem*-dimethyl protons of the cyclobutene ring. No previous examples of *gem*-dimethylbenzocyclobutenes have been published for comparison, but there is no reason to suppose that the chemical shift for such a signal would differ widely from that of a normal *tert*-butylbenzene derivative; *i.e.*, *p-tert*-butyltoluene, δ 1.32; *o-tert*-butylnitrobenzene, δ 1.40; 3-amino-4-*tert*-butyl-5-nitrobenzoic acid, δ 1.50; and *o-tert*-butylphenol,[3] δ 1.37. The singlet at δ 3.11 (2 H) is assigned to the methylene protons of the cyclobutene ring. This chemical shift is in accord with that reported for the methylene protons of benzocyclobutene itself (δ 3.14)[4a] and compatible with that reported for 1,1-dichloro-3,4,5,6-tetramethylbenzocyclobutene (δ 3.8).[4b] The spectrum shows two signals centered at δ 8.10 (1 H) and 8.70 (1 H) assigned

(1) We gratefully acknowledge support by the National Institutes of Health (NIH RO1GM 16031-09).

(2) P. Martinson, *Acta Chem. Scand.*, **22**, 1357 (1968).

(3) K. C. Dewhirst and C. A. Reilly, *J. Org. Chem.*, **30**, 2870 (1965).

(4) (a) F. A. Bovey, "NMR Data Tables for Organic Compounds," Vol. I, Interscience, N. Y., 1967, p 203; (b) H. Hart and R. W. Fish, *J. Amer. Chem. Soc.*, **82**, 749 (1960).

to the meta aromatic protons at C-3 and C-5, respectively, and a singlet at δ 11.57 (1 H) assigned to the carboxylic acid proton.

The acid **4a** is readily converted to the methyl ester **4b**, whose ir, uv, mass, and nmr spectra are completely compatible with this structure. The nmr signals for the two aromatic protons centered at δ 8.02 and 8.59 clearly show a spin–spin coupling constant of 1 Hz which is in the characteristic range for meta hydrogens.

Catalytic reduction of the nitro group of the methyl ester **4b** gave the corresponding amine **5** whose diazonium salt decomposed at 0° to yield 1,1-dimethyl-4-carbomethoxy-6-hydroxybenzocyclobutene (6) whose structure follows from its analysis, method of synthesis, spectral properties, and reactions characteristic of hindered phenols.

This phenol gives a negative ferric chloride test and is insoluble in sodium carbonate but does dissolve in cold 10% sodium hydroxide solution from which it can be regenerated unchanged by neutralization, as expected for a hindered phenol.[5] The evidence that this phenol has structure 6 rather than an isomeric structure such as **7a** or **7b** (R = H) rests on these "cryptophenol" properties. The relatively unhindered phenols repre-

7a　　　　　　　**7b**
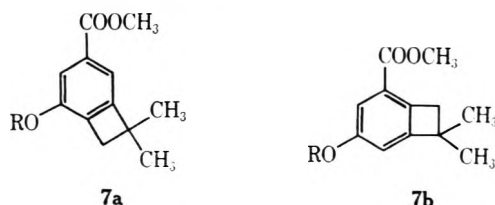
sented by **7a** and **7b** should give a positive ferric chloride test. We therefore conclude that phenol **6** has the unrearranged structure shown and that the structure of the nitro compound is as shown in **4** and not that of an isomeric product.

The phenol 6 was converted to the methyl ether by treatment with sodium hydride and dimethyl sulfate. A degassed vacuum-sealed nmr sample showed no enhancement of the methyl ether signal when the *gem*-dimethyl signal was irradiated (negative nuclear Overhauser effect); however irradiation of the aromatic proton signal caused the methylene signals (which were a close triplet, δ 2.78, 2 H, *J* = 0.8 Hz) to collapse to a singlet.[6] The only reasonable explanation for this decoupling result is that the methylene protons are situated as shown in **6** and experience a long-range coupling to the neighboring aromatic proton. This also rules out the isomeric structures **7a** and **7b**.

We have not made a mechanistic study of this unusual ring closure reaction but a few comments concerning the course of the reaction seem warranted. The diazotization of **3a** in hydrobromic acid followed by warming with cuprous bromide is reported to give the corresponding bromide in the expected manner;[7] we have confirmed this. Therefore the unique benzocyclobutene formation must be associated with the conditions used in the attempted phenol formation. Furthermore, the normal conversion of methyl 3-amino-

4-*tert*-butylbenzoate to its phenol has been reported.[3] Thus our results must be associated in some way with the buttressing effect of the 5-nitro group of **3**.

Our results may be accommodated by postulating an intramolecular electrophilic substitution by the carbon of an aromatic cation on the C–H of the side chain (either "front lobe" or "back lobe" attack of the sp³ orbital) analogous to that discussed by Martinson[2] in the indan cases **1** → **2** or by Barclay and McDonald[9] in the example **8** → **9** → **10** involving a benzylic cation
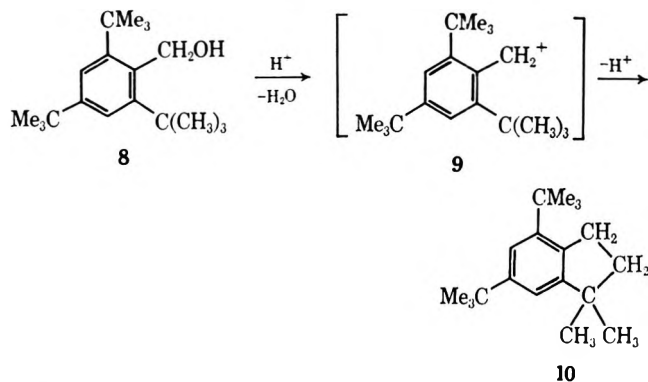
instead of an aromatic cation. This is repeated in the benzocyclobutene case by **12** → **4a**. Alternatively, a benzyne intermediate can be postulated[10] for the present example as shown in sequence **11** → **12** → **13** → **14** in which the benzyne reacts within the solvent cage with isobutylene to give the product **4a**. The 2 + 2 addition of benzynes is well established.[4a,9] Such a
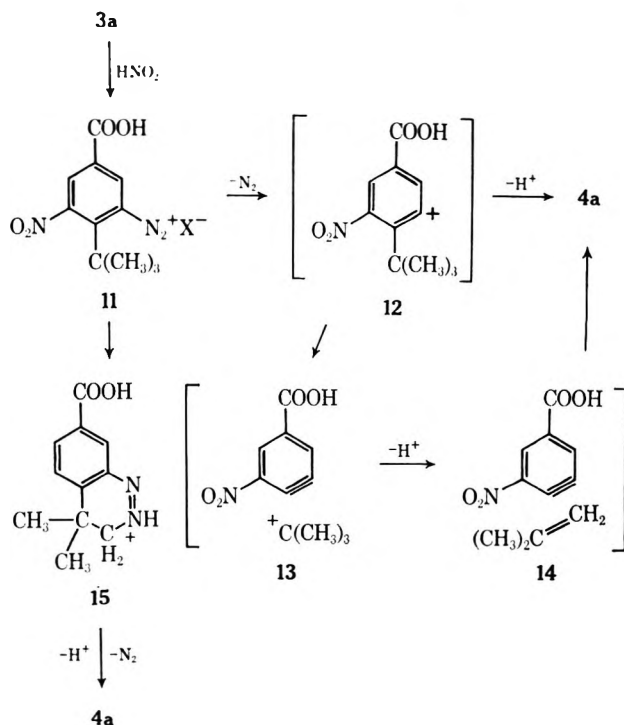
process specifically has been proposed for the decomposition of *o-tert*-butyl-*N*-nitrosoacetanilide[11],[11a] in the pres-

(5) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Amer. Chem. Soc.*, **67**, 303 (1945). *o-tert*-Butylphenol gives a negative ferric chloride test but *o*-isopropylphenol gives a positive test.

(6) We are most grateful to Dr. Lois Durham and Dr. M. Bramwell for conducting the NOE study and the decoupling experiments.

(7) F. Bell, *J. Chem. Soc.*, 120 (1958).

(8) M. S. Leslie and U. J. H. Mayer, *ibid.*, 611 (1961).

(9) L. R. C. Barclay and M. C. MacDonald, *Tetrahedron Lett.*, 881 (1968).

(10) R. W. Hoffmann, "Dehydrobenzenes and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 200.

(11) R. W. Franck and K. Yanagi, *J. Amer. Chem. Soc.*, **90**, 5814 (1968).

(11a) NOTE ADDED IN PROOF.—J. Cadogan, *et al.* [*Chem. Commun.*, 1 (1971)], have found that *in situ* diazotization under anhydrous conditions favors benzyne formation.

ence of furan to give a Diels–Alder type adduct. If such a benzyne were involved, however, it seems very likely that we would have seen some of the isomeric product **7a** resulting from what would appear to be the energetically more favorable mode of addition.

An insertion of the terminal electron-deficient nitrogen of the diazonium salt **11** into a C–H bond of the methyl group, in a manner analogous to a case reported by Lansburg, *et al.*,[12] could be postulated to give an intermediate **15** which might then decompose by losing a proton and extruding nitrogen to give the observed benzocyclobutene **4a**.

Free-radical formation and subsequent intramolecular hydrogen transfer in a manner not unrelated to the Gomberg biaryl synthesis or the Pschorr ring closure is still another possibility. In this scheme the radical **16**

3a ⟶ **11** ⟶
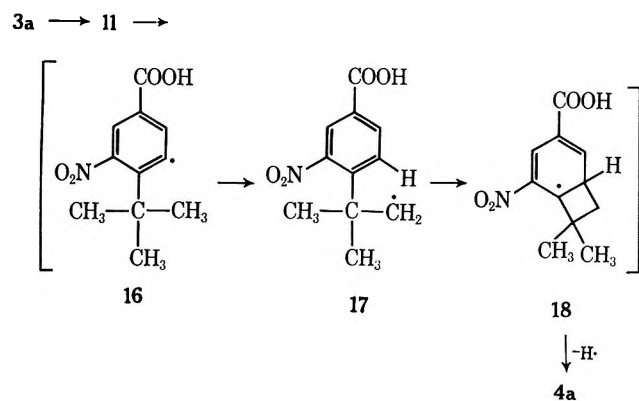
abstracts a hydrogen internally because of the proximity of the *tert*-butyl group to give **17** which ring closes to give **18**, which in turn transfers a hydrogen atom to the solvent to give the observed product **4a**. The fact that the yield of **4a** from **3a** was not enhanced appreciably either by heating the diazonium salt in the presence of copper bronze or by irradiating with uv light, conditions which favor radical decomposition,[13] could be interpreted as evidence against a radical process. We also failed to observe benzocyclobutene formation when the reaction was conducted under the basic conditions of the Gomberg biaryl synthesis. Without more evidence it is futile to speculate further concerning these and other interesting alternatives.

Experimental Section

The infrared spectra were recorded on a Perkin-Elmer 421 spectrometer and the ultraviolet spectra on a Cary Model 14 spectrophotometer. The nuclear magnetic resonance spectra were taken in CDCl₃ on either a Varian A-60 instrument or HR-100 for decoupling experiments; chemical shifts were reported in δ, parts per million (ppm), downfield from tetramethylsilane as an internal standard. Melting points were in capillary, uncorrected.

3,5-Dinitro-5-*tert*-butylbenzoic Acid.—This was made by nitration of *p*-*tert*-butylbenzoic acid,[14] 53% yield.

3-Amino-4-*tert*-butyl-5-nitrobenzoic Acid (3a).—This compound was prepared in 60% yield from 4-*tert*-butyl-3,5-dinitrobenzoic acid according to the procedure of Bell,[7] mp 227–228° (lit. mp 230°).

The methyl ester hydrochloride was made by saturating a methanolic solution of the acid with dry hydrogen chloride, mp 171–172° dec. The free methyl ester, generated from the hydro-

chloride, was converted to the N-acetyl derivative, mp 184–185°, by allowing it to stand at room temperature with acetic anhydride for 18 hr.

Diazotization of 3-Amino-4-*tert*-butyl-5-nitrobenzoic Acid.—A cooled solution of 3-amino-4-*tert*-butyl-5-nitrobenzoic acid (2.38 g) in glacial acetic acid (5 ml) was added dropwise to a solution of sodium nitrite (0.70 g) in concentrated sulfuric acid (6 ml) at 0°. After the mixture was stirred for 15 min, it was poured onto ice, and the resulting mixture was stirred for 15 min. Unreacted starting material (0.70 g) was removed by filtration, and the filtrate was heated at 65° for 10 min, at which time nitrogen evolution had ceased. The mixture was cooled, and a brown precipitate was removed by filtration, washed with water, and dried to yield 0.65 g of crude 1,1-dimethyl-4-carboxy-6-nitrobenzocyclobutene (4a). This crude acid was converted to its methyl ester in methanol saturated with dry hydrogen chloride. Recrystallization of the ester from methanol–water yielded 0.36 g of **4b**: mp 138–139°; uv λ_{max} (C₂H₅OH) 227 nm (ε 21,200), 264 (6150), and 305 (2100); ir (KBr) 1724 (aryl ester C=O), 1611 (aryl), 1525, and 1333 cm⁻¹ (NO₂); nmr (CDCl₃) δ 1.58 (s, 6 H, C(CH₃)₂), 3.11 (s, 2 H, CH₂), 3.96 (s, 3 H, CO₂-CH₃), 8.02 (d, 1 aromatic H, J = 1 Hz), 8.59 ppm (d, 1 aromatic H, J = 1 Hz); mol wt 234 (osmometer, CHCl₃), 235 (mass spectrometer). Chromatography of the mother liquors on silica by eluting with chloroform yielded an additional 0.10 g of **4b** (27% total yield allowing for recovered starting material).

Anal. Calcd for C₁₂H₁₃O₄N: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.00; H, 5.22; N, 5.93.

Crude acid from another run was purified by repeated recrystallization from ethanol–water to yield 0.20 g of **4a**: mp 184–185°; uv λ_{max} (C₂H₅OH) 222 nm (ε 16,100), 269 (5950), and 311 (2100); ir (KBr) 3100–2500 (carboxyl OH), 1685 (aryl carboxyl C=O), 1609 (aryl), 1526, and 1334 cm⁻¹ (NO₂); nmr (CDCl₃) δ 1.73 (s, 6 H, C(CH₃)₂), 3.14 (s, 2CH₂), 8.10 (s, 1 H, aromatic H), 8.70 (s, 1 H, aromatic H), 11.57 ppm (s, 1 H, CO₂H).

Anal. Calcd for C₁₁H₁₁O₄N: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.53; H, 4.96; N, 6.25.

Bell[13] reported the preparation of 3-bromo-4-*tert*-butyl-5-nitrobenzoic acid by diazotization and treatment with cuprous bromide and hydrobromic acid. We have repeated this and found a 47% yield of the bromide, 44% recovery of the starting material, and no benzocyclobutene present in the crude product.

1,1-Dimethyl-4-carbomethoxy-6-hydroxybenzocyclobutene (6). —Hydrogenation of the nitro group of **4b** (100 mg) was effected at atmospheric pressure in methanol (10 ml) with platinum catalyst for 16 hr. After removing the catalyst by filtration, the solvent was evaporated to give a light yellow, crude oil of 1,1-dimethyl-4-carbomethoxy-6-aminobenzocyclobutene, which could not be induced to crystallize: ir (neat) 3400 (NH₂), 1710 cm⁻¹ (aromatic ester C=O); nmr (CTCl₃) δ 1.46 (s, 6 H, C(CH₃)₂), 2.88 (s, 2 H, benzocyclobutene CH₂), 3.85 (s, 3 H, CO₂CH₃), 7.22 ppm (s, 2 H, aromatic H).

The crude amine (100 mg) was dissolved in a mixture of concentrated hydrochloric acid (1 ml) and water (1 ml), and the solution was cooled in an ice-salt mixture. To this mixture was added a solution of sodium nitrite (30 mg) in water (1 ml) cooled to 0°. A yellow oily precipitate was formed immediately, and after 30 min the reaction mixture gave a negative diazonium test with alkaline β-naphthol. The mixture was extracted with ether, and the ether extracts were washed (NaHCO₃ solution, H₂O), dried (MgSO₄), and evaporated to give a light yellow solid which was crystallized from low-boiling petroleum ether (bp 30–60°), 35 mg, mp 125–127°. After several recrystallizations from petroleum ether, the melting point of 6 was raised to 135–136°: ir (Nujol) 3420 (OH), 1710 cm⁻¹ (aryl ester C=O); nmr (CD-Cl₃) δ 1.50 (s, 6 H, C(CH₃)₂), 2.92 (s, 2 H, methylene CH₂), 3.91 (s, 3 H, CO₂CH₃), 7.36 (s, 1, aromatic H), 7.53 ppm (s, 1, aromatic H).

Anal. Calcd for C₁₂H₁₄O₃: C, 69.88; H, 6.84. Found: C, 69.99; H, 6.91.

This product gave a negative test with ethanolic ferric chloride, indicating a strongly hindered phenol.

1,1-Dimethyl-6-methoxy-4-carbomethoxybenzocyclobutene.—A solution of the phenol 6 (185 mg) in dimethoxyethane (10 ml) was treated with a dispersion of sodium hydride (50 mg) and dimethyl sulfate (0.5 ml) at room temperature for 24 hr. The reaction mixture was filtered, diluted with ether, and treated with water, and the ether layer dried to give 190 mg of a colorless oil which was purified by glc (QF-1 fluorosilicone, 0.25 in. ×

(12) P. T. Lansburg, J. G. Colson, and N. R. Mancuss, *J. Amer. Chem. Soc.*, **86**, 5225 (1964).

(13) H. Zollinger, "Azo and Diazo Chemistry of Aliphatic and Aromatic Compounds," Interscience, New York, N. Y., 1961, pp 161, 170.

(14) M. S. Carpenter and W. M. Easter, *J. Org. Chem.*, **19**, 87 (1954).

10 ft, 185°) to give 118 mg of the methyl ether **7a** (R = CH₃): mp 51–53°; nmr (CDCl₃) δ 1.46 (s, 6 H), 2.78 (t, 2 H, J = 0.8 Hz), 3.81 (s, 3 H), 3.87 (s, 3 H), 7.38 ppm (s, broad, 2 H).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.90; H, 7.32. Found: C, 70.99; H, 7.33.

The decoupling experiments are described in the text.

Decomposition of the Diazonium Salt 11 in the Presence of Copper Bronze.—The amino acid **3a** (2.38 g) was dissolved in glacial acetic acid (15 ml), and the solution was cooled in an ice–salt bath until it solidified. The solid was added in portions to a solution of sodium nitrite (0.70 g) in concentrated sulfuric acid (6 ml) and cooled in an ice–salt bath. Lumps which formed in the mixture were crushed. After the mixture was stirred for 15 min, it was poured onto ice. After stirring for 15 min, unreacted starting material (0.56 g) was removed by filtration. The filtrate, still at 0°, was divided into two equal portions which were treated with copper bronze under different conditions.

To one portion was added copper bronze (0.3 g) and the mixture was heated at 65° on the steam bath for 10 min whereupon it showed a negative diazonium test with β-naphthol. The mixture was cooled to 0° and the solids were removed by filtration. Washing these solids with dry methanol removed the organic material, and the methanol solution was treated with dry hydrogen chloride and allowed to stand for 16 hr. Ether was added, and this solution was washed with sodium bicarbonate solution and dried. Removal of the solvent left 0.38 g of crude methyl

ester which was purified by chromatography on silica using chloroform as the eluent to yield 0.18 g of benzocyclobutene **2b** (20% yield considering recovered starting material), mp 135–136°. The second half of the original diazonium compound gave an 18% yield of **4b** when the decomposition in the presence of copper bronze was done for 16 hr at 20°.

Decomposition of the Diazonium Salt 11 in the Presence of Ultraviolet Light.—A filtered solution of the diazonium salt was prepared as in the preceeding section from the amino acid **3a** (1.19 g). The filtrate was cooled to 0° in a quartz vessel and stirred while it was irradiated for 6 hr with ultraviolet light from a Nester-Faust source (2537 Å). A white precipitate was removed by filtration and treated with methanol and dry hydrogen chloride to yield 0.22 g of crude methyl ester. Chromatography of this product on silica gel gave 95 mg of the benzocyclobutene **4b** (12%). The above aqueous filtrate was heated at 65° for 10 min, and 67 mg of a precipitate was removed and converted with the crude methyl ester **4b**. Chromatography on silica gel gave an additional 45 mg of **4b** for a total yield of 18%, mp 135–136°. The infrared spectra of each of the samples of this methyl ester obtained in the four runs were identical.

Registry No.—**3a**, 28538-59-2; **4a**, 28538-60-5; **4b**, 28538-61-6; **5**, 28538-62-7; **6**, 28538-63-8; **7a**, 28538-64-9.

Halogenated Ketenes. XVIII. The Stereochemistry of Some Unsymmetrical Arylketene Cycloadditions[1,2]

WILLIAM T. BRADY,* FRED H. PARRY, III,[3] AND JAMES D. STOCKTON

Department of Chemistry, North Texas State University, Denton, Texas 76201

The (2 + 2) cycloadducts of cyclopentadiene and phenylchloro-, phenylbromo-, phenylmethyl-, phenylethyl-, phenoxymethyl-, and phenoxyketenes were prepared in good yield. The cycloadditions were stereoselective to produce only the *endo*-phenyl or *endo*-phenoxy isomer of the cycloadduct with the exception of phenoxymethyl-ketene which yielded only the *endo*-methyl isomer of the cycloadduct. The cycloadducts of phenylmethylketene and ethyl vinyl ether, dihydropyran, cyclohexene, and cyclooctene were also prepared. Two cycloadduct isomers were formed with each of these olefins with only a small predominance of the *endo*- or *cis*-phenyl isomer. These results are interpreted to suggest that cyclopentadiene may be novel as a cycloaddition partner in ketene cyclo-additions when a large difference exists between the size of the ketene substituents.

The ($_π2_s$ + $_π2_a$) cycloaddition of ketenes and olefins is allowed to be a thermally concerted process whereby the ketene participates in an antarafacial role.[4] When the cycloaddition is effected with unequally substituted ketenes with unsymmetrical olefins, such as cyclopenta-diene, the (2 + 2) cycloadduct may be a mixture of geo-metrical isomers. Recently, the stereochemistry of the cycloaddition of some unequally substituted ketenes

cate a strong preference for endo specificity for the larger ketene substituent; *i.e.*, the isomer with the larger ketene substituent in the endo position has been found to be very strongly sterically preferred. In fact, this isomer has even been formed to the exclusion of the exo isomer when a large difference in size exists between the two ketene substituents.

We now wish to describe the stereochemistry of the cycloaddition of some unsymmetrical arylketenes with cyclopentadiene and also the stereochemistry of the cycloaddition of phenylmethylketene with a variety of olefinic compounds. A preliminary report of this work has appeared.[9]

with cyclopentadiene has been described and revealed a most gratifying correlation with this principle of the conservation of orbital symmetry.[5-8] The results indi-

Results

Phenylchloro- and phenylbromoketenes were prepared by the dehydrochlorination of α-chloro- and α-bromophenylacetyl chlorides at room temperature. The ketenes could not be isolated but could be trapped by heating the dehydrohalogenation mixtures with cyclopentadiene to produce the (2 + 2) cycloadducts in good yield. The best yields of cycloadducts are obtained by conducting the dehydrochlorinations at room temperature and then refluxing the reaction mixtures to

(1) Paper XVII: W. T. Brady and L. Smith, *Tetrahedron Lett.*, 2963 (1970).

(2) Abstracted in part from the Ph.D. thesis of F. H. P., North Texas State University, May 1970.

(3) NDEA, Title IV Fellow.

(4) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

(5) W. T. Brady and R. Roe, Jr., *J. Amer. Chem. Soc.*, **92**, 4618 (1970).

(6) T. DoMinh and O. P. Strausz, *ibid.*, **92**, 1766 (1970).

(7) M. Rey, S. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 417 (1970).

(8) W. T. Brady, E. F. Hoff, R. Roe, Jr., and F. H. Parry, III, *J. Amer. Chem. Soc.*, **91**, 5679 (1969).

(9) W. T. Brady, F. H. Parry, III, R. Roe, Jr., and E. F. Hoff, *Tetrahedron Lett.*, 819 (1970).

effect cycloaddition. The cleanest preparations are achieved employing acetonitrile as the solvent, al-

I, X = Cl
II, X = Br
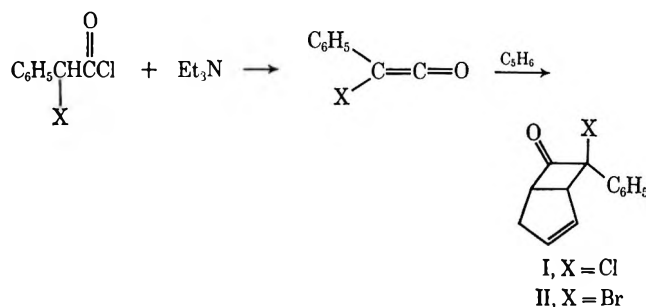
though benzene and hexane also give good yields. Numerous attempts to isolate phenylchloroketene resulted in a tarry polymer of the ketene.

Both the *endo-* and *exo-*phenyl isomers were expected for I and II, since both isomers of the alkylhaloketene–cyclopentadiene cycloadducts are produced.[10] However, distillation and subsequent vpc and nmr analysis indicated that the distillate contained only one isomer, and furthermore this was the *endo-*phenyl isomer. We have previously reported the cross-ring deshielding effect of a halogen in the exo position on C-7 of bicyclo[3.2.0]hept-2-en-6-ones.[5] The assignment of I and II as both being the *endo-*phenyl isomer was made on the basis of the chemical shift of H_5 in I and II, δ 4.35
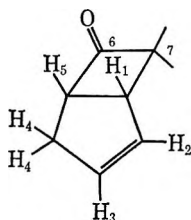
and 4.36, respectively (see Table I). Further evidence that this assignment is correct is the resonance of the vinyl protons. An *endo-*phenyl substituent in the bicyclo[3.2.0]hept-2-en-6-ones causes a multiplet or pair of multiplets for the vinyl protons which are considerably shielded (δ 5.5) from the vinyl absorption in similar compounds without a phenyl substituent in the endo position (δ 5.8–5.9).

The vinyl region of the nmr spectra was split into two multiplets at δ 5.7 and 5.35 for I and δ 5.78 and 5.41 for II. Decoupling at the frequency of the H_4 resonance collapsed the upfield portion of the vinyl resonance into a doublet, while the downfield portion became a pair of doublets. It seemed apparent that H_2 was responsible for the downfield portion of the total vinyl resonance and that the upfield portion was due to H_3. The coupling constants $J_{H_1-H_2}$ and $J_{H_2-H_3}$ could be seen to be 2.0 and 6.5 Hz, respectively.

In an effort to determine if this stereoselectivity was general for unequally substituted arylketenes, phenylmethyl- and phenylethylketenes were prepared and purified by distillation. The cycloadditions with cyclopentadiene took place very smoothly to give a good yield of only one isomer. The vinyl resonances indicated an *endo-*phenyl isomer. Moreover, the methyl resonance for III was consistent only with an *exo-*

(10) W. T. Brady and B. M. Holifield, *Tetrahedron*, **23**, 4251 (1967).

methyl group.[11] Furthermore, bromination of III resulted in a methyl resonance shift of only δ 0.02.[10]

III, R = CH$_3$
IV, R = C$_2$H$_5$
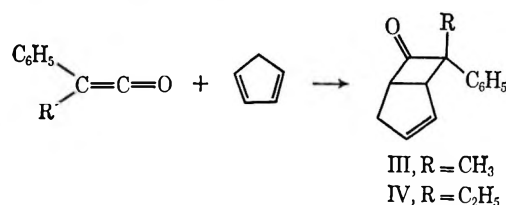
To determine the effect on the stereochemistry of moving the phenyl substituent away from the ketene functionality, phenoxymethylketene was prepared and allowed to undergo *in situ* cycloaddition with cyclopentadiene. The cycloaddition was observed to proceed stereoselectivity as evidenced by only one singlet (δ

V
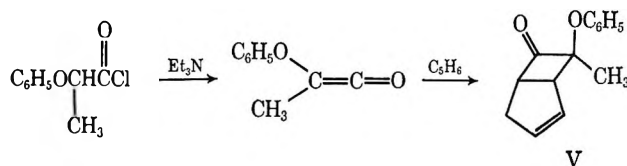
1.26) for the methyl substituent in the nmr spectrum. The chemical shift of the methyl group indicated an *endo-*methyl, which was further verified by observing a downfield shift of the methyl resonance of δ 0.30 upon bromination of V.[10]

Due to this unexpected reversal in the stereochemistry of the phenoxymethylketene cycloaddition, the adduct of phenoxyketene and cyclopentadiene (VI) was produced to aid in elucidating the role of the phenoxy group on the stereochemical outcome of the cycloaddition. The nmr spectrum revealed a pair of doublets for H_7 with coupling constants of $J_{H_1-H_7} = 8.0$ Hz and $J_{H_5-H_7} = 3.0$ Hz, which could only be reconciled with a system of all three cis hydrogens on the four-membered ring.[12] The absence of any absorption about δ 0.5 farther upfield further indicated a stereospecific cycloaddition. While the 3.0-Hz cross-ring coupling is probably consistent with either isomer of the cycloadduct, the vicinyl coupling of 8.0 Hz could only be the result of two hydrogens which were very nearly in the same plane.

We have recently examined the cycloaddition of methylchloro- and methylbromoketenes with a variety of olefins and found that not only were two isomers produced but the isomer distributions were nearly independent of the olefin structure.[13] Since all of the reports on the stereochemistry of the cycloaddition of unsymmetrical ketenes, where a large difference exists between the size of the ketene substituents, have been with cyclopentadiene, it seemed desirable to determine if the endo specificity observed was general for all olefins. Consequently, the cycloaddition of phenylmethylketene with several olefins was effected. The cycloadditions were accomplished by the addition of this pure isolable ketene to an excess of olefin and refluxing the resultant solution. The results are shown in Table II. Both *endo-* or *cis-*methyl and *exo-* or *trans-*methyl isomers were produced with all four olefins.

(11) W. T. Brady, R. Roe, Jr., E. F. Hoff, Jr., and F. H. Parry, III, *J. Amer. Chem. Soc.*, **92**, 146 (1970).
(12) (a) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967); (b) B. Braillon, *J. Mol. Spectrosc.*, **27**, 313 (1968).
(13) W. T. Brady and R. Roe, Jr., *J. Amer. Chem. Soc.*, **93**, 1662 (1971).

TABLE I

NMR SPECTRA OF PHENYLHALO- AND ARYLALKYLKETENE CYCLOADDUCTS OF CYCLOPENTADIENE
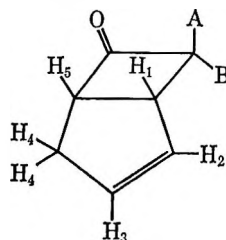
Compd	A (exo)	B (endo)	Registry no.	H_1	H_2	H_3	H_4	H_5
I	Cl	C_6H_5		4.05	5.70	5.35	2.55	4.35
II	Br	C_6H_5		4.05	5.78	5.41	2.55	4.36
III	CH_3 (1.61)	C_6H_5		3.49		5.52	2.52	3.93
IV	C_2H_5	C_6H_5		3.50		5.46	2.45	3.86
V	C_6H_5O	CH_3 (1.26)		3.86		5.83	2.53	4.05
VI	H (5.19)[a]	C_6H_5O		3.48		5.76	2.53	3.86
	C_6H_5	C_6H_5	5452-28-8	4.23	5.71	5.45	2.67	3.78
	Cl	Cl	5307-99-3	4.08		5.9	2.68	4.25
	CH_3 (1.28)	CH_3 (0.93)	767-85-1	3.15		5.8	2.70	3.95
	CH_3 (1.77)	Cl	13363-88-7	3.62		5.9	2.65	3.95
	Cl	CH_3 (1.47)	13363-87-6	3.65		5.9	2.64	4.28

[a] $J_{H_1-H_7} = 8.0$; $J_{H_5-H_7} = 3.0$.

TABLE II

CYCLOADDUCTS OF PHENYLMETHYLKETENE

Compd	Olefin	*exo-* or *trans/endo* or *cis*-methyl ratio
VII	Ethyl vinyl ether	2.3
VIII	Dihydropyran	1.7
IX	Cyclohexene	2
X	Cyclooctene	1.1

The isomer distributions for the adducts with cyclohexene and cyclooctene were determined by vpc and the ratio of methyl singlets in the nmr spectra. The distinction between isomers was made on the basis of the chemical shift of the methyl singlet.

The isomer distributions for the adducts with ethyl vinyl ether and dihydropyran were established in a similar manner. However, in these cycloadducts the resonance of the methinyl proton adjacent to the ether linkage was also significant. The isomer distributions could be confirmed by the ratio of these triplets in the ethyl vinyl ether adduct and a ratio of the doublets in the dihydropyran cycloadduct.

Discussion

In each of the six arylketene cycloadducts with cyclopentadiene, a stereoselective cycloaddition was observed.[14] In all but one instance, the larger ketene substituent was found to be in the endo position of the cycloadduct. These stereochemical results fit a now well-established pattern,[5-8] and, as expected, the methyl substituent is effectively larger than the phenoxy.[15]

The results obtained from the cycloaddition of phenylmethylketene with ethyl vinyl ether, dihydropyran, cyclohexene, and cyclooctene were totally unexpected. These data reveal that there is very little preference for the *endo-* or *cis*-phenyl isomer. Therefore, the obvious

conclusion is that cyclopentadiene appears to be novel as a cycloaddition partner in ketene cycloadditions where a large difference exists between the size of the ketene substituents. Presumably the planarity of the olefin is a determining factor in these cycloadditions. It will indeed be ironic if cyclopentadiene is an anomaly since all of the initial work in this area has been with this olefin.

Experimental Section

Nmr spectra were obtained on a Varian A-60, Varian A-60A, or Varian T-60 nuclear magnetic resonance spectrometer, employing tetramethylsilane as the internal standard at 25°. All solvents were dried and purified by distillation from calcium hydride and subsequently stored over molecular sieves 4A. α-Chloro-α-phenylacetyl chloride was prepared from mandelic acid by the method of Walden.[16] α-Phenylpropionic acid was obtained by the silver oxide oxidation of the commercially available adehyde and converted to α-phenylpropionyl chloride with thionyl chloride.[17] All of the other acid halides were obtained from commercially available acids and thionyl chloride by standard procedures. The preparation of the cycloadduct of phenylchloroketene and cyclopentadiene (I) has been previously described.[18] Phenylethylketene was prepared by the dehydrochlorination of α-phenylbutyryl chloride with triethylamine.[18] Phenylmethylketene was obtained in an analogous manner by the dehydrochlorination of α-phenylpropionyl chloride.

General Method for *in situ* Cycloadditions.—A 0.2-mol portion of triethylamine in 50 ml of dry hexane was added dropwise and with stirring to a solution containing 0.2 mol of the acid halide and 0.9–1.0 mol of fresh cyclopentadiene in 250 ml of hexane at room temperature. After 1 hr of stirring, the reaction mixture was refluxed for 6 hr before filtration of the salt. Concentration of the filtrate and vacuum distillation of the residue afforded the substituted bicyclo[3.2.0]hept-2-en-6-ones. All of the cycloadditions were also run in acetonitrile as the solvent to check the stereochemistry in a more polar solvent. In no case was the stereochemistry effected, but in most cases about a 10% increase in the yield was noted.

*exo-*7-**Bromo**-*endo*-7-**phenylbicyclo**[3.2.0]**hept-2-en-6-ones (II).** —II was prepared in 53% yield: bp 110° (0.8 mm); ir 1801 (C=O) and 1610 cm^{-1} (C=O).

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(14) The cycloadditions were stereoselective to the extent that only one isomer was observed. The limits of detection were <5%.

(15) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(16) P. Walden, *Ber.*, **28**, 1287 (1895).

(17) N. Rabjohn, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 919.

(18) W. T. Brady, E. D. Dorsey, and F. H. Parry, III, *J. Org. Chem.*, **34**, 2846 (1969).

Anal. Calcd for $C_{18}H_{11}BrO$: C, 59.4; H, 4.18. Found: C 59.7; H, 4.08.

endo-7-Methyl-*exo*-7-phenoxybicyclo[3.2.0]hept-2-en-6-one (V).—V was prepared in 69% yield: bp 118° (0.2 mm); ir 1776 (C=O) and 1597 cm⁻¹ (C=C).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.54. Found: C, 78.68; H, 6.85.

Bromine was added slowly, cautiously, and dropwise from a small syringe to a 30% solution of V in CCl_4 in an nmr tube. This addition was done intermittently and continued until the nmr spectrum revealed no resonance for the vinyl protons. During the addition, the methyl singlet at δ 1.26 began to decrease in intensity and a new singlet at δ 1.56 began to appear. Eventually, only the new methyl singlet was present.

endo-7-Phenoxybicyclo[3.2.0]hept-2-one (VI).—Concentration of the filtrate and recrystallization from hexane afforded a 65% yield of VI: mp 55–56°; ir 1789 (C=O) and 1597 cm⁻¹ (C=C).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 78.12; H, 6.06.

Cycloadditions of Phenylmethyl- and Phenylethylketenes with Cyclopentadiene.—A 0.2-mol portion of the ketene in 50 ml of dry hexane was added dropwise to a 0.8-mol portion of fresh cyclopentadiene in 200 ml of hexane. After the addition was complete, the reaction mixture was heated to reflux until the yellow color of the ketene disappeared (6–10 hr). Concentration and recrystallization from ether afforded the pure cycloadducts.

exo-7-Methyl-*endo*-7-phenylbicyclo[3.2.0]hept-2-en-6-one (III). —III was obtained in 85% yield: mp 26–30°; ir 1773 (C=O) and 1603 cm⁻¹ (C=C).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.85; H, 7.13. Found: C, 84.9; H, 7.16.

Bromination in an nmr tube of III, as described above, resulted in the disappearance of the vinyl proton resonance but produced no change in the methyl singlet. However, on an expanded portion of the spectrum, the methyl resonance at δ 1.61 could be seen to disappear and a new singlet appear at δ 1.63.

exo-7-Ethyl-*endo*-7-phenylbicyclo[3.2.0]hept-2-en-6-one (IV).—An 83% yield of IV was obtained with mp 43.5–44°; ir 1761 (C=O) and 1592 cm⁻¹ (C=O).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.9; H, 7.55. Found: C, 85.2; H, 7.67.

General Procedure for Phenylmethylketene Cycloadditions.—A solution of 0.06 mol of phenylmethylketene in 0.5 mol of olefin was refluxed overnight. The unreacted olefin was removed on a rotoevaporator. The isomer distribution was determined by nmr and vpc after mixing the reactants during the reflux period and after concentration of the reaction solution. The isomer distributions were the same in all three determinations in every instance. The concentrated reaction solution was fractionally

distilled under reduced pressure. The yields were based on the total *endo*- and *exo*-methyl isomers.

2-Methyl-2-phenyl-3-ethoxycyclobutanone (VII).—An 82% yield was obtained at 95° (0.6 mm): ir 1780 cm⁻¹ (C=O): nmr (CCl_4) (both isomers) δ 0.8 (t, 2.1 H), 1.15 (t, 0.9 H), 1.39 (s, 1 H), 1.4 (s, 2 H), 3.0 (m, 4 H), 3.8 (t, 0.7 H), 4.1 (t, 0.3 H), and 6.95 (m, 5 H).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.5; H, 7.84: Found: C, 76.37; H, 7.79.

8-Methyl-8-phenyl-2-oxabicyclo[4.2.0]octan-7-one (VIII).—A 77% yield was obtained at 110° (at 0.3 mm): ir 1765 cm⁻¹ (C=O); nmr (CCl_4) (both isomers) δ 1.5 (m, 7 H), 1.4 and 1.55 (two singlets out of multiplet corresponding to *endo*- and *exo*-methyl isomers respectively; 1.7 *exo*-/*endo*-methyl ratio), 3.4 (m, 3 H), 4.2 (d, 0.6 H), 4.35 (d, 0.4 H), and 7.1 (m, 5 H).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.42. Found: C, 77.67; H, 7.67.

8-Methyl-8-phenylbicyclo[4.2.0]octan-7-one (IX).—A 43% yield was obtained at 115° (0.3 mm): ir 1780 cm⁻¹ (C=O); nmr (CCl_4) (both isomers) δ 1.3 (s, *endo*-methyl, 1 H), 1.6 (s, *exo*-methyl, 2 H), 1.45 (m, 11 H, the two methyl singlets were a part of this multiplet), 2.5 (m, 1 H), 3.55 (m, 1 H), and 7.2 (m, 5 H).

Anal. Calcd for $C_{15}H_{18}O$: C, 83.7; H, 8.84. Found: C, 83.92; H, 8.34.

10-Methyl-10-phenylbicyclo[6.2.0]decan-9-one (X).—A 41% yield was obtained at 120° (0.35 mm): ir 1780 cm⁻¹ (C=O); nmr (CCl_4) (both isomers) δ 1.4 (s, *endo*-methyl, 1.4 H), 1.6 (s, *exo*-methyl, 1.6 H), 1.45 (m, 16 H, the two methyl singlets were a part of this multiplet), 3.3 (m, 1 H), and 7.3 (m, 5 H).

Anal. Calcd for $C_{17}H_{22}O$: C, 84.3; H, 9.46. Found C, 84.1; H, 9.58.

Reactions of Phosphorus Compounds. XXIV.[1]
Preparation and Reactions of Phosphonium Betaines

EDWARD E. SCHWEIZER* AND CHARLES M. KOPAY[2]

Department of Chemistry, University of Delaware, Newark, Delaware 19711

A number of active methylene species (dibenzoylmethane, ethyl benzoylacetate, benzoylacetone, dimedon, ethyl acetoacetate, acetylacetone, and diethyl malonate) have been phosphonioethylated with vinyltriphenylphosphonium bromide. A correlation was observed between acidity of the active methylene moiety and ease of di- vs. monophosphonioethylation. The monophosphonioethylated salts obtained were converted into the corresponding betaines, on treatment with base, and isolated. Methylation of the betaines was accomplished. Fusion of the betaines produced 1,1-disubstituted cyclopropanes and/or 2,3-disubstituted 4,5-dihydrofurans.

In 1964 phosphonioethylation reactions were accomplished for the first time[3,4] by allowing compounds

with replaceable protons to react with vinylphosphonium bromides (1).

$$ZH + CH_2=CH\overset{+}{P}R_3\ Br^- \longrightarrow ZCH_2CH_2\overset{+}{P}R_3\ Br^-$$
$$\begin{array}{cc} \textbf{1a}, R = n\text{-Bu} & \textbf{2} \\ \textbf{b}, R = Ph & \end{array}$$

Although the adducts from acetoacetic ester and diethyl malonate were prepared and isolated as their

(1) Previous paper in this series: E. E. Schweizer and A. T. Wehman, *J. Chem. Soc. C*, in press.
(2) From the Ph.D. Dissertation of C. M. Kopay.
(3) P. T. Keough and M. Grayson, *J. Org. Chem.*, **29**, 631 (1964).
(4) E. E. Schweizer and R. D. Bach, *ibid.*, **29**, 1746 (1964).

TABLE I

PHOSPHONIOETHYLATION WITH VINYLTRIPHENYLPHOSPHONIUM BROMIDE

	Addendum (mol)	Solvent	Temp, °C	Time, hr	Adduct	Yield, %
3a	$PhCOCH_2COPh$ (1)	*tert*-BuOH	30	48	$(PhCO)_2CHCH_2CH_2\overset{+}{P}Ph_3Br^-$ 4a	97
3b	$PhCOCH_2CO_2Et$ (3)	DMF	25	16	$\underset{EtO_2C}{\overset{PhCO}{>}}CHCH_2CH_2\overset{+}{P}Ph_3Br^-$ 4b	95
3c	$PhCOCH_2COCH_3$ (3)	DMF	28	20	$\underset{CH_3CO}{\overset{PhCO}{>}}CHCH_2CH_2\overset{+}{P}Ph_3Br^-$ 4c	76
3d		*tert*-BuOH	30	40	 4d	81
3e	$CH_3COCH_2CO_2Et$ (1)	Et_2O-CH_3CN (9:1)	25	16	$\underset{EtO_2C}{\overset{CH_3CO}{>}}C(CH_2CH_2\overset{+}{P}Ph_3Br^-)_2$ 4e	95
3f	$CH_3COCH_2COCH_3$ (1)	DMF	25	18	$(CH_3CO)_2C(CH_2CH_2\overset{+}{P}Ph_3Br^-)_2$ 4f	76
3g	$EtO_2CCH_2CO_2Et$ (1)	Glyme	25	24	$(EtO_2C)_2C(CH_2CH_2\overset{+}{P}Ph_3Br^-)_2$ 4g	73

tetraphenylborate derivatives, no further reactions were undertaken with these reagents.[3] We wish to report the reactions of a number of β diketones and β-keto esters with vinyltriphenylphosphonium bromide (1b) and the synthetic utility of the phosphonium betaines produced from the initially formed phosphonioethylated species.

Phosphonioethylation of dibenzoylmethane (3a), ethyl benzoylacetate (3b), benzoylacetone (3c), and dimedon (3d) with 1b and a catalytic amount of K⁺O⁻-*tert*-Bu gave good yields of 1:1 adducts (4a–d) (Table I). The ¹H nmr spectra of phosphonium salts (4a–c) in CDCl₃ exhibited a characteristic triplet (δ 5.8–6.3 ppm, J = 7.0 Hz) assigned to the methine proton (>CH-CH₂CH₂⁺PPh₃). The presence of any enol tautomer was not detected.[5] The enol tautomer 5 would be a nonplanar, tetrasubstituted ethylene unsuitable for intramolecular hydrogen bonding.[6] The adduct of dimedon (4d) was completely in the enol form as shown by ¹H nmr. The ir spectrum showed a low carbonyl stretching frequency (1590 cm⁻¹), attributed to an α,β-unsaturated ketone and a hydroxyl stretching frequency (3430 cm⁻¹).
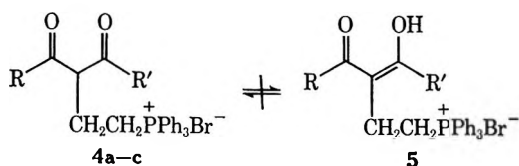
Ethyl acetoacetate (3e), acetylacetone (3f), and diethyl malonate (3g) when treated with 1b gave good yields of 2:1 adducts (Table I). All attempts to pre-

pare 1:1 adducts failed or gave complex mixtures of 1:1 adducts, 2:1 adducts, and starting material.

It appears that the inability to readily isolate 1:1 adducts from the reactions of active methylene species with the vinyl salt 1b may be predictable from the acidity[7] of the active methylene precursors employed. Compounds 3e–g all have pK_a's equal to or greater than acetylacetone (3f) and thus the stabilized anion produced after monophosphonioethylation is nucleophilic enough to undergo ready diphosphonioethylation. The anion of the monophosphonioethylated species produced from active methylene reagents whose original pK_a's are less than (or equal to) benzoylacetone (3c) is of such low nucleophilicity that the reaction is stopped readily at the monoadduct.

When the phosphonium salts 4a and 4b were treated with 1 equiv of butyllithium in DMF, nearly quantitative yields of phosphonium betaines 6a and 6b were obtained. The benzoylacetone adduct 4c was found to undergo cleavage in the presence of BuLi, and considerable amounts of 1-(3-benzoyl)-*n*-propyltriphenylphosphonium bromide, arising from attack of butyllithium at the acetyl carbonyl, were isolated. To obviate this cleavage, the base used for the conversion of 4c to 6c was sodium hydride. The dimedon adduct 4d, upon conversion to its betaine, yielded only a gummy oil which could not be crystallized or purified (Table II). The ir spectra of the betaines showed a shift in the carbonyl stretching frequency of ~200 cm⁻¹. The 60-MHz ¹H nmr indicated the loss of the low field proton, previously assigned to the methine proton of the phosphonium salts, and the ³¹P nmr showed phosphorus resonance at −20 ppm (relative to 85% phosphoric acid) which is indicative of an open betaine

(5) The phosphonium salts were insoluble in nonpolar solvents, and spectra in DMF, DMSO, CHCl₃, AsCl₃, and F₃CCO₂H did not reveal the presence of any 5.

(6) P. Rumpf and R. L. Riviere, *C. R. Acad. Sci.*, **244**, 902 (1957).

(7) J. F. King, "Technique of Organic Chemistry," Vol. VI, K. W. Bentley, Ed., Interscience, New York, N. Y., 1963, p 357.

TABLE II
CONVERSION OF PHOSPHONIUM SALTS TO PHOSPHONIUM BETAINES

	R^1	R^2	Base–solvent		R^1	R^2
4a	Ph	Ph	BuLi–DMF	6a	Ph	Ph
4b	Ph	OEt	BuLi–DMF	6b	Ph	OEt
4c	Ph	CH$_3$	NaH–Benzene	6c	Ph	CH$_3$
4d	CH$_2$—C(CH$_3$)(CH$_3$)—CH$_2$		NaH–CH$_3$CN	6d	CH$_2$—C(CH$_3$)(CH$_3$)—CH$_2$	
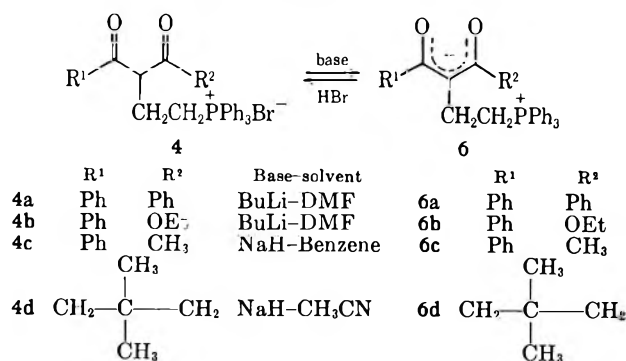
structure, rather than a pentacovalent phosphorus species such as **7**.[8]

7
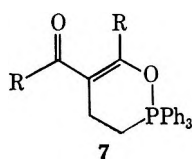
When the betaines **6a–d** were acidified with 10% aqueous HBr, they reverted quantitatively to their respective phosphonium salts **4a–d**. To determine whether there existed an equilibrium between betaine and the tautomeric ylide **8**, betaines **6a–d** were treated with D$_2$O and examined by ^{1}H nmr for deuterium exchange in the position α to phosphorus. After 96 hr at 25° no exchange had taken place, which excludes the possibility of the existence of the ylide tautomer **8**.

8
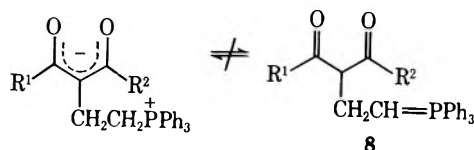
Alkylation of betaines **6a–d** with CH$_3$I gave good yields of only O- or only C-alkylated products; only in the case of **9d** was there observed any mixture of C- and O-alkylation products (Table III).

In light of the work of Denney and Smith[9] on the pyrolysis of phosphonium carboxylates and that of Freeman[10] on the conjugate addition of the Wittig reagent, phosphonium betaines **6a–d** appeared to be potential precursors to 4,5-dihydrofurans or 1,1-disubstituted cyclopropanes (Scheme I).
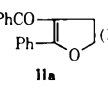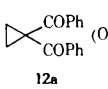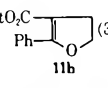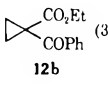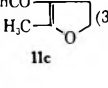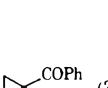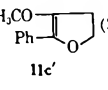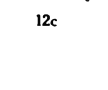
Fusion pyrolysis of **6a** gave a complex mixture of products, 2-phenyl-3-benzoyl-4,5-dihydrofuran (**11a**), dibenzoylmethane (**3a**), phenacyltriphenylphosphorane (**14**), and triphenylphosphine (Table IV). The formation of **11a**, pathway a, may be envisioned as the attack of the oxygen enolate anion in an S$_N$i displacement of Ph$_3$P. By pathway b, the oxygen enolate would abstract the proton α to phosphorus forming the phosphorane intermediate **15**. β elimination of the phosphorane would give **3a**. Intramolecular benzoylation of **15** to **16**, followed by β elimination, would account

TABLE III
ALKYLATION OF PHOSPHONIUM BETAINES WITH CH$_3$I

6 → **9**

10

	R^1	R^2		% yield		% yield
6a	Ph	Ph	9a	0	10a	87^a
6b	Ph	OEt	9b	100^a	10b	0
6c	Ph	CH$_3$	9c	78^a	10c	0
6d	CH$_2$—C(CH$_3$)(CH$_3$)—CH$_2$		9d	82^b	10d	18^b
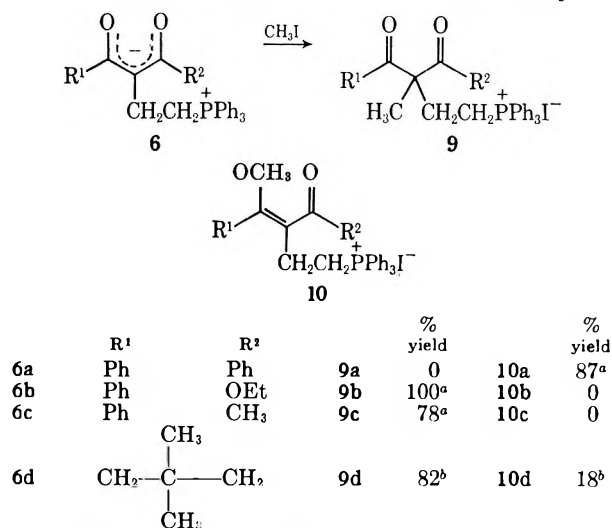
^{a} Overall isolated yield. ^{b} Isolated yield was 78%.

TABLE IV
PYROLYSIS OF BETAINES BY FUSION

Betaine	Temp, °C (mm)	Dihydrofuran (%)	Cyclopropane (%)	Other products (%)
6a	280 (0.1)	**11a** (14)	**12a** (0)	PhCOCH$_2$COPh (10) **3a** PhCOCHPPh$_3$ (6) **14**
6b	200 (0.1)	**11b** (30)	**12b** (38)	
6c	200 (0.1)	**11c** (38) **11c'** (24)	**12c** (20)	
6d	220 (0.1)	**11d** (51)	**12d** (0)	
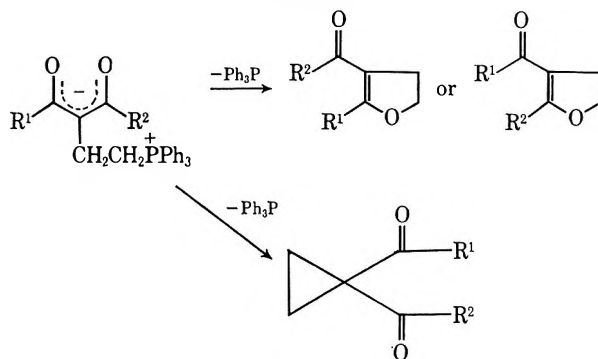
SCHEME I

for phosphorane **14**. The acrylophenone was not isolated (Scheme II).
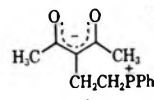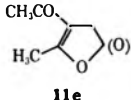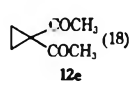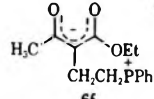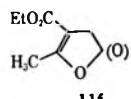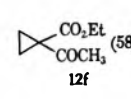
The fusion pyrolysis of **6b** gave a mixture of 2-phenyl-3-carboethoxy-4,5-dihydrofuran (**11b**) and ethyl ben-

(8) J. R. Van Wazer and J. A. Letcher in "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffin, Ed., Interscience, New York, N. Y., 1967, p 169.

(9) D. B. Denney and T. C. Smith, *J. Org. Chem.*, **27**, 3404 (1962).

(10) J. P. Freeman, *ibid.*, **31**, 538 (1966).

TABLE V
PYROLYSIS OF BETAINES

Betaine	Method of pyrolysis (temp)	Dihydrofuran (%)	Cyclopropane (%)
6a	Vpc (300)	11a (41)	12a (0)
6b	Vpc (300)	11b (0)	12b (84)
6c	Vpc (300)	11c (0)	12c (72)
6d	Vpc (300)	11d (74)	12d (0)
6e [a]	Benzene (80)	11e	12e (18)
6f [a]	Toluene (111)	11f	12f (58)

[a] These betaines were never isolated but prepared from the reaction of the sodium salt of the 1,3 diketone or β-keto ester with 1 equiv of 1b.

SCHEME II
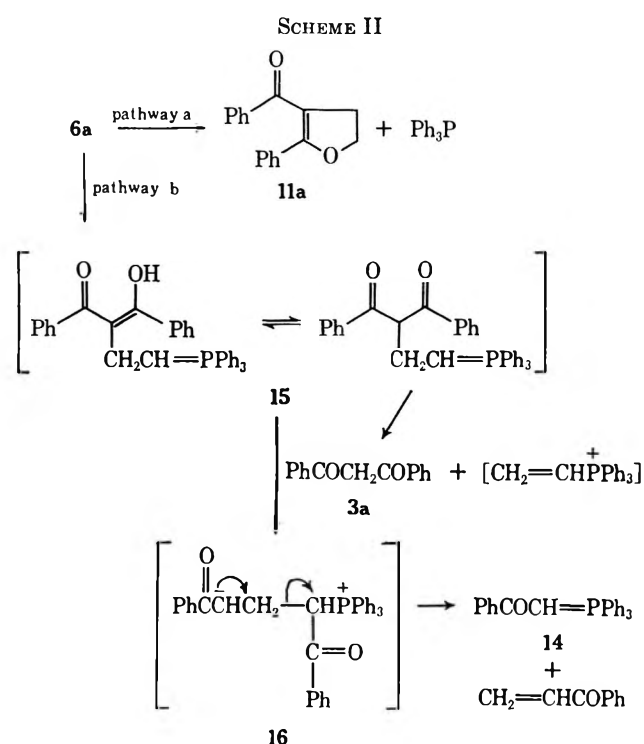
zoylcyclopropane carboxylate (12b) in a total yield of 68%. In this and the subsequent pyrolyses no fragmentation products were observed. Likewise, the pyrolysis of 6c gave a mixture of dihydrofurans (11c, 11c') and cyclopropane (12c). The mixture of isomeric dihydrofurans (11c, 11c') were not separable by either vpc or tlc. These dihydrofurans were identified by C and H analysis, molecular weight by mass spectrum, and their characteristic nmr spectrum. The 2-methylfuran 11c exhibited a methyl resonance (triplet, $J = 1.2$ Hz) being coupled to the 4-methylene protons, whereas the methyl resonance of 11c' showed no such coupling. The thermolysis of 11d gave only dihydrofuran in 51% yield (Table IV).

In an attempt to maximize the yields, the thermolysis of the stable betaines was undertaken in the heated inlet of a gas chromatographic column. The results of these pyrolyses show an increase in the yields of 11a and 11d. More striking, however, is the fact that 6b and 6c gave only cyclopropanes and no furans as ob-

served previously by the fusion pyrolysis (Table V). This may be accounted for by the fact the cyclopropanes are kinetically controlled products and the furans are the more stable thermodynamically controlled products. This interpretation implies the reversible equilibrium between cyclopropane and betaine. Since pyrolysis by vpc afforded an immediate separation of cyclopropane from Ph$_3$P, there would be little chance for the reverse reaction (cyclopropane to betaine) to occur. In the pyrolysis by fusion Ph$_3$P was not removed and the reverse reaction (cyclopropane to betaine) could occur, and the thermodynamically more stable furan formed (Scheme III).

SCHEME III
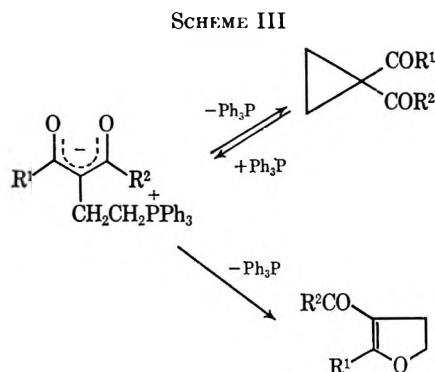
The results of the pyrolysis of the phosphonium betaines in a kinetically controlled process (*i.e.*, vpc pyrolysis–cyclopropane formation) are parallel to and in complete agreement with the results obtained by demercuration of mercurial chlorides[11,12] and our selective alkylations of the betaines (Table III).
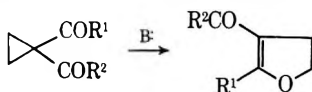
In a previous communication[13] we reported on the Lewis base catalyzed isomerization of cyclopropanes to dihydrofurans. It was found that electrophilically 1,1-disubstituted cyclopropanes underwent the isomerization in quantitative yields (Table VI). These results in addition to the isolation and characterization of the phosphonium betaines confirmed the previous speculation on the cyclopropane–betaine equilibrium

(11) K. Ichikawa, O. Itah, T. Kawamura, M. Fujiwara, and T. Ueno, *J. Org. Chem.*, **31**, 447 (1966), 1240 (1968).

(12) K. Ichikawa, O. Itoh, and T. Kawamura, *Bull. Chem. Soc. Japs.*, **41**, 1240 (1968).

(13) E. E. Schweizer and C. M. Kopay, *Chem. Commun.*, 677 (1970).

TABLE VI

ISOMERIZATION OF CYCLOPROPANES TO DIHYDROFURANS

	R[1]	R[2]	Base (mol %)	Time,[c] hr	Temp, °C	Product (% yield)[a]
12b	Ph	OEt	Ph₃P (20)	7.0	200	11b (>95)
			Et₃N (20)	32.0	200	
12c	Ph	CH₃	Ph₃P (20)	1.0	200	11c, 11c' (57, 43[b])
			Et₃N (20)	28.0	200	11c, 11c' (56, 44[b])
12e	CH₃	CH₃	Ph₃P (20)	1.0	200	11e (>95)
			Et₃N (20)	30.0	200	11e (>95)
12f	CH₃	OEt	Ph₃P (20)	1.0	200	11f (>95)

[a] All yields were determined by nmr and checked by vpc. [b] 57 and 56 are the yields of 9c and 43 and 44 the yields of 9c'. [c] The large time differences between Ph₃P and Et₃N do not reflect the relative nucleophilicity of Ph₃P and Et₃N, since at 200° the concentration of Et₃N in solution was considerably lower than 20 mol %.

in the formation of 4,5-dihydrofurans from cyclopropanes.

Experimental Section

General.—Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. The proton nuclear magnetic resonance (nmr) spectra were obtained on a Varian A-60A spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts in parts per million (δ) are followed by the splitting pattern (m = multiplet, q = quartet, t = triplet, d = doublet, s = singlet), the number of protons, the coupling constant (J), and the assignment of the resonance signal. The ^{31}P nmr spectra were obtained on a Varian HR-60 with phosphoric acid (85%) used as an external standard.

Vapor phase chromatography was performed on an F & M Model 700 instrument using a 10% UC-W98 (silicone) on Chromosorb W (60–80 mesh, 12 ft × 0.25 in.) column. Preparative vpc was performed on a Wilkens Aerograph Model A-90P instrument using a 10% UC-W98 (silicone) on Chromosorb W (60–80 mesh, 10 ft × ³/₈ in.) column. The internal standard procedure was used in yield determinations. Thin layer chromatography (tlc) was performed with 2 × 8 in. glass plates coated with silica gel G; the coatings thickness was 0.25 mm. The solvents used in tlc were 20% methanol in chloroform (for phosphonium salts), ethyl acetate (for phosphine oxides), and hexane (for phosphines). An iodine chamber was used for developing the spots. Melting points were determined on a Fisher-Johns or a Thomas-Hoover melting point apparatus and are uncorrected.

1-(3,3-Dibenzoyl)propyltriphenylphosphonium Bromide (4a).—To a slurry of 35 g (0.094 mol) of vinyltriphenylphosphonium bromide (1b) and 21 g (0.094 mol) of 1,3-diphenyl-1,3-propanedione in 400 ml of dry *tert*-BuOH was added 0.5 ml of 10% K⁺O⁻-*tert*-Bu-*tert*-BuOH. The pasty reaction mixture was stirred vigorously at 30° for 48 hr. The milky white slurry was then poured slowly into 2 l. of anhydrous ether. The solid was filtered and air-dried. Recrystallization from MeOH–Et₂O afforded 54.5 g (97%) of small colorless prisms, mp 265–267°. An analytical sample was obtained by recrystallization from MeOH three times: mp 266–268°; ν^{KBr} 1680 (s, >=O), 1115 cm⁻¹ (s, PC); nmr (CF₃CO₂H) 2.37–3.00 (m, 2, CH₂CH₂P⁺Ph₃), 3.42–4.00 (m, 2, CH₂CH₂P⁺Ph₃), 6.30 (t, 1, J = 5.5 Hz, >H), 7.1–8.0 (m, 25, C₆H₅).

Anal. Calcd for C₃₅H₃₀O₂PBr: C, 70.83; H, 5.10. Found: C, 70.67; H, 5.26.

1-(3-Benzoyl-3-carbethoxy)propyltriphenylphosphonium Bromide (4b).—To a slurry of 27.6 g (0.075 mol) of 1b and 44.0 g of ethyl benzoylacetate in 50 ml of dry DMF was added 0.5 ml of 10% K⁺O⁻-*tert*-Bu-*tert*-BuOH. A pale green solution resulted and was stirred at room temperature for 16 hr. The pale green solution was then rapidly poured into 1 l. of anhydrous ether. The ether was decanted from the resulting oil, and the pale yellow oil was dissolved in 100 ml of CH₂Cl₂ followed by dropwise addition to a vigorously stirred benzene solution. The resulting solid was filtered and recrystallized from CH₂Cl₂–C₆H₆, 38 g (95%), mp 104–106°. The solid was found to contain benzene of crystallization, and all attempts to crystallize the compound from a different solvent system only resulted in gummy oils:

ν^{KBr} 1730 (s, ester >=O), 1675 (s, >=O), 1115 cm⁻¹ (s, PC); nmr (CDCl₃) 1.03 (t, 3, J = 7.0 Hz, OCH₂CH₃), 1.86–2.70 (m, 2, CH₂CH₂P⁺Ph₃), 3.61–4.70 (m, 2, CH₂CH₂P⁺Ph₃), 4.08 (q, 2, J = 7.0 Hz, OCH₂CH₃), 5.88 (t, 1, J = 7.0 Hz, >H), 7.0–7.9 (m, 26, C₆H₅).

Anal. Calcd for C₃₁H₃₀O₃PBr·C₆H₆: C, 69.48; H, 5.67. Found: C, 69.23; H, 5.71.

1-(3-Acetyl-3-benzoyl)propyltriphenylphosphonium Bromide (4c).—To a solution of 31.0 g (0.18 mol) of benzoylacetone and 22.1 g (0.06 mol) of 1b in 50 ml of dry DMF was added 0.5 ml of 10% K⁺O⁻-*tert*-Bu-*tert*-BuOH. The yellow solution was stirred at room temperature for 20 hr and then quickly poured into 2 l. of anhydrous ether. A gummy oil resulted which was dissolved in 200 ml of CH₂Cl₂. The CH₂Cl₂ solution was brought to boiling and benzene added until the solution was slightly turbid. The hot solution was allowed to cool slowly to room temperature. The resulting white solid that had crystallized was filtered and washed with 100 ml of cold benzene. Recrystallization from CH₂Cl₂–C₆H₆ afforded 26.0 g (81%) of a powdery white solid: mp 176–177°; ν^{Nujol} 1710 (s, >=O), 1660 (s >=O), 1108 cm⁻¹ (s, PC); nmr (CDCl₃) 1.75–2.67 (m, 2, CH₂CH₂P⁺Ph₃), 2.25 (s, 3, COCH₃), 3.67–4.42 (m, 2, CH₂CH₂-P⁺Ph₃), 6.20 (t, 1, J = 6.5 Hz, >H), 7.1–8.4 (m, 20, C₆H₅).

Anal. Calcd for C₃₀H₂₈O₂PBr: C, 67.82; H, 5.27. Found: C, 68.11; H, 5.40.

2-(2,6-Dioxo-4,4-dimethylcyclohexyl)ethyltriphenylphosphonium Bromide (4d).—To a slurry of 14.0 g (0.10 mol) of dimedon and 36.9 g (0.10 mol) of 1b in 300 ml of dry *tert*-BuOH was added 11.3 g (0.10 mol) of K⁺O⁻-*tert*-Bu. The solution was stirred at 30° for 40 hr and then poured into 2.5 l. of distilled water. The weakly basic solution was made strongly acidic with 48% HBr. Vigorous stirring afforded colorless prisms which were filtered and washed with two 250-ml portions of distilled water. Recrystallization from CH₂Cl₂–EtOAc furnished 37.5 g (76%) of small colorless needles: mp 174–175°; ν^{KBr} 1590 (s, α,β-unsaturated >=O), 1115 cm⁻¹ (s, PC); nmr (CDCl₃) 1.03 (s, 6, iso-CH₃), 2.17–3.53 (m, 5, CH₂CH₂P⁺Ph₃ and OH), 2.43 (broad s, 4, CH₂CO), 7.5–7.9 (m, 15, C₆H₅).

Anal. Calcd for C₂₈H₃₀O₂PBr: C, 66.01; H, 5.93. Found: C, 66.19; H, 6.27.

3-Acetyl-3-carbethoxypentane-1,5-bistriphenylphosphonium Bromide (4e).—To a suspension of 1.30 g (10 mmol) of ethyl acetoacetate and 3.69 g (10 mmol) of vinyltriphenylphosphonium bromide in 10 ml of acetonitrile and 90 ml of anhydrous ether was added 5 drops of 10% K⁺O⁻-*tert*-Bu-*tert*-BuOH. After being stirred at room temperature for 1 hr, the suspension became gummy, and continuous stirring for 16 hr afforded a fluocculent solid. The white solid was filtered and washed with 100 ml of anhydrous ether. Recrystallization from CH₂Cl₂–EtOAc afforded 4.10 g (95%) of small flocculent needles: mp 167–168°; ν^{KBr} 1725 (s, ester >=O), 1680 (s, >=O), 1105 cm⁻¹ (s, PC); nmr (CDCl₃) 1.13 (t, 3, J = 7.0 Hz, OCH₂CH₃, 2.14 (s, 3, COCH₃), 2.29–2.95 (m, 4, CH₂CH₂P⁺Ph₃), 3.45–4.47 (m, 4, CH₂CH₂P⁺Ph₃), 4.12 (q, 2, J = 7.0 Hz, OCH₂CH₃), 7.5–8.3 (m, 30, C₆H₅).

Anal. Calcd for C₄₆H₄₆O₃P₂Br₂: C, 63.66; H, 5.34. Found: C, 64.02; H, 5.37.

3,3-Diacetylpentane-1,5-bistriphenylphosphonium Bromide (4f).—To a solution of 1.00 g (10 mmol) of acetylacetone and

3.69 g (10 mmol) of vinyltriphenylphosphonium bromide in 10 ml of dry DMF was added 5 drops of 10% K^+O^--*tert*-Bu-*tert*-BuOH. The solution was stirred for 18 hr and then triturated with EtOAc under vigorous stirring. The white powder was filtered and washed with 100 ml of dry ether. Recrystallization from CH_2Cl_2-EtOAc afforded 3.10 g (76%) of a white powder: mp 284–286°; ν^{KBr} 1660 (s, >=O), 1104 cm^{-1} (s, PC); nmr (CDCl$_3$) 2.13 (s, 6, COCH$_3$), 2.49–3.28 (m, 4, CH$_2$CH$_2$P$^+$Ph$_3$), 3.28–4.19 (m, 4, CH$_2$CH$_2$P$^+$Ph$_3$), 7.4–8.3 (m, 30, C$_6$H$_5$).

Anal. Calcd for C$_{45}$H$_{44}$O$_2$P$_2$Br$_2$: C, 64.45; H, 5.29. Found: C, 64.59; H, 5.37.

3,3-Dicarbethoxypentane-1,5-bistriphenylphosphonium Bromide (4g).—To a slurry of 1.85 g (10 mmol) of vinyltriphenylphosphonium bromide and 1.30 g (10 mmol) of diethyl malonate in 10 ml of glyme and 5 ml of *tert*-BuOH was added 5 drops of 10% K^+O^--*tert*-Bu-*tert*-BuOH. The slurry was stirred at room temperature, and after 0.5 hr all of the solid had dissolved. After 4 hr, a solid began to precipitated from solution, and stirring was continued for a total of 24 hr. The white solid was filtered and washed with 100 ml of anhydrous ether. Recrystallization from CH$_2$Cl$_2$-EtOAc afforded 1.80 g (73%) of small flocculent needles: mp 155–157°; ν^{KBr} 1720 (s, ester >=O), 1105 cm^{-1} (s, PC); nmr (CDCl$_3$) 1.12 (t, 3, J = 7.0 Hz, OCH$_2$CH$_3$), 2.17–2.83 (m, 4, CH$_2$CH$_2$P$^+$Ph$_3$), 3.58–4.42 (m, 4, CH$_2$CH$_2$P$^+$Ph$_3$), 4.08 (q, 2, J = 7.0 Hz, OCH$_2$CH$_3$), 7.5–8.2 (m, 30, C$_6$H$_5$).

Anal. Calcd for C$_{47}$H$_{44}$O$_4$P$_2$Br$_2$: C, 62.82; H, 5.28. Found: C, 62.57; H, 5.26.

General Procedure for the Preparation of Phosphonium Betaines (6).—To a solution of 16.8 mmol of phosphonium salt **3** in 50 ml of dry solvent was added 1 equiv of base (Table II). The solution was stirred under a nitrogen atmosphere for 15 min. The yellow solution was then poured into 600 ml of distilled water. Immediately a pale yellow solid formed which was filtered, washed with 200 ml of distilled water, and then washed with 400 ml of anhydrous ether. The pale yellow solid was dried *in vacuo* and then recrystallized from CH$_2$Cl$_2$-benzene.

1-(3,3-Dibenzoyl)propyltriphenylphosphonium betaine (6a): mp 188–189°; ν^{KBr} 1570 (w), 1450 (s, CO), 1110 cm^{-1} (s, PC); nmr (CDCl$_3$) 2.91–3.83 (m, 4, CH$_2$CH$_2$P$^+$Ph$_3$), 6.6–8.1 (m, 25, C$_6$H$_5$); ^{31}P nmr (CHCl$_3$) −20.1 ppm.

Anal. Calcd for C$_{35}$H$_{29}$O$_2$P: C, 82.01; H, 5.70. Found: C, 82.03; H, 5.52.

1-(3-Benzoyl-3-carbethoxy)propyltriphenylphosphonium betaine (6b): mp 113–114°; ν^{KBr} 1600 (s, ester CO), 1470 (s, CO), 1100 cm^{-1} (m, PC); nmr (CDCl$_3$) 0.77 (t, 3, J = 7.0 Hz, OCH$_2$CH$_3$), 2.67–4.21 (m, 4, CH$_2$CH$_2$P$^+$Ph$_3$), 3.80 (q, 2, J = 7.0 Hz, OCH$_2$CH$_3$), 7.1–8.2 (m, 20, C$_6$H$_5$); ^{31}P nmr (CHCl$_3$) −21.6 ppm.

Anal. Calcd for C$_{39}$H$_{29}$O$_3$P: C, 77.48; H, 6.08. Found: C, 77.38; H, 6.30.

1-(3-Acetyl-3-benzoyl)propyltriphenylphosphonium betaine (6c): mp 181–182° dec; ν^{Nujol} 1550 (m, CO), 1440 (s, CO), 1105 cm^{-1} (s, PC); nmr (CDCl$_3$) 1.77 (s, 3, COCH$_3$), 2.67–3.67 (m, 4, CH$_2$CH$_2$P$^+$Ph$_3$), 7.1–8.0 (m, 20, C$_6$H$_5$); ^{31}P nmr (CHCl$_3$) −21.6 ppm.

Anal. Calcd for C$_{30}$H$_{27}$O$_2$P: C, 79.97; H, 6.04. Found: C, 79.99; H, 6.18.

General Procedure for the Treatment of Phosphonium Betaines 6 with HBr.—To a solution of 100 mg of betaine in 2.0 ml of methanol was added 1.0 ml of 10% HBr. The yellow solution turned colorless immediately. The addition of 20 ml of distilled water, scratching, and chilling furnished the corresponding phosphonium salt.

General Procedure for the Treatment of Phosphonium Betaines 6 with CH$_3$I.—A solution of 300 mg of betaine in 10 ml of CH$_3$I was refluxed for 0.5 hr. The solution had changed from yellow to colorless. The CH$_3$I solution was then concentrated *in vacuo* and triturated with EtOAc. The white solid was filtered and recrystallized from CH$_2$Cl$_2$-EtOAc. All filtrates were examined by nmr and tlc for other products and in all cases none were found.

1-(3-Benzoyl-4-methoxy-4-phenyl)-3-butenyltriphenylphosphonium iodide (10a): yield 325 mg (87%); mp 216–218°; ν^{KBr} 1600 (s, α,β-unsaturated >=O), 1100 cm^{-1} (s, PO); nmr (CDCl$_3$) 2.51–3.14 (m, 2, CH$_2$CH$_2$CH$_2$P$^+$Ph$_3$), 3.59 (s, 3, OCH$_3$), 3.33–4.08 (m, 2, CH$_2$CH$_2$P$^+$Ph$_3$), 6.9–8.2 (m, 25, C$_6$H$_5$).

Anal. Calcd for C$_{36}$H$_{32}$O$_2$PI: C, 65.63; H, 4.72. Found: C, 65.82; H, 4.76.

1-(3-Benzoyl-3-carbethoxy)butyltriphenylphosphonium iodide (9b): yield 380 mg (100%); mp 85–95°; ν^{KBr} 1715 (s, ester

>=O), 1660 (s, >=O), 1100 cm^{-1} (s, PC); nmr (CDCl$_3$) 0.96 (t, 3, J = 7.0 Hz, OCH$_2$CH$_3$), 1.73 (s, 3, CCH$_3$), 1.91–2.55 (m, 2, CH$_2$CH$_2$P$^+$Ph$_3$), 3.19–3.92 (m, 2, CH$_2$CH$_2$P$^+$Ph$_3$), 4.08 (q, 2, J = 7.0 Hz, OCH$_2$CH$_3$), 7.2–8.0 (m, 20, C$_6$H$_5$).

Anal. Calcd for C$_{32}$H$_{32}$O$_3$PI: C, 61.74; H, 5.18. Found: C, 61.70; H, 5.27.

1-(3-Acetyl-3-benzoyl)butyltriphenylphosphonium iodide (9c): yield 300 mg (78%); mp 168–170°; ν^{Nujol} 1665 (s, >=O), 1105 cm^{-1} (s, PC); nmr (CDCl$_3$) 1.77 (s, 3, CCH$_3$), 1.78–2.50 (m, 2, CH$_2$CH$_2$P$^+$Ph$_3$), 2.17 (s, 3, COCH$_3$), 2.75–3.72 (m, 2, CH$_2$CH$_2$P$^+$Ph$_3$), 7.2–8.0 (m, 20, C$_6$H$_5$).

Anal. Calcd for C$_{31}$H$_{30}$O$_2$PI: C, 62.85; H, 5.10. Found: C, 63.10; H, 5.12.

2-(1-Methyl-2,6-dioxo-4,4-dimethylcyclohexyl)ethyltriphenylphosphonium iodide (9d) and 2-(2-methoxy-6-oxo-4,4-dimethylcyclohex-1-enyl)ethyltriphenylphosphonium iodide (10d): ν^{Nujol} 1710 (s), 1680 (s), 1590 (w, >=O), 1110 cm^{-1} (s, PC); nmr (CDCl$_3$) 0.88 (s, 3, CCH$_3$), 1.13 (s, 3, CCH$_3$), 1.29 (s, 3, CCH$_3$), 1.8–3.5 (m, 16, CH$_2$CH$_2$P$^+$Ph$_3$, CH$_2$CO), 3.98 (s, 3, OCH$_3$), 7.5–8.0 (m, 30, C$_6$H$_5$).

Anal. Calcd for C$_{29}$H$_{32}$O$_2$PI: C, 61.06; H, 5.66. Found: C, 61.17; H, 5.60.

Pyrolysis of 6a.—In a short-path distillation apparatus 3.40 g (6.65 mol) of 1-(3,3-dibenzoyl)propyltriphenylphosphonium betaine (6a) was slowly evacuated to 0.10 mm. The flask was then immersed in a Wood's metal bath at 260° and the distillate was collected in a receiver cooled by Dry Ice. A yellow oil (2.05 g) collected. The oil was chromatographed on Florisil and eluted with benzene. Fraction one afforded a colorless oil. The colorless oil was refluxed overnight with 30 ml of anhydrous Et$_2$O and 2.0 ml of methyl iodide. Filtration of the white solid and washing with 20 ml of cold Et$_2$O afforded 450 mg of methyltriphenylphosphonium iodide: mp 193–194°; ir and nmr were identical with those of an authentic sample.

The solvent was then changed to 20% EtOAc-C$_6$H$_6$. The second fraction collected was concentrated *in vacuo* to 240 mg (14%) of a pale yellow oil. Preparative vpc afforded an analytical sample of 2-phenyl-3-benzoyl-4,5-dihydrofuran (11a): ν^{neat} 1600 (s, >=O), 1220 cm^{-1} (m, vinyl ether); nmr (CDCl$_3$) 3.23 (t, 2, J = 10.5 Hz, OCH$_2$CH$_2$), 4.55 (t, 2, J = 10.5 Hz, OCH$_2$CH$_2$), 7.3–8.1 (m, 10, C$_6$H$_5$); mass spectrum *m/e* 250.

Anal. Calcd for C$_{17}$H$_{14}$O$_2$: C, 81.57; H, 5.64. Found: C, 81.76; H, 5.71.

Elution was continued and the third fraction upon concentration and crystallization from methanol afforded 140 mg (10%) of dibenzoylmethane: mp 72–73°; mixture melting point with an authentic sample showed no depression.

Elution was then started with methanol and the fourth and final fraction was collected. Concentration and treatment with HBr afforded 173 mg (6%) of phenacyltriphenylphosphonium bromide: mp 281–282°; ir and nmr identical with that of an authentic sample. In a separate experiment the phenacyltriphenylphosphorane was isolated and shown to be identical with an authentic sample. Examination of the distillation residue by tlc showed the presence of a small amount of triphenylphosphine and mostly polymeric material.

General Procedure for the Pyrolysis of Betaines 6b–d.—In a short-path distillation apparatus betaine was slowly evacuated to 0.10 mm, the flask was then immersed in a Wood's metal bath at 200°, and the distillate was collected in a receiver cooled by Dry Ice. The cyclopropane and dihydrofuran were separated by preparative vpc and analytical samples obtained.

Ethyl 1-benzoylcyclopropanecarboxylate (12b) and 2-phenyl-3-carbethoxy-4,5-dihydrofuran (11b) spectra were identical with those of authentic samples.[14]

1-Acetyl-1-benzoylcyclopropane (12c): ν^{neat} 1680 (s, >=O), 1660 (s, >=O), 1010 cm^{-1} (m, cyclopropyl); nmr (CDCl$_3$) 1.55 (dd, 4, J = 4.0, 1.0 Hz, cyclopropyl H's), 2.07 (s, 3, COCH$_3$), 7.3–8.1 (m, 5, C$_6$H$_5$); mass spectrum *m/c* 188.

Anal. Calcd for C$_{12}$H$_{12}$O$_2$: C, 76.57; H, 6.43. Found: C, 76.46; H, 6.42.

2-Methyl-3-benzoyl-4,5-dihydrofuran (11c') and 2-phenyl-3-acetyl-4,5-dihydrofuran (11c): ν^{neat} 1680 (m, >=O), 1660 (s, >=O), 1220 (s, COC), 885 cm^{-1} (m); nmr (CDCl$_3$) 1.84 (t, 3, J = 1.2 Hz, CH$_3$CO), 1.97 (s, 3, COCH$_3$), 3.10 (t, 2, J = 10.0 Hz, OCH$_2$CH$_2$), 3.14 (t, 2, J = 10.0 Hz, OCH$_2$CH$_2$), 4.45 (t, 2, J = 10.0 Hz, OCH$_2$CH$_2$), 4.53 (t, 2, J = 10.0 Hz, OCH$_2$CH$_2$), 7.2–8.0 (m, 10, C$_6$H$_5$); mass spectrum *m/c* 188.

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Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.41; H, 6.35.

4-Oxo-6,6-dimethyl-4,5,6,7-tetrahydrocoumaran (11d).—Spectra were identical with that reported by Ichikawa, *et al.*[12]

Preparation of 1,1-Diacetylcyclopropane (12e).—To a solution of 3.00 g (30 mmol) of acetylacetone in 200 ml of anhydrous ether was added 1 equiv of K^+O^--*tert*-Bu. The reaction mixture was stirred for 2 hr, 11.10 g (30 mmol) of vinyltriphenylphosphonium bromide added, and the mixture stirred overnight. The solid was filtered and washed with 200 ml of ether. The solid was transferred to a Soxhlet and extracted with benzene for 24 hr. The benzene solution was concentrated *in vacuo* and the residue dissolved in ether. The ether solution was refluxed overnight with 5 ml of CH_3I. The white methyltriphenylphosphonium iodide was filtered. The ether filtrate was concentrated *in vacuo* and distilled to give 650 mg of 12e.[11]

Preparation of 1-Acetyl-1-carbethoxycyclopropane (12d).—To a solution of 2.60 g (0.02 mol) of ethyl acetoacetate in 300 ml of anhydrous ether was added 2.26 g (0.02 mol) of K^+O^--*tert*-Bu. The reaction mixture was stirred at room temperature for 1 hr. To the white flocculent solid was added 7.38 g of vinyltriphenylphosphonium bromide, and the reaction mixture stirred for an additional 2 hr. The yellow solid was filtered and washed with 200 ml of anhydrous Et_2O. The yellow solid was placed in a Soxhlet extractor and extracted with toluene for 24 hr. The yellow toluene solution was concentrated *in vacuo* and the residue dissolved in 100 ml of ether and refluxed overnight with 5 ml of CH_3I. The white methyltriphenylphosphonium iodide was filtered, 4.96 g; melting point and spectra were identical with that of an authentic sample. The ether filtrate was concentrated *in vacuo* and distilled to give 1.84 g (58%) of 12d; vpc retention time and spectra were identical with those of an authentic sample prepared by the method of Perkin.[15]

General Procedure for the Base-Catalyzed Rearrangement of Cyclopropanes.—In a sealed nmr tube was placed 80 mol % of cyclopropane and 20 mol % of triphenylphosphine or triethylamine. The tube was heated in a silicone oil bath at 200 ± 5°. The reaction was monitored by nmr for the appearance of 4,5-

(15) T. R. Marshall and W. H. Perkin, *J. Chem. Soc.*, **59**, 880 (1891).

dihydrofuran and the disappearance of cyclopropane. The yield was determined by nmr and then checked by vpc upon completion of the reaction. All cyclopropane samples were heated at 200° without base present for the same period of time to determine whether or not the furan arose by a thermal pathway. None of the cyclopropanes showed any change after the heating period.

2-Phenyl-3-carbethoxy-4,5-dihydrofuran (11b).—Spectra and vpc retention time were identical with those of a previous sample of 11b.

2-Methyl-3-benzoyl-4,5-dihydrofuran (11c) and 2-Phenyl-3-acetyl-4,5-dihydrofuran (11c').—Spectra and vpc retention time were identical with those of a previous sample of 11c and 11c'.

2-Methyl-3-acetyl-4,5-dihydrofuran (11e): ν^{neat} 1660 (m, >=O), 1230 cm^{-1} (s, COC); nmr (CDCl$_3$) 2.21 (s, 6, COCH$_3$ and CH$_3$C(O)=), 2.93 (t, 2, J = 10.0 Hz, OCH$_2$CH$_2$), 4.40 (t, 2, J = 10.0 Hz, OCH$_2$CH$_2$); mass spectrum m/e 126.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.56; H, 7.94.

2-Methyl-3-carbethoxy-4,5-dihydrofuran (11f): ν^{neat} 1700 (s, α,β-unsaturated >=O), 1650 (s, >=O), 1200 cm^{-1} (s, COC); nmr (CDCl$_3$) 1.23 (t, 3, J = 7.0 Hz, OCH$_2$CH$_3$), 2.18 (t, 3, J = 1.2 Hz, CH$_3$), 2.81 (t, 2, J = 10.0 Hz, OCH$_2$CH$_2$, 4.18 (q, 2, J = 7.0 Hz, OCH$_2$CH$_3$), 4.33 (t, 2, J = 10.0 Hz, OCH$_2$-CH$_2$); mass spectrum m/e 156.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.71. Found: C, 61.86; H, 7.63.

Registry No.—4a, 28638-64-4; **4b,** 28638-65-5; **4c,** 28638-66-6; **4d,** 28638-67-7; **4e,** 28638-68-8; **4f,** 28638-69-9; **4g,** 28638-70-2; **6a,** 28638-71-3; **6b,** 28638-72-4; **6c,** 28638-73-5; **9b,** 28638-74-6; **9c,** 28638-75-7; **9d,** 28638-76-8; **10a,** 28638-77-9; **10d,** 28638-78-0; **11a,** 28638-79-1; **11c,** 28638-80-4; **11c',** 28638-81-5; **11e,** 5831-64-1; **11f,** 2986-03-0; **12c,** 5186-09-4.

Double-Bond Migration in 1-Methyl-4-(carbethoxymethylene)phosphorinane[1]

Louis D. Quin,* John W. Russell, Jr., René D. Prince, and Howard E. Shook, Jr.

Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

The product from the Wittig reaction of 1-methyl-4-phosphorinanone with carbethoxymethylenephosphorane was unexpectedly a mixture of 1-methyl-4-(carbethoxymethylene)phosphorinane (2) and 1-methyl-4-carbethoxymethyl-1,2,5,6-tetrahydrophosphorin (3). However, reaction of the ketone with the carbanion of triethylphosphonoacetate gave only 2. This compound was found to be readily isomerized to 3 under basic or thermal conditions, accounting for the formation of the isomer mixture in the Wittig procedure. The same conditions were without effect on ethyl cyclohexylideneacetate, although the thermal treatment did cause extensive rearrangement of *N*-methyl-4-(carbethoxymethylene)piperidine. The pronounced tendency for the phosphine and the amine to rearrange was attributed to intramolecular catalysis of enolization by the basic centers.

One of the valuable features of the Wittig olefin synthesis is the specificity with which the product is obtained; isomer formation is not known to occur in this process. However, we found that 1-methyl-4-phosphorinanone (1), on reaction with the phosphorane prepared *in situ* from carbethoxymethyltriphenylphos-

phonium bromide and sodium ethoxide, gave an unsaturated product consisting of almost equal amounts of two isomers, 2 and 3. This observation prompted an investigation of the factors responsible for the formation of isomer 3 and a comparison of the behavior of ketone 1 with that of cyclohexanone and of *N*-methyl-4-piperidone in this reaction.

The study was facilitated by the obtention of pure 2 in 55% yield when the ketone was reacted with the carbanion of triethylphosphonoacetate.[2] The structure of the product was easily established by its spectral features. The uv spectrum was that of an α,β-unsaturated

(1) Supported by Public Health Service Research Grant CA-05507 from the National Cancer Institute.

(2) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961). This reagent is preferred for introducing the carbethoxymethylene group into cyclic ketones.[3]

(3) (a) S. Sugasawa and H. Matsuo, *Chem. Pharm. Bull.*, **8**, 819 (1960); (b) S. Trippett and D. W. Walker, *Chem. Ind. (London)*, 990 (1961).

ester ($\lambda_{max}^{ethanol}$ 210 mμ, ϵ 13,700), as was the ir spectrum ($\nu_{C=O}$ 1716 and intense $\nu_{C=C}$ at 1645 cm^{-1}). The nmr spectrum, which confirmed the assignment, was of special interest in that the two allylic CH$_2$ groups had quite different chemical shifts (δ 3.15 and 2.24 ppm). This is due to the anisotropic effect of the carbonyl group, deshielding that CH$_2$ which is cis to it. That *both* protons of the cis CH$_2$ are affected is significant, for in the related cyclohexylidene derivatives 4[4] and 5,[5]

4

5
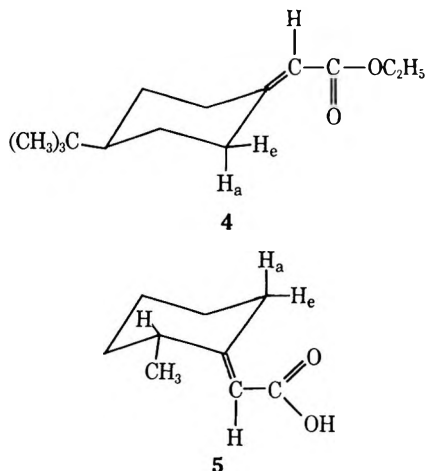
only the cis proton in the equatorial position is deshielded by carbonyl (to roughly the same extent seen in 2). The different behavior for 2 can be related to the failure of the CH$_3$ group on phosphorus, which is configurationally stable, to exert a preference for the equatorial over the axial position.[6] The conformational equilibrium is not biased and permits no distinction between the equatorial and axial protons at the allylic position with regard to the deshielding effect of the carbonyl group.
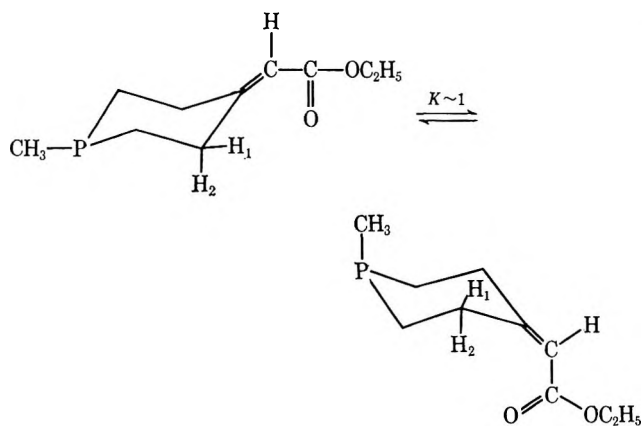
The presence of **3** in the product from the reaction of 1 with carbethoxymethylenephosphorane (either preformed or generated *in situ*) was evident from the gas chromatogram, as well as from the ir spectrum which showed a second C=O band at higher frequency (1738 cm^{-1}). Isomer **3** gave a different nmr spectrum, possessing a singlet (δ 2.88, broad) attributable to CH$_2$ exo to the ring. The rearrangement was then found to

(4) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(5) H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965).

(6) H. E. Shook, Jr., and L. D. Quin, *J. Amer. Chem. Soc.*, **89**, 1841 (1967); to be treated more fully in a forthcoming paper (L. D. Quin and J. H. Somers).

have occurred during the distillation, for gas chromatography showed that at the conclusion of the reaction prior to this step only 2 was present.

That compound 2 was thermally unstable relative to 3 was established by heating pure 2 for 5 hr at 170° whereupon an isomer mixture of 86% 3–14% 2 resulted. No change occurred on further heating. Base also caused rearrangement; holding an ethanolic solution of 2 (0.5 *M*) and sodium ethoxide (8 × 10^{-3} *M*) at 35° gave after 13 days a 1:1 isomer mixture, while after 64 days the mixture consisted of 86% 3–14% 2. Traces of base remaining in the crude product to be distilled, in combination with high pot temperatures, could therefore bring about the rearrangement observed in the purification of the Wittig product. That the phosphonate carbanion procedure gave a pure product may be due to the routine inclusion in this procedure of a water-washing step, which would have removed residual base prior to the distillation. While the difference between the two procedures was not further investigated, it is clear that the phosphonate carbanion method is preferred for the synthesis of 2, giving a higher yield of pure product.

In a classical study of many years ago,[7] the tendency of cyclohexylidene esters (*e.g.*, **6**) to undergo base-catalyzed rearrangement was established. Nevertheless, cyclohexanone has been reported to form 6 in the Wittig reaction without the production of isomer[2,3] and we have confirmed this. However, when a small excess of sodium ethoxide (10%) was intentionally used to generate the phosphorane, the product both before and after distillation contained about 30% isomer 7.

6   **7**
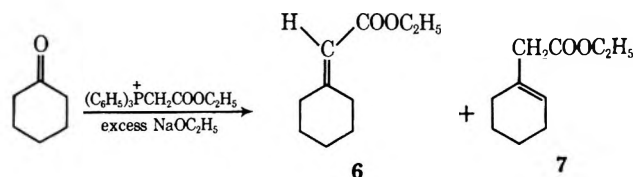
Its presence was readily detected by gas chromatography and by ir spectroscopy ($\nu_{C=O}$ 1739 cm^{-1}). That the cyclohexylidene system was nevertheless much less prone to rearrange than was the phosphine analog 2 was noted from the failure of the same thermal or basic treatment so destructive to 2 to have any effect on 6.

The nitrogen counterpart 8 of phosphine 2 was obtained free of isomer by the phosphonate carbanion method applied to N-methyl-4-piperidone. It was characterized by spectral features similar to those useful for 2, including the specific deshielding by carbonyl of the allylic CH$_2$ cis to it. While 8 was unaffected by the basic treatment causing phosphine 2 to rearrange, it did undergo thermal rearrangement, providing a mixture of 75% 9–25% 8 after 5 hr at 170°.

Apparently, the presence of similarly located basic atoms is the common feature in phosphine 2 and amine 8 leading to their rapid rearrangement under conditions not affecting their carbocyclic counterpart 6. The rearrangement is associated with the tendency for the resonance-stabilized enolate ion to form, by loss of a proton at the allylic position. That those compounds with a basic center rearrange so rapidly suggests the

(7) G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, 1269 (1929); G. A. R. Kon, R. P. Linstead, and G. W. R. Maclennan, *ibid.*, 2454 (1932).
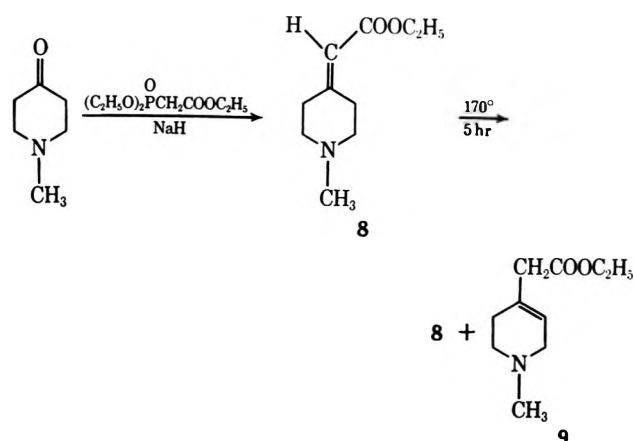
participation of this center in the enolization. This may be expressed by the intramolecular proton transfer process shown below.

X = CH₃N or CH₃P
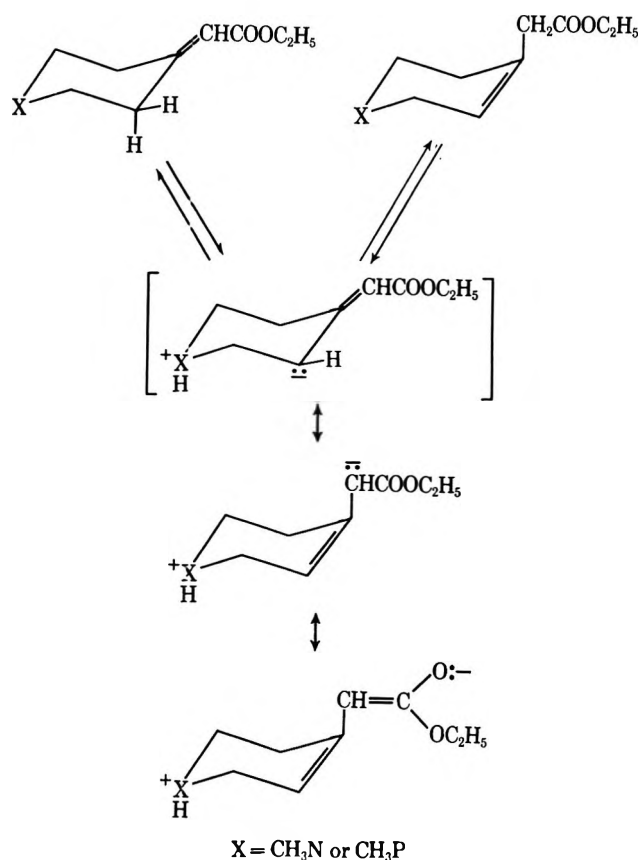
Mention is made of such intramolecular catalysis of enolization to explain the pronounced tendency of compound **10** to rearrange to **11**,[8] a property absent in
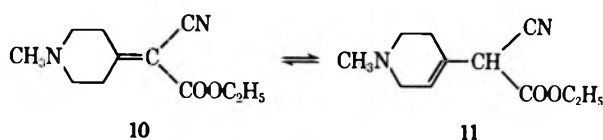
the carboxyclic analog.[9] The greater stability of compounds **3** and **9**, with the double bond endo, than of their isomers with the exo double bond (**2** and **8**, respectively), is not unexpected, based on the numerous observations of the same phenomenon for cyclohexane

derivatives.[7,10] The novel feature of the present study is the more pronounced tendency of the phosphine system to undergo the rearrangement, leading to the unusual result of the formation of an isomer mixture in a Wittig product.[11]

Two other Wittig reaction were performed with 4-phosphorinanones without the formation of isomerized material. With methylenetriphenylphosphorane, ketone **1** gave the expected product **12**, while 1-ethyl-4-phosphorinanone gave only **13** with benzylidenetriphe-

nylphosphorane. The allylic protons of **13** appeared as a 4-H broad multiplet; the phenyl group did not cause their differentiation as the carbonyl did in **2**. While the rearrangement would be expected to be slow with these compounds lacking the capability of forming the resonance-stabilized enolate, another factor needs also to be considered. Phosphorane generation in each case requires the use of stronger base (*n*-butyllithium) than the sodium ethoxide used for generating the more stable carbethoxymethylene ylide. Following each condensation, the reaction mixture was washed with water, thus removing residual base which might promote rearrangement during product distillation. These experiments suggest that the problem of isomer formation in Wittig reactions of phosphorinanones may be limited to special cases and may be solved by use of modified isolation procedures or of the phosphonate carbanion method.
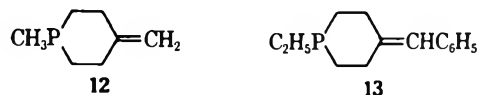
In one attempted Wittig preparation of **2**, a product containing only 10% of this isomer (with 90% **3**) was obtained. This mixture was subjected to lithium aluminum hydride reduction to form a mixture of unsaturated alcohols **14** and **15**, used in previously re-

ported work.[12] The reduction proceeded in good yield with retention of the starting isomer ratio.
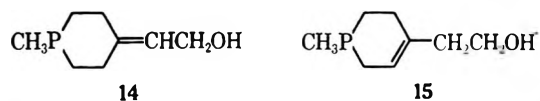
Experimental Section

All operations involving phosphines were conducted in a nitrogen atmosphere. 1-Methyl-4-phosphorinanone (**1**) was prepared as described previously.[6] 1,2-Dimethoxyethane was distilled over sodium hydride; ethanol was digested with calcium oxide and then subjected to azeotropic distillation with benzene. Ir spectra were obtained with Perkin-Elmer 137 or 237 spectrophotometers, uv spectra with a Beckman DB-G spectrophotometer, and nmr spectra with a Varian A-60 spectrometer. Nmr chemical shifts are relative to tetramethylsilane as internal standard. Gas chromatography (gc) was performed with a Varian-Aerograph Model 202-1B instrument, using a 5 ft by 0.25

(8) S. M. McElvain and R. E. Lyle, *J. Amer. Chem. Soc.*, **72**, 384 (1950).
(9) E. Vargha and I. Mester, *Stud. Univ. Babes-Bolyai, Ser. Chem.*, 127 (1962); *Chem. Abstr.*, **61**, 2983 (1964).

(10) For recent discussions, see P. Coppens, E. Gil-Av, J. Herling, and J. Shabtai, *J. Amer. Chem. Soc.*, **87**, 4111 (1965); N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *ibid.*, **90**, 5773 (1968).

(11) This appears not to be an isolated instance of intramolecular participation of tertiary phosphorus in enolization, as we have observed other effects explicable on the same basis. Thus, in connection with another study to be reported in full elsewhere, we have found that ketone **1** can be extensively deuterated at the 3,5 positions merely by exposing it to a dioxane–D₂O mixture at room temperature. 4-Methylcyclohexanone was not deuterated in this medium: L. D. Quin and J. J. Breen, unpublished results.

(12) L. D. Quin and H. E. Shook, Jr., *J. Org. Chem.*, **32**, 1604 (1967).

in. stainless steel column packed with 20% SE-30 on 60–80 mesh acid-washed Chromosorb W. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Synthesis of 1-Methyl-4-(carbethoxymethylene)phosphorinane (2).—The carbanion of triethylphosphonoacetate (6.4 g, 0.0285 mol) was prepared by adding it to a suspension of 1.15 g (0.0285 mol) of sodium hydride (56.9% dispersion) in 60 ml of 1,2-dimethoxyethane. The temperature was kept below 20° during the addition (45 min), following which the mixture was stirred at room temperature for 1 hr. To this solution was added 4.0 g (0.0285 mol) of 1-methyl-4-phosphorinanone (1) over a 20-min period, maintaining the temperature below 30°. The mixture was stirred additionally for 30 min, during which time a viscous semisolid precipitated. The entire mixture was taken up in excess water and the solution extracted with three 250-ml portions of ether. The extracts, after drying over magnesium sulfate, were stripped of solvent on a rotary evaporator, and the residue was distilled to give 3.7 g (55%) of 2 at 58–59° (0.03 mm), pure by gc: uv $\lambda_{max}^{95\% \ EtOH}$ 210 mμ (ϵ 13,700); ir (neat), $\nu_{C=O}$ 1716 (strong), $\nu_{C=C}$ 1645 cm^{-1} (moderately strong); nmr (CDCl$_3$) δ 5.69 (broad s, 1, C=CH), 4.12 (q, 2, J = 7 Hz, OCH$_2$CH$_3$), 3.15 (m, 2, cis-EtO$_2$CC=C—CH$_2$), 2.24 (m, 2, trans-EtO$_2$CC=C—CH$_2$), 1.4–3.4 (m, 2, ring CH$_2$), 1.12 (t, 3, J = 7 Hz, OCH$_2$CH$_3$), 0.90 ppm (d, 3, J_{PCH} = 3.5 Hz, PCH$_3$).

Anal. Calcd for C$_{10}$H$_{17}$PO$_3$: C, 59.98; H, 8.55; P, 15.46. Found: C, 59.73; H, 8.53; P, 15.62.

Reaction of Carbethoxymethylenetriphenylphosphorane with 1-Methyl-4-phosphorinanone (1).—The phosphorane was prepared from 17.0 g (0.040 mol) of carbethoxymethyltriphenylphosphonium bromide and a solution of 0.81 g (0.0356 g-atom) of sodium in 80 ml of ethanol. After being stirred for 1 hr at room temperature, the solution was treated with 5.0 g (0.0356 mol) of 1 and the mixture was stirred for 7 days at room temperature, conditions found useful for reactions with cyclic ketones.[3a] Periodic and final analysis by gc showed the presence of 2 as the only significant product. Solvent was then removed on a rotary evaporator, and the residual oil taken up in 60 ml of ether. After refrigeration overnight, triphenylphosphine oxide precipitated and was removed by filtration. Solvent was stripped and the residue again analyzed by gc, revealing only 2 as the major product. Distillation then gave 1.05 g (15%) of product at 88–90° (1.5 mm), shown by gc to contain 45% 3–55% 2. The ir spectrum contained a second $\nu_{C=C}$ for 3 at 1738 cm^{-1}.

A higher yield of the isomer mixture was obtained using preformed carbethoxymethylenetriphenylphosphorane. A solution of 12.5 g (0.0358 mol) of the phosphorane in 80 ml of ethanol was treated with 5.0 g (0.0356 mol) of ketone 1 and the solution stirred for 7 days at room temperature. Work-up as before gave 2.2 g (31%) of product distilling at 63–65° (0.03 mm), consisting of 37% 3–63% 2. Gc monitoring again revealed the presence of no 3 prior to the distillation.

Base Catalysis of Rearrangement of 1-Methyl-4-(carbethoxymethylene)phosphorinane (2).—To a 5-ml volumetric flask was added 0.5005 g (0.0025 mol) of 2 and 1 ml of 0.040 *M* ethanolic sodium ethoxide. The mixture was diluted to the mark with ethanol and placed in a constant temperature bath at 35°. The solution was analyzed periodically by gc. After 13 days, the solution contained equal amounts of 2 and 3, and after 64 days 84% 3–16% 2.

Thermal Rearrangement of 2.—In each of several capillary tubes was placed 10 μl of 2. These were sealed and placed in an oil bath at 170 ± 1°. Periodically, a tube was withdrawn and chilled, and its contents were analyzed by gc. After 5 hr, a mixture of 86% 3–14% 2 had been reached and was unchanged in samples heated several additional hours.

A 1:5 mixture of 2 and 3 (2.65 g) was held in a 150° bath for 36 hr. The material was distilled, but only 0.01 g was obtained, bp 86° (0.45 mm), since extensive decomposition had occurred. Gc showed the product to be 93% 3–7% 2. The purity was sufficient to make spectral measurements for 3: uv $\lambda_{max}^{95\% \ EtOH}$ 206 mμ (ϵ 4500); ir (neat) $\nu_{C=O}$ 1736, $\nu_{C=C}$ 1653 (weak) cm^{-1}; nmr (CDCl$_3$) δ 5.59 (s, 2, C=CH), 4.08 (q, 2, J = 7 Hz, OCH$_2$CH$_3$), 2.88 (broad s, 2, CH$_2$COOR), 1.3–2.5 (m, 6, ring protons), 1.16 (t, 3, J = 7 Hz, OCH$_2$CH$_3$), 0.89 ppm (d, 3, J_{PCH} = 3.5 Hz, PCH$_3$).

Ethyl Cyclohexylideneacetate (6).—The carbanion from triethylphosphonoacetate (11.2 g, 0.05 mol) was prepared as described previously and treated with 4.9 g (0.05 mol) of cyclohexanone. The same work-up procedure was used, and the product (4.7 g, 56%) distilled at 34.5–35° (0.11 mm) [lit.[2] bp 89–90° (10 mm)]. No isomer 7 was indicated by gc: uv $\lambda_{max}^{95\% \ EtOH}$

221 mμ (ϵ 13,300) [lit.[3] 219 mμ (ϵ 13,500)]; ir (neat) $\nu_{C=O}$ 1720 (strong), $\nu_{C=C}$ 1650 (moderately strong); nmr (neat) δ 5.62 (broad s, 1, C=CH), 4.16 (q, 2, J = 7 Hz, OCH$_2$CH$_3$), 2.84 (m, 2, cis-EtO$_2$CC=C—CH$_2$), 2.18 (m, 2, trans-EtO$_2$CC=C—CH$_2$), 1.45–2.85 (m, 4, other ring methylenes), 1.28 ppm (t, 3, J = 7 Hz, OCH$_2$CH$_3$).

6 was also prepared in 33% yield from preformed carbethoxymethylenetriphenylphosphorane (17.4 g, 0.05 mol) and cyclohexanone (4.9 g, 0.05 mol) in ethanol (100 ml) for 7 days at room temperature. Triphenylphosphine oxide was precipitated from the residue left from solvent stripping by adding ether and refrigerating. The distilled product (2.8 g) was free of 7 by gc and had properties identical with those of the above sample.

When the phosphorane was generated *in situ* as in the reaction with ketone 1, a 40% yield of 6, free of 7, was obtained. With an excess of sodium ethoxide (0.055 mol) to the phosphonium salt (0.05 mol) and cyclohexanone (0.05 mol), the product, prior to stripping ethanol solvent, was shown by gc to contain 28% 7–72% 6. After work-up as before, the final product contained 30% 7–70% 6. The ir spectrum had $\nu_{C=O}$ for 6 at 1718 and for 7 at 1739 cm^{-1}.

Attempted Rearrangement of Ethyl Cyclohexylideneacetate (6).—Conditions for base-catalyzed and thermal rearrangement used for 2 were applied to 6. Gc revealed the presence of no isomer 7 after 64 days in base, or after 5 hr at 170°.

N-Methyl-4-(carbethoxymethylene)piperidine (8).—Following the procedure already described, triethylphosphonoacetate (11.2 g, 0.05 mol) was converted to its carbanion and reacted with 5.65 g (0.05 mol) of N-methyl-4-piperidone. The product (6.3 g, 68%) had bp 44–45° (0.05 mm) and gc revealed no isomer to be present: uv $\lambda_{max}^{95\% \ EtOH}$ 215 mμ (ϵ 13,900); ir (neat) $\nu_{C=O}$ 1718, $\nu_{C=C}$ 1655 cm^{-1}, both strong; nmr (CDCl$_3$) δ 5.65 (broad s, 1, C=CH), 4.14 (q, 2, J = 7 Hz, OCH$_2$CH$_3$), 3.04 (m, 2, cis-EtO$_2$CC=C—CH$_2$), 2.17–3.69 (m, 4, ring CH$_2$ including allylic CH$_2$ trans to COOEt), 2.27 (s, 3, NCH$_3$), 1.25 ppm (t, 3, J = 7 Hz, OCH$_2$-CH$_3$).

Anal. Calcd for C$_{10}$H$_{17}$NO$_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.30; H, 9.44; N, 7.68.

Preparation of 8 *via* the Wittig method, using *in situ* ylide generation, gave a 50% yield, with no isomer present.

Rearrangement of N-Methyl-4-(carbethoxymethylene)piperidine (8).—The technique used for thermal rearrangement of 2 was followed. After 5 hr at 170°, the composition, 25% 8–75% 9, had been reached. The basic conditions used for rearranging 2 were without effect on 8 after 64 days.

1-Methyl-4-methylenephosphorinane (12).—To a solution of 0.030 mol of n-butyllithium (19.2 ml of 1.6 *M* hexane solution) in 100 ml of anhydrous ether was added 10.7 g (0.030 mol) of methyltriphenylphosphonium bromide over a period of 10 min. The mixture was stirred for 5 hr at room temperature; some yellow solid precipitated. To the mixture was added 2.88 g (0.022 mol) of 1-methyl-4-phosphorinanone (1) in 100 ml of ether. Heat of the reaction caused the ether to reflux. The mixture was held at reflux for 17 hr. A fine precipitate that formed was removed by filtration on Whatman No. 41 paper. The residue was washed with ether. The filtrate was extracted with water; after four 100-ml washes, the water extract was neutral. The ether wash of the solid and the ether layer from the water extraction were combined, dried over magnesium sulfate, and stripped of ether. The residue was distilled, yielding 1.22 g (43%) at 30–40° (5 mm): ir (neat) $\nu_{C=C}$ 1645, $\sigma_{=CH_2}$ 890 cm^{-1}; nmr (neat) δ 4.51 (s, 2, =CH$_2$), 1.2–2.6 (m, 8, ring CH$_2$ groups), 1.02 ppm (d, 3, J_{PCH} = 3 Hz, PCH$_3$).

The methiodide, prepared in ether and recrystallized from ethanol, had mp 262.5–264°.

Anal. Calcd for C$_8$H$_{16}$IP: C, 35.57; H, 5.97; P, 11.47. Found: C, 35.51; H, 6.00; P, 11.52.

1-Ethyl-4-benzylidenephosphorinane (13).—A procedure similar to that used for preparing 12 was employed, consisting of reaction of 0.04 mol of n-butyllithium, 13.3 g (0.04 mol) of benzyltriphenylphosphonium bromide, and 4.3 g (0.03 mol) of 1-ethyl-4-phosphorinanone. Distillation gave 3.0 g (46%) of 14, bp 120–121° (0.5 mm), having a single gc peak; nmr spectrum (CDCl$_3$) δ 7.2 (s, 5, C$_6$H$_5$), 6.3 (s, 1, C=CH), 2.2–2.8 (m, 4, allylic CH$_2$ groups), 0.8–2.0 ppm (m, 9, other ring CH$_2$ groups and CH$_3$CH$_2$).

Anal. Calcd for C$_{14}$H$_{19}$P: C, 77.02; H, 8.77; P, 14.19. Found: C, 77.27; H, 8.92; P, 14.05.

1-Methyl-4-(2-hydroxyethylidene)phosphorinane (14) and 1-Methyl-4-(2-hydroxyethyl)-1,2,5,6-tetrahydrophosphorin (15).—To a suspension of lithium aluminum hydride (11.4 g, 0.3 mol)

in 300 ml of anhydrous ether was added 23.1 g (0.155 mol) of a mixture of the esters 2 and 3 (1:9) in 100 ml of anhydrous ether. During the 1-hr addition, the mixture was cooled with an ice bath. After refluxing for 3 hr, excess hydride was destroyed by the addition of wet ether (100 ml) and then water (200 ml). The mixture was then stirred for 1 hr. A 5% sodium sulfate solution (400 ml) was added, and the aqueous phase was separated from the organic layer. The aqueous phase was extracted with two 300-ml portions of ether. Removal of the solvent on a rotary evaporator and vacuum distillation of the residue gave 16.3 g (90.0%) of a mixture of alcohols 14 and 15, bp 90–94° (0.4 mm). On redistillation, a cut with bp 88° (0.35 mm) was taken for analysis: ir (neat) ν_{OH} 3350 (broad, strong), $\nu_{C=C}$ 1670 cm^{-1}; nmr (CD$_3$COCD$_3$) δ 5.3–5.7 (m, C=CH), 4.07 (d,

J = 7 Hz, C=CHCH$_2$OH), 3.2–4.2 (m, CH$_2$CH$_2$OH and OH), 1.2–2.5 (m, ring CH$_2$), 0.95 ppm (d, J_{PCH} = 3.0 Hz, PCH$_3$). Addition of D$_2$O simplified the 3.2–4.2 multiplet to a triplet (J = 7 Hz) for CH$_2$CH$_2$OH; from the area of this and the C=CH-CH$_2$OH signal, the composition of the mixture was 12% 14–88% 15.

Anal. Calcd for C$_8$H$_{15}$OP: C, 60.74; H, 9.56; P, 19.58. Found: C, 60.74; H, 9.65; P, 19.33.

Registry No.—1, 16327-48-3; 2, 28399-79-3; 3, 28399-80-6; 6, 1552-92-7; 8, 28399-82-8; 12, 28399-83-9; 12 methiodide, 28399-85-1; 13, 28399-84-0; 14, 28405-55-2; 15, 16469-47-9.

Ferrocene Studies. XIX.[1a] Synthesis of 1,2-Terferrocene[1b,c]

Stanley I. Goldberg* and John G. Breland[1d]

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

An unequivocal route of synthesis of 1,2-terferrocene (2) has been developed. Cyclocondensation of ferrocil (9) and acetone was accomplished in 79% yield to give 3,4-diferrocenyl-4-hydroxy-2-cyclopenten-1-one (10), which was reduced to 3,4-diferrocenyl-2-cyclopenten-1-one (11) by the action of titanium(III) chloride in 95% yield. The cyclopentenone was converted to the corresponding diferrocenylcyclopentenol (12). The latter compound proved to be rather sensitive to most reaction conditions, but its dehydration was eventually effected in acceptable yield. The resulting diene was shown to be a single substance, 1,2-diferrocenyl-1,3-cyclopentadiene (4). It was converted to its aromatic anion by treatment with *n*-butyllithium, and the former allowed to react with iron(II) chloride in the presence of cyclopentadienyl anion. While ferrocene itself was the major product of the reaction, 1,2-terferrocene also resulted in small yield. The title compound, which is an orange crystalline substance, was characterized by the usual set of spectral data.

Despite an increasing interest in systems containing directly bonded ferrocene nuclei,[2] only one of the three constitutionally isomeric possibilities for assembly of three ferrocene nuclei (1, 2, and 3) has heretofore been

1   **2**   **3**
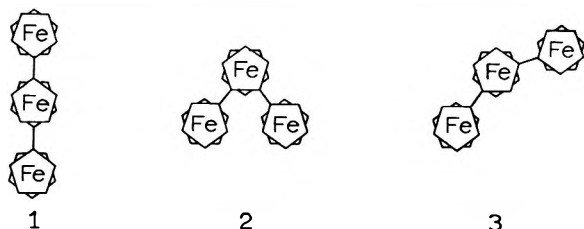
synthesized. 1,1'-Terferrocene (1) was obtained *via* construction of the central ferrocene nucleus[3] and *via* direct coupling[4] of ferrocene nuclei, but no unequivocal synthesis of either of the two remaining isomeric terferrocenes (2 and 3) has been previously reported. Synthesis of 1,2-terferrocene (2), however, has been accomplished in this laboratory, and we now report on that work.

Our synthesis scheme pivoted on an unequivocal preparation of 1,2-diferrocenylcyclopentadiene (4).[5] In this way structural ambiguity as regards disposition of the two ferrocenyl groups on the central ferrocene nucleus would be avoided. Formation of the central ferrocene nucleus, *via* complexing of 4 and cyclopentadiene (both as anions) about the central iron atom, was projected as the final step. This plan proved to be successful, although the final ferrocene-forming step occurred in disappointingly low yield.

4
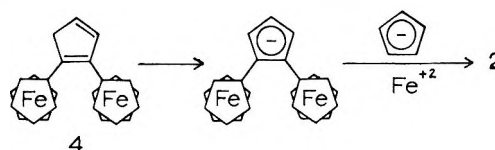
Our initial approach toward development of a synthesis of 4 lay in attempts to effect intramolecular pinacol formation of the dione 5, followed by didehydration of the pinacol (6). We were, however, unsuccessful in all attempts to achieve this goal. While the majority of these experiments led only to recovery of the starting dione, electrolytic reduction, a technique that worked well with benzophenone to give benzopinacol,[6] appeared promising in that the red color characteristic of 5 was discharged. However, the product of electrolytic reduction (yellow) underwent decomposition (dark brown) during every attempt to isolate it.

Weliky and Gould[7] found that benzoylferrocene was converted to its pinacol with methylmagnesium bro-

(1) (a) Previous paper: S. I. Goldberg, W. D. Bailey, and M. L. McGregor, *J. Org. Chem.*, **36**, 761 (1971); (b) Abstracts, 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967, No. 309; (c) taken in part from the doctoral dissertation submitted by J. G. B. to the Graduate School of the University of South Carolina, July 1967, in partial fulfillment of the requirements for the Ph.D. Degree; (d) Fellow of the National Science Foundation, 1963–1964, and holder of the C. Jules Seideman Memorial Fellowship, 1965–1966, established by Columbia Organic Chemicals Co., Inc.

(2) See D. E. Bublitz and K. L. Rinehart, Jr., *Org. React.*, **17**, 1 (1969), and M. D. Rausch, *Chem. Commun.*, 502 (1970), for accounts of, and references to, much of the work in this area.

(3) K. L. Rinehart, Jr., D. G. Ries, and P. A. Kittle, 149th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, Abstracts, P-23.

(4) A. N. Nesmeyanov, V. N. Drozd, V. A. Sazonova, V. I. Romanenko, A. K. Prokofev, and L. A. Nikonova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 667 (1963).

(5) Obviously, any combination of the three possible double bond isomers was acceptable. In actual fact, however, only 4 was obtained.

(6) S. Swann, S. W. Briggs, V. C. Neklutin, and A. T. Jerome, *Trans. Electrochem. Soc.*, **80**, 163 (1941).

(7) N. Weliky and E. S. Gould, *J. Amer. Chem. Soc.*, **79**, 2742 (1957).
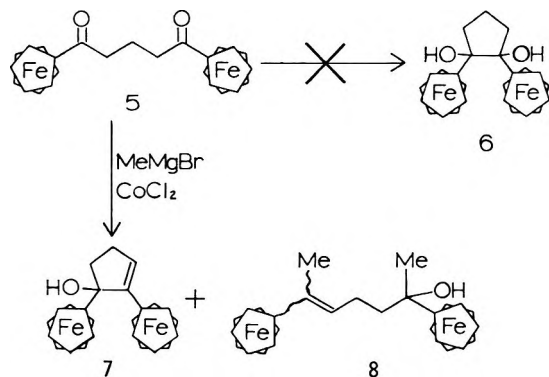
mide in the presence of cobaltous chloride when other methods failed. In the present case, this method gave a product whose spectral properties were consistent with a mixture of **7** and **8**. Additional efforts to develop the pinacol route were made, but the reaction was abandoned in favor of an alternative synthesis of **4**.

The successful synthesis of **4** was finally achieved through development of the first step of the sequence, cyclic aldol condensation of acetone and ferrocil (**9**).
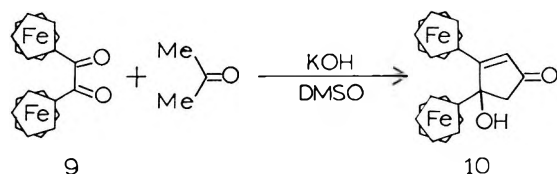
Ferrocil (**9**) was dissolved in a mixture of thoroughly deoxygenated ethanol and dimethyl sulfoxide, followed by addition of potassium hydroxide. The resulting solution was maintained near 60° while acetone was slowly added. The reaction, which was monitored by means of thin layer chromatography, was complete in 5.5 hr. It gave 3,4-diferrocenyl-4-hydroxy-2-cyclopenten-1-one (**10**) in dark red crystalline form in 79% yield after purification.

Each of the two oxygen functions in **10** represented a potential means for introduction of the desired second double bond. We first explored the feasibility of reduction of the carbonyl function by means of the Wolff–Kishner process, to be followed by dehydration of the resulting tertiary alcohol to **4** or its equivalent. However, each attempt to effect Wolff–Kishner reduction of **10** resulted only in extensive decomposition. We then turned to the second option, removal of the hydroxyl group in **10** followed by use of the remaining carbonyl function for introduction of the second double bond.

Pauson and Csendes[8] effected removal of the tertiary hydroxyl groups in 1,1′-bis(diphenylhydroxymethyl)-ferrocene to 1,1′-bis(diphenylmethyl)ferrocene by treatment of the former with titanium(III) chloride. In the present work, the action of titanium(III) chloride on **10** in a mixture of glacial acetic and hydrochloric acids provided a smooth and highly efficient (95% yield) means of replacement of the hydroxyl group with hydrogen. The product (**11**) was obtained as a high melting, deep red, crystalline material which was easily decomposed during alumina chromatography, but which was purified by recrystallization from methyl-

ene dichloride. Reduction of **11** with sodium borohydride gave the corresponding alcohol (**12**) which proved to be a very difficult substance to handle owing to its ease of decomposition. The highly sensitive nature of **12** also made it difficult to effect its dehydration without extensive decomposition. Dehydration of **12** was, however, finally accomplished by allowing a dilute solution of the unsaturated alcohol in methylene chloride to percolate through a narrow layer of neutral alumina which was sandwiched between layers of silicic acid. This process provided **4** in 46% yield over the two steps from **11**.
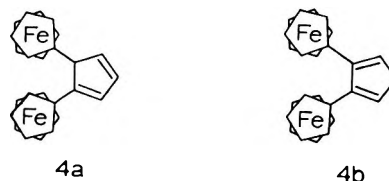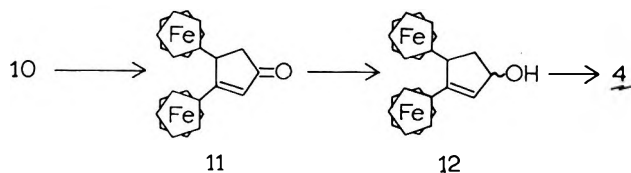
Although there are three constitutional double bond isomers possible for 1,2-diferrocenylcyclopentadiene (**4**, **4a**, and **4b**), the material obtained from dehydration of **12** gave a nuclear magnetic resonance spectrum consistent only with **4**. Thus, display of two different vinyl protons (δ 6.17 and 6.55) and two allylic protons (δ 3.33) argued strongly against the presence of detectable amounts of either one or both of the other isomers (**4a** and **4b**). Structure **4a** possesses three vinyl protons and one allylic proton, while the two vinyl protons in **4b** would not be expected to exhibit different chemical shifts.

n-Butyllithium was used to convert **4** to its aromatic anion, and the latter was allowed to react with iron(III) chloride and cyclopentadienyl anion. As expected this process gave mostly ferrocene. It also gave the desired 1,2-terferrocene (**2**) in low yield (10% crude and 2.2% purified material), but the third possibility, 1,1′,2,2′-tetraferrocenylferrocene, was not detected.

1,2-Terferrocene is an orange crystalline compound with mp 191–193°. It is characterized by a rather simple infrared spectrum and a nuclear magnetic resonance spectrum with a single set of complex signals centered at δ 4.05. The presence of a complex set of conformational equilibria is suggested by the rather significant change in appearance of these signals in the spectrum determined at a slightly higher temperature.

Experimental Section

General.—Temperature readings are uncorrected. Ultraviolet spectra were measured in ethanol–methylene chloride [19:1 (v/v)] solutions with either a Cary Model 14 or a Perkin-Elmer Model 202 spectrophotometer. Infrared spectra were recorded (individually cited sampling) on a Perkin-Elmer Model 337 spectrophotometer. Proton magnetic resonance (pmr) spectra were determined at 60 MHz with a Varian A-60 instrument near 36° in solutions (individually cited) containing 2–3% tetra-

(8) P. Pauson and E. Csendes, as cited in M. Rosenblum's doctoral dissertation, Harvard University, 1953.

methylsilane (TMS). Chemical shifts were recorded under the δ convention in parts per million relative to TMS (0 ppm). An AEI Model MS-9 mass spectrometer was used[9] to obtain the mass spectral data.

Column elution chromatography was carried out on either alumina (Merck, acid-washed or Woelm, nonalkaline) or silicic acid (Bio-Rad, Sil A). Eluting solvents are cited below. Thin layer chromatography (tlc) was carried out on silicic acid (Merck, silica gel G) which was coated (0.25 mm) onto glass and activated at 120° during 12–15 hr. A solvent system of hexane, xylene, and ethyl acetate (2:1:1 by volumes) was used. Combustion analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

1,3-Diferrocenoylpropane (5).—A solution containing glutaryl chloride (17.2 g, 0.102 mol) and anhydrous aluminum chloride (34.0 g, 0.255 mol) in methylene chloride (100 ml) was added dropwise to a stirred solution of ferrocene (45.5 g, 0.245 mol) in methylene chloride (250 ml) which was kept near 0° and under a blanket of dry nitrogen. The initial light amber colored solution slowly became deep violet as the addition progressed. When the addition was complete the reaction mixture was allowed to warm to room temperature. The stirring was continued (nitrogen blanket) while the reaction mixture was protected from light during 10–12 hr, after which time evolution of hydrogen chloride had ceased. The reaction mixture was cooled by an external ice bath, and its was hydrolyzed by dropwise addition of an aqueous solution of ammonium chloride [150 ml, 15% (w/w)]. Before the hydrolysate was allowed to warm to room temperature, ascorbic acid (5 g) was added to reduce the ferricinium species (light blue) present. After the hydrolysate was extracted with methylene chloride (seven 100-ml portions), the extracts were combined and washed with several portions of aqueous sodium hydroxide solution, followed by several portions of water, and finally with several portions of saturated aqueous sodium chloride solution. All aqueous extracts were combined and acidified (external indicator) with hydrochloric acid to give γ-ferrocenoylbutyric acid, 2.6 g (8.5% yield), mp 132–136° (lit.[10] mp 136–137°).

The organic residue left from the series of aqueous extracts was dried (CaCl₂) and evaporated to a dark red material which was chromatographed on alumina (Merck, acid-washed). Initial elution with hexane caused development of a fast-moving yellow band which gave ferrocene, 12.6 g (27.3% recovery). Not until a mixture of benzene and ether [7:3 (v/v)] was used did further development of the column take place. A red-colored band was eluted to provide 1,3-diferrocenoylpropane (5): 15.6 g (35.7% yield); mp 132–133° (recrystallized from cyclohexane); ir (CH₂Cl₂) 3085, 3040, 1100, 998 (ferrocenyl), 2970–2880 (aliphatic CH), and 1665 cm⁻¹ (conjugated ketone); pmr (CCl₄) δ 4.85 (4 H, t, J = 2 Hz, α-ferrocenyl protons), 4.50 (4 H, t, J = 2 Hz, β-ferrocenyl protons), 4.20 (10 H, s, protons of unsubstituted ferrocenyl rings), 2.85 (4 H, apparent t, J = 6 Hz, COCH₂), and 2.10 (2 H, m, COCH₂CCO).

Anal. Calcd for C₂₅H₂₄Fe₂O₂: C, 64.14; H, 5.17; Fe, 23.56. Found: C, 64.56; H, 5.25; Fe, 23.58.

Reaction of 1,3-Diferrocenoylpropane (5) with Methylmagnesium Bromide and Cobalt(II) Chloride.—While a fair number of methods, under various conditions, were investigated for their ability to effect an intramolecular condensation of 5, only the treatment of 5 with methylmagnesium bromide and cobalt(II) chloride showed promise. An account of the other attempts is given in an earlier section of this paper.

Gaseous methyl bromide was led into a mixture (nitrogen blanket) of magnesium turnings (1.27 g, 52.3 mg-atoms), tetrahydrofuran (100 ml), and ether (100 ml) at a rate sufficient to maintain a gentle reflux. After all of the magnesium metal was consumed (about 30 min), the mixture was cooled to 0° and finely powdered anhydrous cobalt(II) chloride (0.324 g, 2.49 mmol) was added. The solution immediately evolved a gas and became dark red. After a solution of 1,3-diferrocenoylpropane (5) (2.12 g, 4.52 mmol) in tetrahydrofuran (100 ml) was added dropwise, the whole mixture was stirred during 30 min at 0° before it was allowed to warm to room temperature where it was maintained and stirred for an additional 12-hr period. Hydrolysis was effected by addition of 100 ml of ice water. The hydroly-

zate was exhaustively extracted with ether, and the combined ethereal extracts, after several washings with water, were dried and evaporated to a dark brown oil. The residue was chromatographed on alumina (Merck, acid-washed). Elution with hexane provided an orange oil (0.218 g); a black tar (1.22 g) was obtained from a dark-colored band eluted with hexane–ethyl acetate [1:1 (v/v)]; the starting material (0.436 g, 20.2% recovery) was eluted with hexane–ethyl acetate [1:2 (v/v)].

Purification of the orange oil by molecular distillation [100° (0.7 mm), air bath] gave a condensate (orange oil) that was submitted to mass spectral analysis.[9] Spectra, determined at 14 and 70 eV, and at various temperatues, showed the material to be a mixture consisting of two components, m/e 452 (M⁺) and 482 (M⁺). This information together with the ir data (give below) indicated the probable presence of 2,3-diferrocenyl-3-hydroxy-1-cyclopentene (7) and 2,6-diferrocenyl-6-hydroxy-2-heptene (8): ir (CH₂Cl₂) 3640 (OH nonbonded), 3100, 3050, 1100, 998 (ferrocenyl), 3000, 1650, 850–790 (conjugated, trisubstituted double bond), 2960, 2860, 1460, 1390 (CH₃), 2925, 2855, and 1470 cm⁻¹ (CH₂). Further investigation of the mixture was not pursued.

Desoxyferrocoin.—A mixture of ferrocenylacetic acid[11] (5.34 g, 21.9 mmol) in 25 ml of freshly distilled phosphorus trichloride was kept at 40° (stirring) for 3.5 hr. After the resulting solution (light brown) was decanted, it was evaporated to leave a residue of crude ferroceneacetyl chloride. This material was taken up in 100 ml of methylene dichloride and added dropwise to a cold (0°), stirred solution of freshly sublimed ferrocene (5.18 g, 27.8 mmol) in 200 ml of methylene dichloride. After that addition was complete, a second solution, consisting of boron trifluoride etherate (6.0 g, 35 mmol) in 100 ml of methylene dichloride, was also added dropwise to the cold reaction mixture. The reaction mixture, which had changed to deep violet, was stirred for 0.5 hr at 0° before an additional quantity of boron trifluoride etherate (5.7 g, 34 mmol in 75 ml of methylene dichloride) was added, and the whole mixture was allowed to come to room temperature and stirred overnight.

Addition of 100 ml of 10% aqueous sodium acetate solution was followed by successive washings of the organic phase of the hydrolysate with water (six 200-ml portions) and saturated sodium chloride solution (100-ml portions). After the organic solution was dried (CaCl₂), it was evaporated to a residue which was chromatographed on alumina (Merck, acid-washed). Hexane developed and eluted a band from which ferrocene (4.06 g, 78.3% recovery) was obtained. A mixture of hexane, methylene chloride, and ethyl acetate [1:1:1 (v/v/v)] was used to elute a red band which provided desoxyferrocoin: 2.24 g (24.8% yield based on ferrocenylacetic acid); mp 160–163° (lit.[12] mp 159–161°); ir (CH₂Cl₂) 3100, 3050, 1100, 998 (ferrocenyl), and 1600 cm⁻¹ (conjugated ketone).

Ferrocil (9).—A solution of desoxyferrocoin (6.27 g, 15.2 mmol) in 225 ml of methylene dichloride, containing freshly prepared[13] activated maganese dioxide (13.0 g), was stirred at room temperature during 6 hr before it was filtered and the filtrate evaporated to dryness. Examination of the residue by thin layer chromatography (tlc) revealed a large amount of unchanged desoxyferrocoin (R_f 0.62). Consequently, the residue was retreated with activated maganese dioxide (12 g) in methylene dichloride overnight. The product of the second treatment was chromatographed on alumina (Merck, acid-washed). Only one large, diffuse, red band was developed (benzene). This was slowly collected in many fractions which were analyzed by tlc to determine those fractions that contained the desired product, ferrocil (9): 5.03 g (77.6% yield); mp 191–194° (lit.[14] mp 193.5–195.5°); ir (CH₂Cl₂) 3100, 3050, 1100, 995 (ferrocenyl), and 1650 (broad, conjugated diketone); nmr (CDCl₃) δ 4.95 (4 H, t, J = 3 Hz, α-Fc H), 4.65 (4 H, t, J = 3 Hz, β-Fc H), and 4.25 (10 H, s, unsubtd Fc H).

3,4-Diferrocenyl-4-hydroxy-2-cyclopenten-1-one (10).—A mixture of anhydrous ethanol (200 ml) and pure dry dimethyl sulfoxide (300 ml) maintained at 60° was thoroughly deoxygenated by bubbling purified nitrogen through it for 1 hr. The system was kept under a nitrogen blanket and protected from light while

(9) We are indebted to Dr. Henry M. Fales of the National Heart Institute, Bethesda, Md., for the mass spectral data cited herein.

(10) K. L. Rinehart, Jr., D. J. Curby, and P. E. Sokol, *J. Amer. Chem. Soc.*, **79**, 3420 (1957).

(11) D. Lednicer, J. K. Lindsay, and C. R. Hauser, *J. Org. Chem.*, **23**, 653 (1958).

(12) K. L. Rinehart, Jr., C. J. Michejda, and P. A. Kittle, *J. Amer. Chem. Soc.*, **81**, 3162 (1959).

(13) J. A. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Herms, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(14) K. L. Rinehart, Jr., A. F. Ellis, C. J. Michejda, and P. A. Kittle, *J. Amer. Chem. Soc.*, **82**, 4112 (1960).
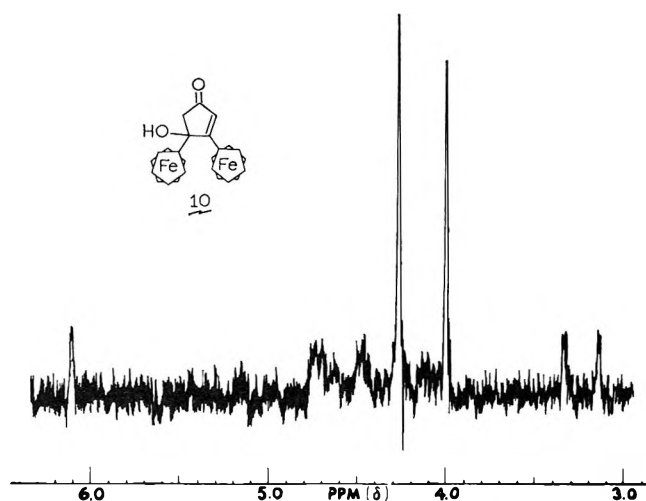
Figure 1.—Nmr spectrum of 3,4-diferrocenyl-4-hydroxyl-2-cyclopenten-1-one.

Figure 2.—Nmr spectrum of 3,4-diferrocenyl-2-cyclopenten-1-one.

potassium hydroxide (5.0 g, 89 mmol) and ferrocil (9) (4.64 g, 10.9 mmol) were introduced. After the reaction mixture was stirred for several minutes, and while it was kept between 55 and 60°, anhydrous acetone (30 ml, 24 g, 0.50 mol) was added at a rate of 5–6 ml/hr. The course of the reaction was monitored by tlc over the period of the addition: complete disappearance of the ferrocil spot (R_f 0.62) with formation of the product spot (R_f 0.23) after 5.5 hr.

The reaction mixture was diluted with 1 l. of ice–water, and the resulting suspension was exhaustively extracted with methylene dichloride. The basic aqueous residue was acidified with phosphoric acid and extracted with three 100-ml portions of methylene dichloride. The combined organic extracts were washed with water before they were dried ($CaCl_2$) and evaporated to a dark red oil. This material proved to be too sensitive to alumina to allow chromatography without extensive decomposition. It was, however, purified by initial crystallization and recrystallization from cold ether–hexane [1:5 (v/v)] solutions to give 3,4-diferrocenyl-4-hydroxy-2-cyclopenten-1-one (10): 3.99 g (78.9% yield); mp 210–213° dec; ir (CH_2Cl_2) 3560 (hydroxyl), 3100, 3040, 1100, 998 (ferrocenyl), 1690, and 1590 (cyclopentenone); nmr ($CDCl_3$) δ 6.12 (1 H, apparent s, vinyl proton), 4.8–4.0 (8–9 H, complex, α- and β-Fc H and OH), 4.26 (5 H, s, unsubstd Fc H), 4.0 (5 H, s, unsubstd Fc H), 3.34 (1 H, apparent d, J = 1–2 Hz), and 3.14 (1 H, apparent d, J = 1–2 Hz) (see Figure 1); uv [EtOH–H_2O–CH_2Cl_2, 19:1:1 (v/v/v)] 220 nm (ε 19,900), 255 (13,000), and 312 (8400); mass spectrum[9] m/e (intensity relative to M+) 468 (M+ + 2, 6.2), 467 (M+ + 1, 33), 466 (M+, 100), 465 (M+ − 1, 5.0), 464 (M+ − 2, 14) [calcd[15] for $C_{25}H_{22}Fe_2O_2$: 468 (M+ + 2, 6.1), 467 (M+ + 1, 32.3), 466 (M+, 100), 465 (M+ − 1, 3.6), and 464 (M+ − 2, 12.7)]; other prominent high mass peaks 448 (48), 420 (15), 384 (17), 328 (58), and 300 (42).

Anal. Calcd for $C_{25}H_{22}Fe_2O_2$: C, 64.40; H, 4.76. Found: C, 64.85; H, 4.78.

3,4-Diferrocenyl-2-cyclopenten-1-one (11).—A mixture of glacial acetic acid (40 ml), water (8 ml), and 12 N hydrochloric acid (2 ml) was heated to a temperature just below boiling and thoroughly deoxygenated by allowing a stream of purified nitrogen to bubble through. After the mixture was allowed to cool to room temperature, it was stirred while anhydrous titanium-(III) chloride (Stauffer Chemical Co.) (1.0 g, 6.5 mmol) was added. The resulting blue solution was added dropwise to a solution of 3,4-diferrocenyl-4-hydroxy-2-cyclopenten-1-one (10) (1.01 g, 2.17 mmol) in 100 ml of deoxygenated glacial acetic acid, while the latter solution was stirred and kept at 50°. After the addition was complete, the reaction mixture was stirred at 50° during an additional 3.5-hr period. The reaction mixture was then hydrolyzed by addition of 700 ml of ice–water and exhaustively extracted with methylene dichloride. The combined extracts were washed successively with water, dilute sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution before they were dried and evaporated to a red powder,

(15) Computer program by Albert Shirley, Senior Research Project, University of South Carolina, 1968.
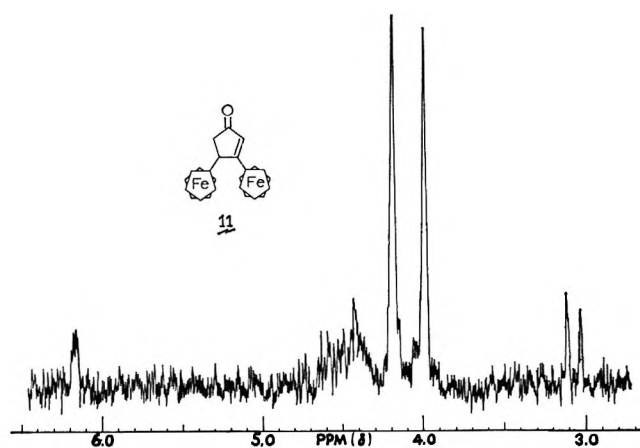
3,4-diferrocenyl-2-cyclopenten-1-one (11), 0.93 g (95% yield). Thin layer chromatographic analysis showed this material (R_f 0.38) to be contaminated by only a trace of starting material (R_f 0.22). A portion of the product was recrystallized from cold (−30°) methylene chloride to give deep red crystals: mp 226–227° dec; ir (CH_2Cl_2) 3100, 3050, 1100, 998 (ferrocenyl), 1685, and 1590 cm⁻¹ (cyclopentenone); nmr ($CDCl_3$) δ 6.18 (1 H, apparent t, J = 1–2 Hz, vinyl proton), 4.8–4.3 (9 H, complex, methine proton, α- and β-Fc H), 4.20 (5 H, s, unsubstd Fc H), 4.00 (5 H, s, unsubstd Fc H), 3.12 (1 H, apparent d, J = 1–2 Hz), and 3.05 (1 H, apparent d, J = 1–2 Hz) (see Figure 2); uv [EtOH–H_2O–CH_2Cl_2, 19:1:1 (v/v/v)] 214 nm (ε 24,000), 256 (9000), and 311 (11,000).

Anal. Calcd for $C_{25}H_{22}Fe_2O$: C, 66.71; H, 4.93. Found: C, 66.42; H, 5.13.

1,2-Diferrocenyl-1,3-cyclopentadiene (4).—A solution of 3,4-diferrocenyl-2-cyclopenten-1-one (11) (87.3 mg, 1.94 mmol) in tetrahydrofuran (25 ml) was added slowly to a stirred solution of sodium borohydride (4.0 g, 96 mmol) in anhydrous ethanol (30 ml), while the system was maintained near 55° by external heating. After 5 hr the initial deep red mixture had changed to light yellow. It was cooled before 50 ml of 5% (v/v) aqueous ammonium chloride solution was added. Exhaustive extraction of the hydrolyzate with ether, followed by evaporation of the combined and dried ($CaCl_2$) extracts under nitrogen, gave an orange oil whose infrared spectrum showed the presence of the desired diferrocenylcyclopentenol: ir (CH_2Cl_2) 3590, 3445 (hydroxyl), 3090, 3040, 1100, 998 (ferrocenyl), and 1630 cm⁻¹ (double bond). Attempts to prepare an analytical sample of the material were unsuccessful owing to its ease of decomposition, particularly during chromatography. Successful conversion to 1,2-diferrocenylcyclopentadiene (below) in good yield, however, clearly established that the material obtained from the sodium borohydride reduction was mainly the cyclopentenol.

The crude reduction product (orange oil) was dissolved in 15 ml of methylene chloride and allowed percolate through a narrow column (12 mm) which consisted of a 1.5-cm layer of alumina (Woelm, neutral) sandwiched between two 10-cm layers of silicic acid. The column was washed with methylene chloride until the effluent was colorless (total volume, about 200 ml). The combined effluent was then passed through another column containing a 10-cm section of silicic acid before the solvent was carefully evaporated in a nitrogen stream to leave 1,2-diferrocenyl-1,3-cyclopentadiene (4): orange oil; 385 mg (45.7% yield over two steps); ir (CH_2Cl_2) 3100, 3050, 1100, 998 (ferrocenyl), 3080, 2950, 2860, and 1660 cm⁻¹ (cyclopentadienyl); nmr ($CDCl_3$) δ 6.55 (1 H, doublet of triplets, J = 5.5 and 1.5 Hz, C_3 H), 6.17 (1 H, doublet of triplet, J = 5.5 and 1.5 Hz, C_4 H), 4.32 (4 H, two overlapped triplets, α-Fc H), 4.10 (4 H, two overlapped triplets, β-Fc H), 3.98 (5 H, s, unsubstd Fc H), 3.92 (5 H, s, unsubstd Fc H), and 3.33 (2 H, t, J = 1.5 Hz, CH_2) (see Figure 3); uv [EtOH–H_2O–CH_2Cl_2, 19:1:1 (v/v/v)] 220 nm (ε 20,000) and 320 (5500); mass spectrum[9] m/e (intensity relative to M+) 436 (M+ + 2, 8.0), 435 (M+ + 1, 34), 434 (M+, 100) 433 (M+ − 1, 7.0), 432 (M+ − 2, 16) [calcd[15] for $C_{25}H_{22}Fe_2$: 436 (M+ + 2, 5.7), 435 (M+ + 1, 32.2), 434 (M+, 100), 433 (M+ − 1, 3.6), and 432 (M+ − 2, 12.7)]; other prominent peaks 368 (16), 366 (16), 312 (19), 191 (38), 190 (42), 189 (54), 165 (20), and 121 (89).
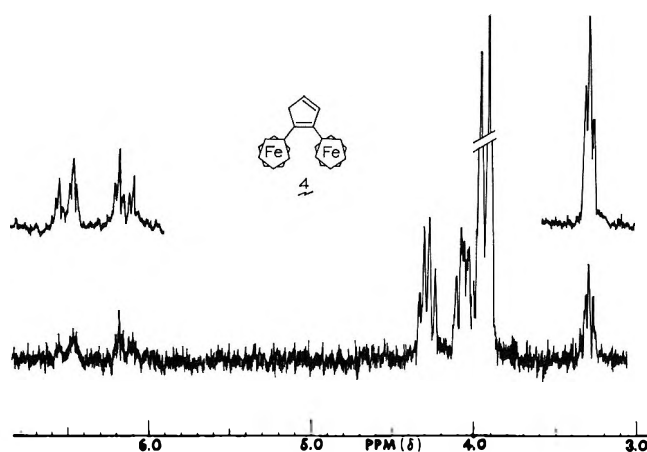
Figure 3.—Nmr spectrum of 1,2-diferrocenyl-1,3-cyclopentadiene.
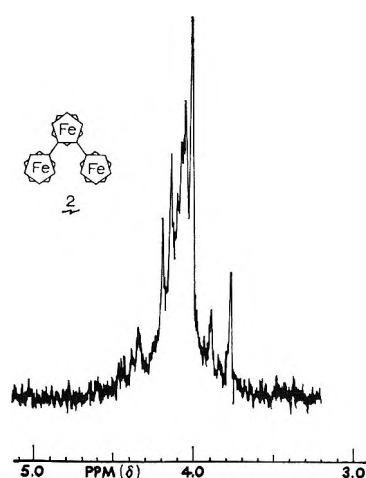
Figure 4.—Nmr spectrum of 1,2-terferrocene.

1,2-Terferrocene (2).—In a thoroughly dried three-necked flask, equipped with a stirrer, nitrogen inlet, condenser, and a rubber septum injection port, was mixed a solution of 1,2-diferrocenyl-1,3-cyclopentadiene (4) (348 mg, 0.802 mmol) in 20 ml of anhydrous ether and a solution of *n*-butyllithium [4 ml (6 mmol) of a 15% (w/w) solution in hexane (Foote Mineral Co.)] in 100 ml of anhydrous ether. The mixture was stirred at room temperature for 1 hr before freshly prepared cyclopentadiene (3.3 g, 50 mmol) and *n*-butyllithium (10 ml, 16 mmol) were added. The mixture was stirred for an additional 3-hr period when iron-(II) chloride[16] (1.0 g, 7.9 mmol) was added, and the whole mixture was stirred overnight. After addition of 25 ml of 5% aqueous ammonium chloride solution, the separated aqueous phase was exhaustively extracted with ether, and the ether extracts were combined with the original ethereal phase before the whole mixture was dried ($CaCl_2$) and evaporated. The residue, a brown solid, was chromatographed on alumina (Merck, acid-washed). Elution with hexane gave ferrocene, 1.4 g. Further column development and elution with a mixture of hexane and benzene (1:1 (v/v)] produced 46 mg of crude 1,2-terferrocene (2) which was initially obtained as an orange-brown solid. This material was successively (five times) recrystallized from hexane–benzene

(16) P. Kovacic and N. O. Brace, *J. Amer. Chem. Soc.*, **76**, 5491 (1954).

to yield a 10-mg orange crystalline, constant-melting (mp 191–193°, sealed, evacuated capillary) sample of 1,2-terferrocene which was chromatographically pure (R_f 0.90) and characterized by the following spectral properties: ir (CH_2Cl_2) 3100, 3050, 1100, and 1000 cm^{-1}; uv (EtOH) 215 nm broad (ϵ 24,000) and 290 sh (5000); nmr ($CDCl_3$) showed only a complex cluster of signals centered at δ 4.05 indicating the presence of only ferrocenyl protons (see Figure 4) [determination of the spectrum at 45° (near 36° initially) caused significant changes in the detailed structure of the signal complex indicating perhaps a rather facile and complex conformational equilibria]; mass spectrum[9] m/e (intensity relative to M$^+$) 556 (M$^+$ + 2, 8.5), 555 (M$^+$ + 1, 38), 554 (M$^+$, 100), 553 (M$^+$ − 1, 7.3), and 552 (M$^+$ − 2, 23) [calcd[15] for $C_{30}H_{26}Fe_3$: 556 (M$^+$ + 2, 8.9), 555 (M$^+$ + 1, 40), 554 (M$^+$, 100), 553 (M$^+$ − 1, 6.7), and 552 (M$^+$ − 2, 19)].

Anal. Calcd for $C_{30}H_{26}Fe_3$: C, 65.03; H, 4.73. Found: C, 64.92; H, 4.86.

Registry No.—2, 12504-91-5; 4, 12504-84-6; 5, 12504-88-0; 7, 12504-87-9; 8, 12504-90-4; 9, 12113-85-8; 10, 12504-86-8; 11, 12504-85-7; desoxyferrocoin, 12504-83-5.

A Facile Synthesis of 3-Acylaminoisocoumarins[1a]

J. N. Wells,* W. J. Wheeler,[1b] and L. M. Davisson[1c]

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Indiana 47907

The synthesis of some 3-acylaminoisocoumarins is reported. Spectral data and chemical reactivity are discussed. 3-Aminoisocoumarin was prepared and acylated to afford 3-acylaminoisocoumarin by an alternative route.

During a program for the synthesis of some tetracyclic indole compounds, we had need of 5-(2-carboxy-5-chlorophenyl)levulinic acid (1) as a precursor. It was hoped that 3-carbethoxypropionic 5-chloro-α-cyano-2-toluic anhydride (2) could be condensed under basic conditions to form ethyl 5-(2-carboxy-5-chlorophenyl)-5-cyanolevulinate (3). Hydrolysis of 3 and subsequent decarboxylation would yield 1.

It was planned to synthesize 2 by the reaction of 5-chloro-α-cyano-2-toluic acid (4) with 3-carbethoxypropionyl chloride[2] in the presence of pyridine. Attempts

to prepare 4 by the reaction of 5-chlorophthalide,[3] with potassium cyanide utilizing Price's procedure,[4] yielded only tars. Adequate yields of 4 could be obtained when the reaction was carried out in dimethyl sulfoxide at 100–110°.

Upon reaction of 4 with 3-carbethoxypropionyl chloride[2] in the presence of 2 equiv of pyridine, no anhydride was isolated. Instead a high-melting solid, mp 198–199°, 5 was isolated in 39.6% yield. The infrared spectrum indicated loss of the nitrile and showed no absorption below 5.7 μ (the characteristic carbonyl

(1) (a) Abstracted in part from the Ph.D. thesis of W. J. Wheeler, Purdue University, June 1970; (b) Fellow of the American Foundation for Pharmaceutical Education, 1968–1970; (c) NSF Undergraduate Research Participant, 1969.

(2) I. Heilbron and H. M. Bunbury, Ed., "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953, p 384.

(3) L. P. Levy and H. Stephan, *J. Chem. Soc.*, 867 (1931).

(4) C. C. Price, *Org. Syn.*, **22**, 61 (1942).

2

3
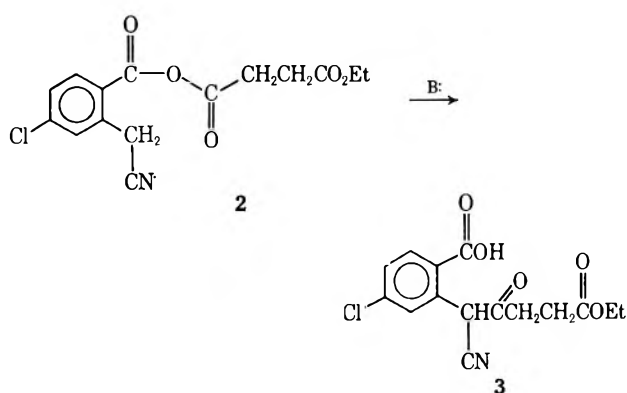
doublet of anhydrides[5] was absent). The nmr spectrum (DMSO-d_6) showed a three-proton triplet at δ 1.07 ppm (ester methyl) and a four-proton singlet at δ 2.58 ppm (superimposed on the DMSO-d_5 signal) which is presumably the methylene protons of the succinate residue. In addition, there were a two-proton quartet at δ 4.04 ppm (ester methylene) and a one-proton singlet at δ 7.05 ppm, as well as additional aromatic protons. There was also a broad one-proton singlet at δ 11.06 ppm. The mass spectrum indicated an apparent molecular ion at m/e 323 as well as a large M − 128 peak at m/e 195 (base peak). There were also significant peaks at m/e 129 and 101. Reaction of **4a** with acetyl chloride similarly yielded **5b**.

A minor product (**6**, the enol lactone of **3**) was also obtained from this reaction. The nmr spectrum of **6** (CDCl₃) showed a three-proton triplet at δ 1.25 ppm (ester methyl), a four-proton A₂B₂ multiplet at δ 3.05 ppm (ethylene), a two-proton quartet at δ 4.2 ppm (ester methylene), and the aromatic signals centered at δ 7.90 ppm. The mass spectrum had an apparent molecular ion at m/e 305 as well as a reasonable fragmentation pattern.
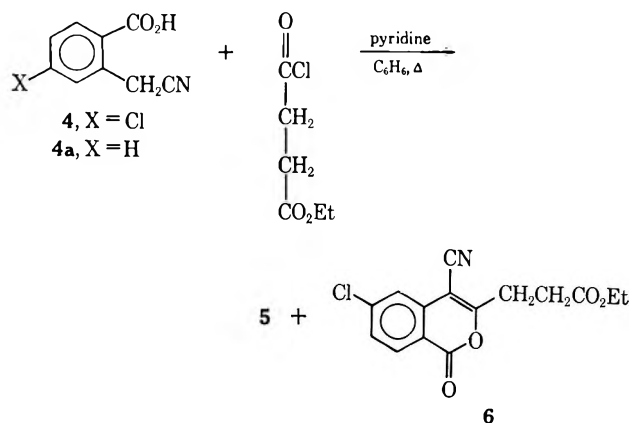
Since condensations under similarly mild conditions are known (*e.g.*, the intramolecular condensation of 2,4-dibenzoyloxyacetophenone in the presence of Na-HCO₃[6]), **5** was initially postulated to be **3**. The following evidence indicated otherwise. The material was slowly dissolved in base but could not be recovered upon acidification. The conversion of **5** to **6** was unsuccessful under a variety of conditions. Additionally, hydrolysis of **5** under both acidic and basic conditions yielded 5-chlorohomophthalic acid and succinic acid. Ethanol-

ysis of **5** yielded diethyl 5-chlorohomophthalate and diethyl succinate.

On the basis of both the spectral and chemical data, **5** is postulated to be an acylated 3-aminoisocoumarin. The formation of **5** could be visualized to proceed *via* the following mechanism.

5, X = Cl, R = CH₂CH₂CO₂Et
5a, X = H, R = CH₂CH₂CO₂CH₃
5b, X = H, R = CH₃
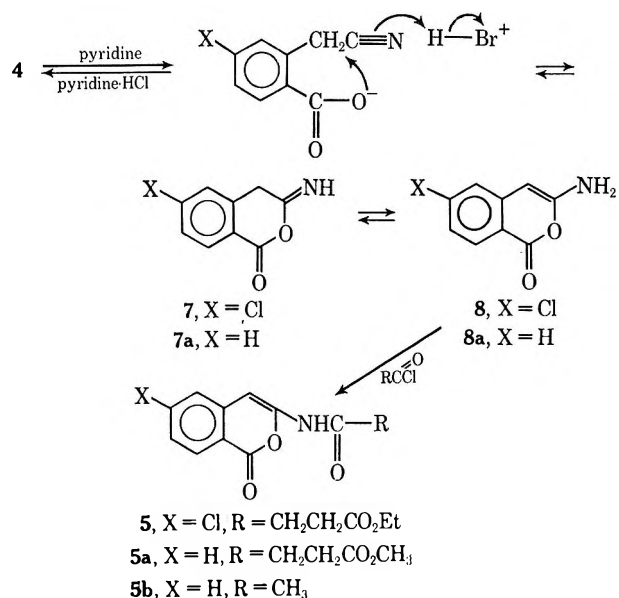
Although other pathways could be envisioned, carbon acylation of **7** could also explain the formation of **6** (*via* **3**) since isoimides are thought to give rise to nitriles under similar conditions.[7] 3-Aminoisocoumarin (**8a**) has recently been proposed as an intermediate in the thermolysis of 2-carboxyphenylacetonitrile.[8]

Formulation of the product as **5** explains the lack of —C≡N absorption in the ir spectrum, as well as the facile hydrolysis to 5-chlorohomophthalic acid and succinic acid. Although 3-aminoisocoumarins have not been reported in the literature, there is ample precedence for the intermediacy of isoimide **7**. Alkyl-[9] and aryl-substituted 3-iminophthalides[10,11] have been synthesized and isolated. Isoimides have been proposed as intermediates in the conversion of phthalamic acid to ethyl 2-cyanobenzoate,[12] in the reaction of ketenimines with carboxylic acids,[13] in the interconversion of aromatic acids and arylnitriles,[14] and in the reaction of amides with acid anhydrides and acid chlorides.[15] It has been suggested that isoimides are easily acylated in the presence of acid chlorides.[15]

Careful examination of the fragments of the mass spectrum of **5** further substantiates the 3-acylaminoisocoumarin structure. The base peak m/e 195 results from hydrogen migration and expulsion of a ketene (the usual base peak from acylanilides[16]) and corresponds to **8**.

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, pp 125–129.

(6) W. Baker, *J. Chem. Soc.*, 1381 (1933).

(7) B. Liberek, *Bull. Acad. Polo. Sci., Ser. Sci. Chim.*, **10**, 227 (1962).

(8) G. Pangon, G. Thuillier, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1991 (1970).

(9) Hoogewerff and W. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **13**, 93 (1894).

(10) W. A. Roderick and P. L. Bhatia, *J. Org. Chem.*, **28**, 2018 (1963).

(11) E. G. Diaz de Toranzo and J. A. Brieux, *J. Med. Chem.*, **10**, 982 (1967).

(12) C. K. Sauers and R. J. Cotter, *J. Org. Chem.*, **26**, 6 (1961).

(13) C. L. Stevens and M. Munk, *J. Amer. Chem. Soc.*, **80**, 4065 (1959).

(14) W. G. Toland and L. Ferstandig, *J. Org. Chem.*, **23**, 1350 (1958).

(15) D. Davidson and H. Skovronck, *J. Amer. Chem. Soc.*, **80**, 376 (1958).

(16) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 350.

The uv spectrum of **5** showed maxima at 224, 251, 290, 298 sh, and 347 mμ. The uv spectrum of an acylated 3-hydroxyisocoumarin, 3-ethoxycarbonyloxy-isocoumarin, showed maxima at 240, 263, 370 sh, and 324 mμ.[17] These spectra are quite similar except for a bathochromic shift of the maxima in that of **5**. This is not unexpected, however, since the maxima for aniline appear at longer wavelengths than those of phenol.[18]

Additional evidence for structure **5** arises from the following experiments. When the silver salt of 2-carboxyphenylacetonitrile was treated with 3-carbomethoxypropionyl chloride,[19] the corresponding 3-acylaminoisocoumarin **5a** was formed. When 2-carbome-

5a
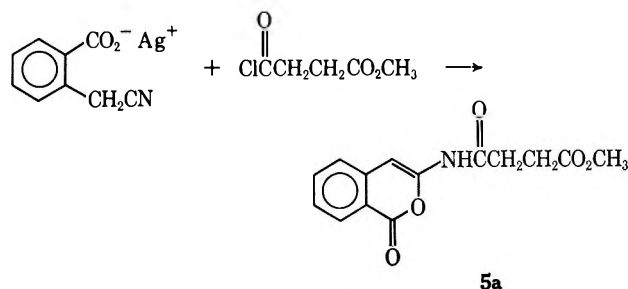
thoxyphenylacetonitrile[20] was treated with 3-carbomethoxypropionyl chloride,[19] no **5** was isolated or detected, indicating participation of the carboxyl group in the formation of **5**.

In hope to further substantiate the 3-acylaminoisocoumarin structure **5** and perhaps shed some light on the mechanism of the reaction, attempts were made to synthesize isoimide **7a** or its tautomer **8a**. Davies and Poole attempted the synthesis of **8a** by the reaction of 3-chloroisocoumarin (**9**) with anhydrous ammonia.[21] Although **9** was remarkably unreactive toward neutral and acidic hydrolytic agents (*e.g.*, NaI, HCl, HCO₂H), reaction of **9** with NH₃ in benzene without the exclusion of moisture yielded 2-carboxyphenylacetonitrile.

9

Sauer and Cotter[12] synthesized the five-membered isoimide **10** under a variety of conditions.

10

Homophthalamic acid, readily obtained from the reaction of 2-carboxyphenylacetonitrile with basic hy-

drogen peroxide,[22] was dehydrated with dicyclohexyl-carbodiimide to yield **8a**.

The nmr spectrum of **8a** showed a one-proton singlet at δ 5.30 ppm and a two-proton singlet at δ 6.50 ppm, which were exchangeable with D₂O. The ir spectrum showed N–H absorption at 2.95 μ and C=O absorption at 5.88 μ as well as the 6.05, 6.49 μ maxima characteristic of isocoumarins.[16] The uv spectrum showed maxima at 232, 291, and 380 mμ. The mass spectrum had a molecular ion at *m/e* 161 and a fragmentation pattern similar to the acylated analogs.

Acylation of **8a** with 3-carbomethoxypropionyl chloride[19] in the presence of pyridine at room temperature yielded **5a**. The compounds (**5a**) from the two different reactions showed no depression of mixture melting point and identical spectra.

It was hoped that **4a** could be converted to **8a** with pyridine; however, reaction of both **4a** and **8a** with pyridine under identical conditions yielded the same equilibrium mixture as evidenced by tlc (silica gel PF₂₅₄, developed with CHCl₃–MeOH 95:5, visualized with short wavelength uv light).

Experimental Section[23]

5-Chloro-2-carboxyphenylacetonitrile (4).—5-Chlorophthalide[3] (74.5 g, 0.44 mol) and potassium cyanide (43.2 g, 0.66 mol) were mixed in 475 ml of dimethyl sulfoxide. After an initial exothermic reaction, the mixture was warmed to 100°. The color of the solution gradually darkened from yellow to dark red. Heating was continued for 18 hr, whereupon the mixture was allowed to cool to room temperature.

The mixture was neutralized with 150 ml of 6 *N* hydrochloric acid. The acidified solution was poured over 2 l. of ice and a solid gradually precipitated (87 g) which was collected by filtration and washed with water. The solid was dissolved in 10% aqueous sodium bicarbonate and treated with charcoal. Precipitation with 6 *N* hydrochloric acid yielded 62 g (72%) of **4**: mp 121–125° dec (recrystallization from ether–*n*-hexane raised this to 143–145° dec); nmr (CDCl₃–DMSO) δ 4.17 (2, s, CH₂), 7.2 (1, d, *J* = 2.5 cps, 6 H), 7.4 (1, dd, *J* = 2.5 cps and *J* = 9 cps, 4 H), 7.95 (1, d, *J* = 9 cps, 3 H), and 13.34 ppm (1, bs, COOH, exchangeable with D₂O); ir (KBr) 2.3 (OH), 3.35 (CH), 4.45 (C≡N), 5.95 μ (C=O).

Anal. Calcd for C₉H₆ClNO₂: C, 55.26; H, 3.09. Found: C, 55.07; H, 3.28.

Attempted Synthesis of 3-Carbethoxypropionic 5-Chloro-α-cyano-2-toluic Anhydride (2).—3-Carbethoxypropionyl chloride[2] (10.8 g, 0.06 mol) was added dropwise (over 0.5 hr) to a mixture of **4** (12 g, 0.06 mol) and pyridine (10.32 g, 0.13 mol) in 200 ml of anhydrous benzene. There was a slight exothermic reaction and an initial precipitate of pyridine hydrochloride formed. After the addition was complete, stirring was continued at room temperature for 1 hr, followed by heating at reflux for 36 hr.

The mixture was filtered to remove the pyridine hydrochloride and the filtrate was allowed to cool to room temperature. An initial precipitate (3.8 g) was formed. An additional 6.6 g of compound was isolated after concentration of the benzene solution. Recrystallization of the combined fractions from absolute ethanol yielded 7.7 g (39.6%) of 6-chloro-3-(3-carbethoxypropionylamino)isocoumarin (**5**): mp 198–199°; nmr (DMSO-*d₆*) δ 1.17 (3, t, ester methyl), 2.68 (>4, s, CH₂CH₂ and DMSO-*d₅*), 4.14 (2, q, OCH₂), 7.05 (1, s, =CH), 7.4 (1, dd, *J* = 9 and 1.5 cps, 7 H), 7.63 (1, d, *J* = 1.5 cps, 5 H), 8.02 (1, d, *J* = 9 cps,

(17) J. Schneckenburger, *Arch. Pharm.* (*Weinheim*), **298**, 411 (1965).

(18) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 101.

(19) J. Carson, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 169.

(20) H. S. Forrest, R. D. Haworth, A. R. Pinder, and T. S. Stevens, *J. Chem. Soc.*, 311 (1949).

(21) W. Davies and H. G. Poole, *ibid.*, 1616 (1928).

(22) R. D. Haworth and H. S. Pink, *ibid.*, 1368 (1925).

(23) Melting points were determined using a Büchi capillary melting point apparatus with open capillary tubes and were uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 21 or Model 237-B infrared spectrophotometer. Mass spectral data were obtained on a Perkin-Elmer Hitachi RMU-6A mass spectrometer. A Varian Associates A-60-A spectrometer was used at a sweep width of 500 cps using TMS as an internal standard. The samples were dissolved in the solvent specified. Ultraviolet spectra were determined on a Bausch and Lomb Model 505 or Cary 14 ultraviolet spectrophotometer. Elemental analyses were determined by Midwest Microlabs, Inc., Indianapolis, Ind.

8 H), and 11.16 ppm (1, bs, NH); ir (CHCl₃) 5.75 (ester C=O), 5.80 (lactone C=O), 6.05 (amide C=O and C=C), and 6.25 μ (C=C stretch); mass spectrum M⁺ 323 (10), 277 (54), 249 (20), 221 (10), 195 (100), 179 (28), 167 (60), 139 (19), 129 (71), 123 (56), 101 (94); uv λ_{M}^{EtOH} 244, 251, 290, 298 sh, and 347 mμ (log ϵ_M 4.58, 4.58, 4.39, 4.28, and 4.01, respectively).

Anal. Calcd for C₁₅H₁₄ClNO₅: C, 55.65; H, 4.36. Found, C, 55.44; H, 4.53.

Further evaporation of the benzene from above yielded 800 mg of 6-chloro-3-(3-carbethoxyethyl)-4-cyanoisocoumarin (6): mp 104.5–105.5° after recrystallization from 95% ethanol; nmr (CDCl₃) δ 1.25 (3, t, ester methyl), 3.05 (4, A₂B₂ sextet, CH₂, CH₂), 4.2 (2, q, ester methylene), and 7.9 ppm (3, m, aromatic); ir (CHCl₃) 3.42 (CH str), 3.5 (CH str), 4.47 (CN), 5.67 (lactone C=O), and 5.75 μ (ester C=O); mass spectrum M⁺ 305 (14), 260 (13), 231 (100), 190 (10), 148 (15), 122 (17).

Anal. Calcd for C₁₅H₁₂ClNO₄: C, 58.78; H, 4.21. Found: C, 58.76; H, 4.18.

Hydrolysis of 5. Method A.—A mixture of 5 (3.23 g, 0.01 mol), concentrated hydrochloric acid (7.5 ml), water (7.5 ml), and acetic acid (30 ml) was stirred at reflux under nitrogen for 24 hr. The water and acetic acid were removed *in vacuo*, whereupon a light yellow solid was obtained. The solid was partially dissolved in ether and filtered to remove the ammonium chloride. Evaporation of the ether left a residue, mp 157–161°. Recrystallization from ether–hexane yielded 1.8 g of 5-chlorohomophthalic acid: mp 153.5–156.5°; nmr (CDCl₃–pyridine) δ 4.1 ppm (2, s, CH₂), in addition to the aromatic protons from the sample and pyridine. There was also contamination from succinic acid.

From the recrystallization there was also obtained an ether-insoluble fraction, mp 178–182°, 800 mg. This compound was identical in all respects with authentic succinic acid.

Method B.—A mixture of 5 (6.46 g, 0.02 mol), potassium hydroxide (4.93 g, 0.09 mol), and 150 ml of 80% aqueous ethanol was stirred under reflux until ammonia evolution ceased (approximately 48 hr). The ethanol was removed and the residue was dissolved in water. Acidification to pH 2 with 6 N hydrochloric acid yielded a solid which was extracted with ether. The ether was dried (Na₂SO₄) and removed *in vacuo* to yield 4.1 g of a white solid which the nmr spectrum indicated to be a mixture of succinic acid and 5-chlorohomophthalic acid. Thin layer chromatography (silica gel, developed with ethanol–ammonia–water 80:4:16, visualized with cerric sulfate) confirmed this result.

Attempted Synthesis of 3-Carbomethoxypropionic α-Cyano-2-toluic Anhydride.—Following the directions of Vogel,[24] the silver salt of 2-carboxyphenylacetonitrile[4] (15.1 g, 0.1 mol) was prepared and suspended in benzene (200 ml) in the dark. 3-Carbomethoxypropionyl chloride[19] was added dropwise. The mixture was then stirred with refluxing for 7 hr.

The mixture was filtered to remove silver chloride (15.35 g, 100%). Upon cooling a light yellow solid (3 g) slowly crystallized: mp 199–201°; nmr (DMSO-d_6) δ 2.5 (>4, m, CH₂CH₂ and DMSO-d_5), 3.55 (3, s, OMe), 6.9 (1, s, =CH), 7.0–8.2 (4, m, aromatic), and 10.7 ppm (1, bs, NH). This material was shown to be 3-(3-carbomethoxypropionylamino)isocoumarin (5a).

Evaporation of the benzene yielded unreacted starting material as well as a fraction with carbonyl absorption at 5.57, 5.65, and 5.75 μ in the ir spectrum. There was not a sufficient quantity of this material for identification.

(24) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Wiley, New York, N. Y., 1966, p 388.

3-Acetylaminoisocoumarin (5b).—Acetyl chloride (4.8 g, 0.06 mol) was reacted with 2-carboxyphenylacetonitrile[4] (9 g, 0.06 mol) in the presence of pyridine as above to yield 4.65 g (40%) of 5b which was recrystallized from DMSO: mp 230–231°; nmr (DMSO-d_6) δ 1.94 (s, 3, CH₃), 6.88 (s, 1, =CH), 7.1–8.0 (4, m, aromatic), and 10.6 ppm (1, bs, NH).

Anal. Calcd for C₁₁H₉NO₃: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.91; H, 4.45; N, 6.68.

3-Aminoisocoumarin (8a).—Dicyclohexylcarbodiimide (28 g, 0.13 mol) in 50 ml of ethyl acetate was added dropwise to a suspension of homophthalamic acid[22] (21 g, 0.12 mol) in 450 ml of ethyl acetate at room temperature. The white suspension gradually became yellow. The mixture was stirred at room temperature for 12 hr.

The dicyclohexylurea was removed by filtration [28 g, mp 230–232° (lit.[25] mp 229–230°)] and the filtrate was concentrated *in vacuo* to yield 8a, as a yellow solid. Recrystallization from ethyl acetate yielded 6.7 g (35%): mp 127–128.5°; nmr (DMSO-d_6) δ 5.32 (1, s, =CH), 6.5 (2, s, NH₂), and 6.9–8.0 ppm (4, m, aromatic) (the signals at δ 5.32 and 6.5 were removed slowly by washing the sample with D₂O); ir (Nujol mull) 2.95 μ (NH); uv λ_{M}^{EtOH} 232, 291, and 390 mμ (log ϵ_M 4.36, 4.26, and 3.60, respectively); mass spectrum M⁺ 161 (86), 133 (100), 105 (56), 104 (86), 89 (48).

Anal. Calcd for C₉H₇NO₂: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.17; H, 4.61; N, 8.55.

Reaction of 2-Carboxyphenylacetonitrile and 3-Aminoisocoumarin (8a) with Pyridine.—2-Carboxyphenylacetonitrile[4] (1.0 g, 6 mmol) and pyridine (0.47 g, 6 mmol) were dissolved in benzene (100 ml) and stirred under reflux for 48 hr. Likewise, 8a (1.0 g, 6 mmol) was reacted in the same manner. Thin layer chromatography (silica gel PF₂₅₄, developed with CHCl₃–MeOH 95.5, visualized with short wavelength uv light) showed that these systems were identical.

3-(3-Carbomethoxypropionylamino)isocoumarin (5a). Method A.—Acylation of 8a (1.0 g, 6 mmol) with 3-carbomethoxypropionyl chloride[19] (0.9 g, 6 mmol) in the presence of pyridine (0.5 ml, 6 mmol) yielded 0.38 g (23%) of 5a after recrystallization from acetonitrile: mp 199–201°; nmr (DMSO-d_6) δ 2.6 (4, s, CH₂CH₂), 3.6 (3, s, OMe), 7.0 (1, s, =CH), 7 5 (5, m, aromatic), and 11.06 ppm (1, bs, NH).

Anal. Calcd for C₁₄H₁₃NO₅: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.28; H, 4.82; N, 5.03.

This material was identical in all respects with that material from the silver salt reaction above (mp 199–201°, nmr identical).

Method B.—Reaction of 2-carboxyphenylacetonitrile (1.0 g, 6 mmol) with 3-carbomethoxypropionyl chloride[19] (0.9 g, 6 mmol) as above yielded 0.37 g (23%) of 5a after recrystallization from acetonitrile, mp 199–201°. This material was identical with 5a prepared above (mp 199–201°, nmr identical).

(25) A. Skita and H. Rolfes, *Chem. Ber.*, **53**, 124 (1920).

C-Glycosyl Nucleosides. I. Studies on the Synthesis of Pseudouridine and Related Compounds

U. Lerch,[1] M. G. Burdon,[2] and J. G. Moffatt*

Contribution No. 81 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California 94304

Received October 22, 1970

Condensation of 2,4-di-*tert*-butoxypyrimidin-5-yllithium with 2,4:3,5-di-*O*-benzylidene-*aldehydo*-D-ribose gives, in good yield, the allo and altro isomers of 5-(2,4:3,5-di-*O*-benzylidene-D-pentahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (5a and 6a) that can be separated chromatographically. Cyclization of both isomers in dilute hydrochloric acid gives almost exclusively the α- and β-furanose forms of pseudouridine. Milder acidic treatment of 5a and 6a using 80% acetic acid at room temperature gives the allo and altro isomers of 5-(2,4:3,5-di-*O*-benzylidene-D-pentahydroxypentyl)uracil (7b, 8b) while at 100° both the *tert*-butyl and benzylidene groups are removed giving the corresponding 5-(pentahydroxypentyl)uracils (9a, 10a). Acidic cyclization of the latter compounds occurs under mild conditions, the altro isomer giving almost exclusively natural β-pseudouridine (1) while the allo isomer initially gives predominantly α-pseudouridine (2) which rapidly equilibrates to 1. Oxidation of either 5a or 6a gives a common ketone which can be reduced almost stereospecifically to the allo alcohol 5a with metal hydrides. Since such a reduction can be done using sodium borotritiide, the overall process provides a unique route for the synthesis of pseudouridines labeled selectively at $C_{1'}$ of the sugar. Acetylation of the pentitols (9a and 10a) gives the corresponding pentaacetates which, upon reaction with ammonia, are converted into the 1'-acetamido-1'-deoxy compound 17.

The presence of 5-(β-D-ribofuranosyl)uracil (1) as the principal minor component in transfer RNA has led to considerable interest in this C-glycosyl nucleoside.[3] Syntheses of both the naturally occurring β isomer 1 and of its α-furanosyl isomer 2 were achieved by Shapiro and Chambers[4] *via* condensation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride with 2,4-dimethoxypyrimidin-5-yllithium, but the yields were only 2 and 1%.

1   **2**
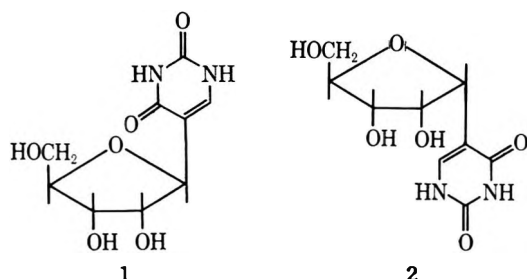
A substantial improvement in this synthesis was achieved by Brown, *et al.*,[5] who condensed 2,4-di-*tert*-butoxypyrimidin-5-yllithium (3) with 2,4:3,5-di-*O*-benzylidene-*aldehydo*-D-ribose (4) giving a mixture of epimeric alcohols (5a and 6a) that were not isolated as such but rather directly treated with methanol containing 10% concentrated hydrochloric acid at 60° for 2 min. This treatment effected removal of the *tert*-butyl and benzylidene protecting groups and led to simultaneous formation of the 1,4-anhydro sugars giving 1 and 2 in yields of 18 and 8%. Only traces of the pyranose isomers were formed. Subsequently, Asbun and Binkley have condensed 2,4-dibenzyloxypyrimidin-5-yllithium with several protected aldehydo sugars[6a] and aldonolactones[6b] as an approach to the synthesis of sugar analogs of pseudouridine.

With the objective of clarifying the mild and selective formation of anhydro sugar rings during the synthesis of 1 and 2 by the method of Brown, *et al.*,[5] we have reinvestigated these reactions in some depth and present our findings in this paper. In addition, we were motivated by the possibility of using certain intermediate products for the preparation of tritium-labeled pseudouridines which might be of interest for biochemical studies.

In our hands the condensation of 3 and 4 in tetrahydrofuran proceeded very rapidly at a low temperature and gave two major products of very similar polarity together with some 2,4-di-*tert*-butoxypyrimidine and unidentified carbohydrate products. A partial separation of the isomeric products (5a and 6a) in a combined yield of 69% could be obtained by chromatography on a column of silicic acid. Complete resolution was achieved by preparative tlc of the overlapping fractions giving the less polar isomer 5-(2,4:3,5-di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (5) in 25% yield and the corresponding altro isomer 6 in 37% yield.

5a, R = H
b, R = *p*-iodobenzoyl

6a, R = H
b, R = *p*-iodobenzoyl
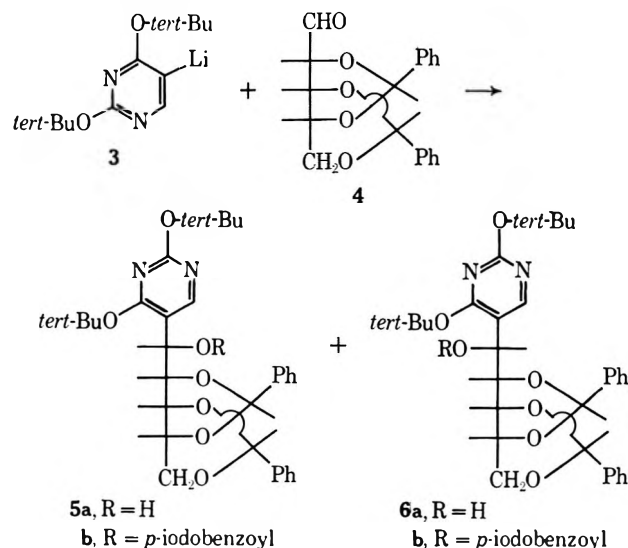
The assignments of configurations to 5a and 6a is based predominantly upon optical rotatory dispersion (ORD) spectra which are shown in Figure 1. It has

(1) Syntex Postdoctoral Fellow, 1966–1968.
(2) Syntex Postdoctoral Fellow, 1964–1965.
(3) For a review on the chemistry and biochemisry of pseudouridine, see (a) R. W. Chambers, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 349 (1966); (b) E. Goldwasser and R. L. Heinrickson, *ibid.*, **5**, 399 (1966).
(4) R. Shapiro and R. W. Chambers, *J. Amer. Chem. Soc.*, **83**, 3920 (1961).
(5) (a) D. M. Brown, M. G. Burdon, and R. P. Slatcher, *Chem. Commun.*, 77 (1965); (b) D. M. Brown, M. G. Burdon, and R. P. Slatcher, *J. Chem. Soc.*, 1051 (1968).
(6) (a) W. A. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 3315 (1966); (b) W. A. Asbun and S. B. Binkley, *ibid.*, **33**, 140 (1968).

Figure 1.—ORD spectra (MeOH) of compounds **5a** (—) and **6a** (---).

7a, R = *p*-iodobenzoyl
b, R = H

8a, R = *p*-iodobenzoyl
b, R = H

long been recognized that the sign of the $[\alpha]_D$ of aromatic and heterocyclic polyols is governed by the configuration of the asymmetric center adjacent to the unsaturated ring. Thus, polyol derivatives of benzimidazoles,[7] pyrazoles,[8] triazines,[9] and other simple aromatics[10] are shown to have positive rotations when the $C_{1'}$ hydroxyl is on the right-hand side of a normal Fischer projection and negative rotations when on the left. More recently, these rules have been extended to show that various heterocyclic polyols with S chirality at $C_{1'}$ (OH on the right in the Fischer projection) give positive Cotton effects while those with R chirality give negative Cotton effects.[11] Since the longer wavelength Cotton effect (centered about the λ_{max}) of the less polar compound is positive, we have assigned this compound the allo configuration **5a** while the more polar isomer is considered to be the altro isomer **6a**. It will be seen that many compounds derived from **5** also show positive Cotton effects while those originating from **6** retain negative Cotton effects, thereby strengthening these assignments.

We have attempted to use the method of Horeau[12] to independently determine the configurations of **5a** and **6a** but, unfortunately, both compounds lead to residual acid with very small negative rotations. We have also attempted to prepare derivatives suitable for X-ray crystallographic analysis but have as yet been unsuccessful. Thus, reactions of **5a** and **6a** with *p*-iodobenzoyl chloride gave the appropriate 1'-*O*-*p*-iodobenzoates (**5b** and **6b**) only as amorphous solids. Brief treatment of **5b** and **6b** with 80% acetic acid selectively removed the *tert*-butoxy groups from the pyrimidine rings giving the free uracil derivatives **7a** and **8a** in crystalline form. Unfortunately, both compounds could be obtained only as tiny crystals that were not sufficiently large for X-ray analysis.

It has been previously shown that brief treatment of a mixture of **5a** and **6a** with hot methanolic hydrochloric acid leads to a mixture of β- and α-pseudouridine (**1** and **2**).[5] The same is true for the pure isomers, separate treatment of **5a** and **6a** with concentrated hydrochloric acid–methanol (1:9) under reflux for 1 min giving the β- and α-furanose isomers **1** and **2** in ratios of 1.1:1 and 2.6:1, respectively, as judged by borate electrophoresis at pH 9.6.[13] No appreciable pyranose isomers were formed. Examination of aliquots following shorter treatments with acid showed that almost complete formation of **1** and **2** had occurred during the first 30 sec and that the degree of stereospecificity was greater during the early phases of the reaction. Thus, treatment of **6a** led initially to almost exclusively β-pseudouridine (**1**) which then partially isomerized to its α anomer before **6a** had disappeared. Similar treatment of **5a** led initially to a preponderance of the α isomer **2**, but the rate of anomeric isomerization was rapid and gave an $\alpha:\beta$ mixture of 6:4 by the time cyclization was complete. In preparative reactions, treatment of **6a** with ethanolic hydrochloric acid under reflux for 40 sec gave a mixture of 76% β-pseudouridine (**1**), 12% α-pseudouridine (**2**), and 12% monobenzylidene compounds. Only traces of pyranosides were formed. From this mixture pure **1** could be obtained in 56% yield by direct crystallization. Similar treatment of **5a** gave a 6:4 mixture of **2** and **1** which was separated by borate ion exchange chromatography giving crystalline **2** and **1** in yields of 40 and 27%. Since removal of the hydrochloric acid on a larger scale can prove troublesome, the latter reaction was also done using sulfuric acid in aqueous methanol followed by precipitation of barium sulfate. Acidic cyclization of **6a** could also be conducted in methanol–hydrochloric acid (9:1) at room temperature for 24 hr and, once again, pure **1** was obtained in 50% yield by direct crystallization. Similar treatment of **5a** gave a mixture of **1** and **2** that required ion exchange separation.

In order to determine the sequence of steps in the acidic conversion of **5a** and **6a** to **1** and **2**, milder treatments were studied. Thus, it could be shown that the first point of attack is the *tert*-butyl ethers on the uracil rings. Treatment of **5a** with 80% acetic acid at room temperature for 2.5 hr gave essentially a single product that was isolated in crystalline form in 80% yield and shown to be 5-(2,4:3,5-di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)uracil (**7b**) by analytical and spectroscopic methods. Similar treatment of **6a** gave the crystalline D-altro isomer **8b** in a yield of 74%.

(7) N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, **64**, 1612 (1942).

(8) (a) H. El Khadem, *J. Org. Chem.*, **28**, 2478 (1963); (b) J. A. Mills, *Aust. J. Chem.*, **17**, 277 (1964).

(9) M. Bobek, J. Farkaš, and F. Šorm, *Collect. Czech. Chem. Commun.*, **32**, 3572 (1967).

(10) H. El Khadem and Z. M. El-Shafei, *Tetrahedron Lett.*, 1887 (1963).

(11) W. S. Chilton and R. C. Krahn, *J. Amer. Chem. Soc.*, **89**, 4129 (1967); (b) W. S. Chilton and R. C. Krahn, *ibid.*, **90**, 1318 (1968); (c) G. G. Lyle and M. J. Piazza, *J. Org. Chem.*, **33**, 2478 (1968).

(12) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(13) Under these conditions there is a clear separation between the four furanose and pyranose isomers of 5-ribosyluracil.

As with the parent compounds, the ORD spectra of **7b** and **8b** gave opposite Cotton effects centered about 240 mμ with **8b** being negative in sign. The spectra of both compounds also show small troughs in the 285-290-mμ region which presumably originate from a spectral transition of the benzylidene groups that are common to both molecules.

More vigorous hydrolysis of **5a** and **6a** using 60-80% acetic acid at 100° led to the removal of both the *tert*-butyl and benzylidene groups and gave the crystalline, isomeric 5-(pentahydroxypentyl)uracils (**9a** and **10a**) with the D-allo and D-altro configurations, respectively, in yields of 61 and 72%. Once again these products showed Cotton effects of opposite sign and directly related to those of **5a** and **6a**. Some minor cyclization to pseudouridines accompanied this treatment and, to simplify the work-up, the reactions were usually terminated before the benzylidene group was completely removed. In one case, the mother liquors from a preparation of **10a** were purified by preparative tlc giving a 17% yield of the monobenzylidene derivative **11**. Since this compound did not reduce periodate, it was shown to have the 2,4-*O*-benzylidene structure rather than being its 3,5-substituted isomer. A chromatographically similar compound was also formed during preparation of **9** but has not been isolated.

9a, R = H
b, R = Ac

10a, R = H
b, R = Ac

11
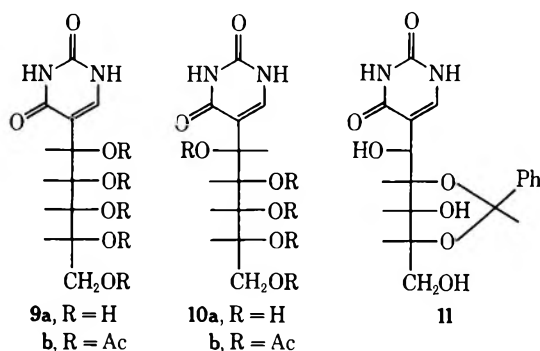
Cyclization of the pentitols **9a** and **10a** can also be readily achieved by mild acidic treatment and here the stereochemistry of the process can be more clearly defined. Thus a suspension of **10a** in 1 *N* hydrochloric acid was stirred at room temperature and gave a clear solution after roughly 3 hr. After 6-8 hr, extensive formation of almost exclusively β-pseudouridine (1) had occurred and even after 24 hr the mixture contained only the β isomer **1** and roughly 5% of **2**. In a preparative reaction, pure **1** was isolated from such a reaction in 75% yield by direct crystallization, and this could undoubtedly be improved by chromatography of the mother liquors. On the other hand, **9a** was more readily soluble in 1 *N* hydrochloric acid and had completely cyclized within 3 hr giving predominantly α-pseudouridine (2) and only about 10% of the β isomer. Prolonged acidic treatment led to increased isomerization, the ratio of 2:1 being roughly 4:1 after 5 hr and 1:1 after 30 hr. No pyranose isomers were present by borate electrophoresis. The equilibration of the various pseudouridine isomers has been studied in 1 *N* hydrochloric acid at 100° by Cohn[14] in his classical paper on the structure of the natural product and has been mechanistically rationalized by

Chambers, *et al.*[15] The much more facile anomerization of **2** relative to **1** does not, however, appear to have been previously noted. The cyclization reaction has been suggested to proceed *via* an SN1 process involving a common, allylically stabilized carbonium ion derived from C$_1'$ of **9a** or **10a**. Since **10a** leads almost exclusively to **1** while **9a** gives initially a preponderance of **2**, a common, *free* carbonium ion is probably not involved. An inspection of molecular models shows that the conversions of **9a** to **2** and of **10a** to **1** both involve an inversion of configuration at C$_1'$ of the pentitol moiety. Thus, the cyclization reaction may well involve an SN2 type of displacement of the protonated C$_1'$-hydroxyl group by the C$_4'$ hydroxyl. The alternative intermediacy of a solvent-stabilized C$_1'$-carbonium ion that is attacked by C$_4'$ OH with net inversion of configuration cannot be excluded. A direct SN2 displacement reaction has also been postulated[16] for the acid-catalyzed cyclization of simple pentitols, but, in this case, it is the primary hydroxyl group that is protonated thus leading to retention of configuration. It is interesting to note that acid-catalyzed cyclization of the 6-aza analogs of **9a** and **10a**, prepared in an ingenious way by Bobek, *et al.*,[17] leads to the 2',5'- rather than the desired 1',4'-anhydro compounds. This has been explained[17] by a decreased ability of the 6-azauracil moiety, relative to that of uracil, to stabilize a 1'-carbonium ion. In the present work we are confident that the anhydro bridge formed is the desired 1',4' structure. This is based upon the identical physical properties of **1** to the natural product and, in particular, on the nmr spectra of **1** and **2** in pentadeuteriopyridine. In these spectra the C$_1'$ protons appear as quartets at 5.43 and 5.62 ppm showing small allylic coupling to C$_6$ H of the uracil ring.[18] Acetylation of **1** and **2** gave the triacetates in which the 2', 3', and 5' protons were typically deshielded by up to 1 ppm while C$_1'$ H remained essentially unchanged. This clearly shows that there is not an hydroxyl group at C$_1'$ as would be the case in the 2',5'-anhydro compounds such as **12**.

In the course of their work on the synthesis of 5-substituted uracils, Asbun and Binkley[6a] have also obtained, by a different route, a compound referred to as 5-α-D-ribitol uracil and considered to be **9a** from its ORD spectrum. The reported melting point is close to that of both **9a** and **10a**, and the reported positive Cotton effect suggests that this assignment is correct. This assignment is based, however, upon an ORD spectrum of **1** that appears to bear no similarity at all to that obtained by us (see Experimental Section). This compound was obtained following treatment with 0.2 *N* sulfuric acid for 16 hr and has led to the suggestion that cyclization does not occur readily even under more vigorous conditions. In a subsequent paper, these authors[6b] have also prepared **1** in an overall yield of 10% by a process that involves the intermediate formation of **9a** or **10a** which was not isolated but which did cyclize with 0.2 *N* sulfuric acid. In our

(14) W. E. Cohn, *J. Biol. Chem.*, **235**, 1488 (1960).

(15) R. W. Chambers, V. Kurkov, and R. Shapiro, *Biochemistry*, **2**, 1192 (1963).

(16) B. G. Hudson and R. Barker, *J. Org. Chem.*, **32**, 3650 (1967).

(17) M. Bobek, J. Farkaš, and F. Šorm, *Collect. Czech. Chem. Commun.*, **34**, 1673 (1969).

(18) A similar allylic coupling of the anomeric proton in naturally occurring **1** has recently been observed in D$_2$O by F. E. Hruska, A. A. Grey, and I. P. C. Smith, *J. Amer. Chem. Soc.*, **92**, 4088 (1970).

hands 0.2 *N* sulfuric acid at 23° proved to be inefficient for the cyclization of both **9a** and **10a**, only about 10% conversion to **1** and **2** being achieved in 16 hr. The use of 1 *N* hydrochloric acid as above does, however, clarify the stereochemistry of the cyclization process.

Oxidation of both **5a** and **6a** using dimethyl sulfoxide activated by either acetic anhydride[19] or dicyclohexyl-carbodiimide[20] gave crystalline 5-(2,4:3,5-di-*O*-benzylidene-1-keto-D-*ribo*-tetrahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (**13**) in high yield. This oxidation can also be achieved using manganese dioxide in acetonitrile.[21] Reduction of this ketone with either sodium borohydride or lithium aluminum hydride was essentially stereospecific giving **5a** and **6a** in ratios of 94:6 and 96:4, respectively. Since **5a** can be readily converted into both **1** and **2**, the reduction of **13** with sodium borotritiide would appear to provide a facile route for the synthesis of **1** or **2** bearing a specific tritium label at $C_{1'}$ of the sugar. Such an isotopic synthesis has not been carried out but might prove useful for biochemical studies on pseudouridines.

Selective removal of the *tert*-butyl groups from **13** could be achieved by treatment with 80% acetic acid at room temperature giving **14** in almost quantitative yield. More vigorous treatment of **13** with 50% acetic acid at 100° leads to extensive decomposition and the reaction has not been examined further.

12   **13**

14
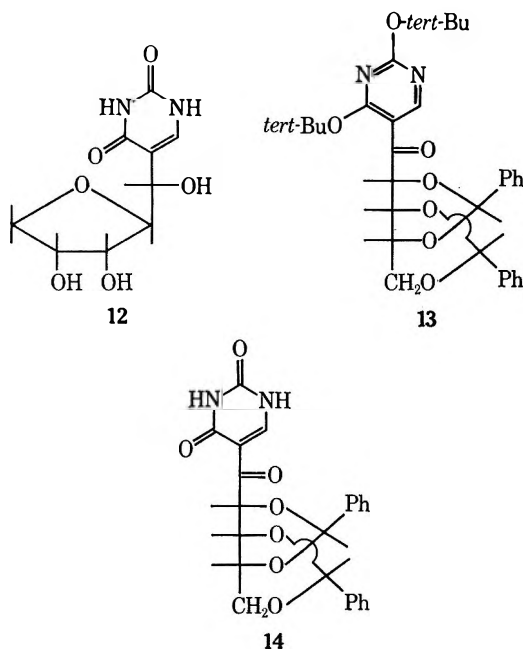
Acetylation of **9a** and **10a** gave the corresponding pentacetates **9b** and **10b** in high yields. Deacetylation of these derivatives with methanolic ammonia or ammonium hydroxide did not, however, regenerate the original pentitols. Thus, treatment of either **9b** or **10b** led to very similar paper chromatographic patterns containing a major spot which showed some tendency to partially separate into a second minor component. By preparative tlc on microcrystalline cellulose, the major product from **10b** was obtained in crystalline form in 57% yield. By paper chromatography in

several solvents this compound behaved very similarly to **2**, but borate electrophoresis (pH 9.2) showed it to be slower moving than either **1** or **2**. This compound had the typical ultraviolet spectrum of a pseudouridine derivative and rapidly consumed 2.90 mol of periodate[22] with release of 1.00 mol of formaldehyde.[23] The nmr spectrum of this compound did not show resolution of the sugar protons but contained a 3-proton singlet at 1.91 ppm typical of an *N*-acetyl derivative. Based upon the elemental analysis of this compound, we consider it to be the acetamidotetraol (**17**). This structure could arise by rapid base-catalyzed elimination of acetate from $C_{1'}$ of **10b** giving the olefin **15** which then undergoes conjugate addition of ammonia giving **16** followed by O → N acetyl migration.

10b   **15**

16   **17**
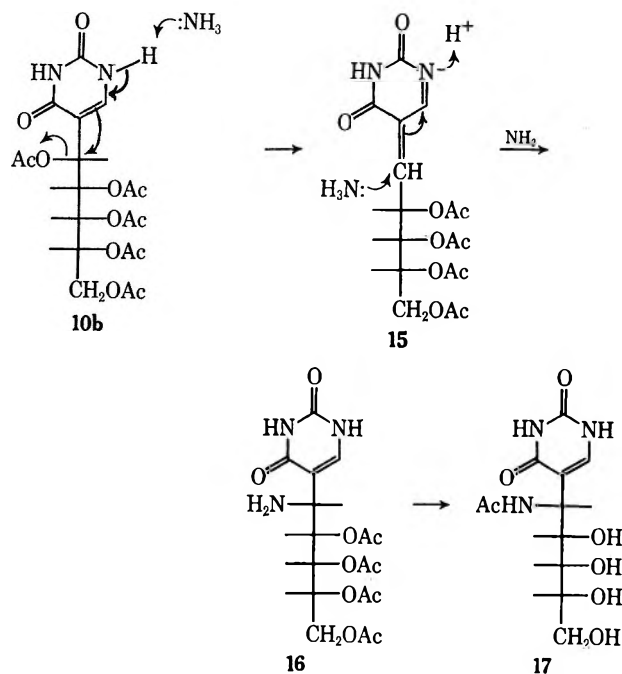
Since **17** shows a negative Cotton effect in its ORD spectrum, we tentatively assign it the D-altro configuration. This sequence of events is very similar to that known to occur during reaction of penta-*O*-acetyl-1-deoxy-1-nitrohexitols,[24] or the nitro olefins derived from them,[25] with ammonia giving 2-acetamido-1,2-dideoxy-1-nitrohexitols. A related participation of the uracil ring has also been shown to occur during the conversion of 5-acetoxymethyluracil to 5-methoxymethyluracil with sodium methoxide.[26] By the pathway **10b** → **17**, both **9b** and **10b** would be expected to give the same ultimate mixture of acetamido epimers dictated by the steric restraints on **15**. While a shortage of **9b** has prevented its preparative conversion to pure **17**, the chromatographic and electrophoretic patterns of the crude reaction mixtures are so similar as to make this seem likely.

The synthetic routes described in this paper would appear to make pure samples of both isotopically labeled and unlabeled **1** and **2** quite readily available.

(19) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967).

(20) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965).

(21) R. M. Evans, *Quart. Rev. Chem. Soc.*, **13**, 61 (1959).

(22) J. S. Dixon and D. Lipkin, *Anal. Chem.*, **26**, 1092 (1954).

(23) R. M. Burton, *Methods Enzymol.*, **3**, 246 (1957).

(24) C. Satoh and A. Kiyomoto, *Carbohyd. Res.*, **7**, 138 (1968).

(25) (a) A. N. O'Neill, *Can. J. Chem.*, **37**, 1747 (1959); (b) M. B. Perry and J. Furdova, *ibid.*, **46**, 2859 (1968).

(26) D. V. Santi and A. L. Pogolotti, *Tetrahedron Lett.*, 6159 (1968).

Experimental Section

Thin layer chromatography (tlc) was performed using 0.25-mm layers of Merck silica gel GF and preparative tlc on 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF. Nuclear magnetic resonance spectra were obtained using a Varian HA-100 spectrometer and are reported as parts per million downfield from an internal standard of tetramethylsilane. The assignments of sugar protons were generally confirmed by spin decoupling. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their cooperation in nmr studies. Optical rotatory dispersion (ORD) spectra were obtained using a Jasco ORD/UV-5 instrument. Elemental analyses were obtained by Dr. A. Bernhardt, Mühlheim, Germany, and other instrumental analyses were by the staff of the Analytical Laboratory of Syntex Research.

5-Bromo-2,4-di-*tert*-butoxypyrimidine.—This compound was prepared from 5-bromo-2,4-dichloropyrimidine essentially according to Brown, *et al.*,[5b] and purified by sublimation in 83% yield: λ_{max}^{MeOH} 225 mμ (ϵ 10,700), 276 (5900); nmr (CDCl$_3$) 1.59 and 1.69 ppm (s, 9, *tert*-BuO), 8.24 (s, 1, C$_6$H).

2,4:3,5-Di-*O*-benzylidene-*aldehydo*-D-ribose (4) and Its Methyl Hemiacetal.—The hydrated aldehydo sugar was prepared essentially according to Zinner[27] and was dried *in vacuo* at 100° for 3 hr prior to use: ν_{max} (KBr) 1740 cm^{-1}. Crystallization from methanol gave a methyl hemiacetal with mp 153–155°; $[\alpha]^{23}$D −30.1° (*c* 1.0, CHCl$_3$); nmr (CDCl$_3$) 3.49 (s, 3, OMe), 4.0 (m, 4, C$_3$·H, C$_4$·H, and C$_5$·H$_2$), 4.41 (m, 1, C$_2$·H), 4.8 (m, 1, C$_1$·H sharpening with D$_2$O), 5.69 (s, 1, ArCHO$_2$), 5.81 (s, 1, ArCHO$_2$), 7.4 ppm (m, 10, arom).

Anal. Calcd for C$_{20}$H$_{22}$O$_6$: C, 67.03; H, 6.19; O, 26.79. Found: C, 67.06; H, 6.03; O, 26.99.

Upon heating *in vacuo* at 185° for 2 min, the hemiacetal was converted to the free aldehyde which distilled to the cooler parts of the flask and was identified by an intense carbonyl band at 1740 cm^{-1}.

5-(2,4:3,5-Di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (5a) and Its D-Altro Isomer (6a).—A solution of 5-bromo-2,4-di-*tert*-butoxypyrimidine (10.7 g, 35 mmol) in anhydrous tetrahydrofuran (100 ml) was cooled to −70° in an atmosphere of argon. To this stirred solution was added, *via* a rubber septum, a solution of butyllithium (24.5 ml of 1.5 *M*, 36.7 mmol), and the resulting yellow solution was stirred for 25 min. A solution of freshly dried (100° at 1 mm for 3 hr) 4 (11.4 g, 35 mmol) in tetrahydrofuran (150 ml) was added dropwise over 30 min, and the mixture was then allowed to warm to room temperature overnight. After removal of roughly half the solvent *in vacuo*, the residue was partitioned between ether and water and the aqueous phase was extracted several times with ether. The combined ether extracts were dried (MgSO$_4$) and evaporated leaving a syrup (20 g) that was chromatographed on a column containing 1 kg of silicic acid using chloroform. This clearly separated a little 2,4-di-*tert*-butoxypyrimidine [bp 60° (0.1 mm); mp 47–50°; nmr 1.47 (s, 18, *tert*-BuO), 6.06 (d, 1, $J_{5,6}$ = 5.5 Hz, C$_5$H), 7.93 ppm (d, 1, $J_{5,6}$ = 5.5 Hz, C$_6$H)[28] from 5a and 6a which were partially separated. The overlapping fractions were further purified by tlc using three passes with carbon tetrachloride–acetone (87:13). The less polar compound 5a (4.80 g, 25%) was obtained in crystalline form and had mp 170–171° from ether–hexane; λ_{max}^{MeOH} 266 mμ (ϵ 5800); $[\alpha]^{23}$D +17.5° (*c* 0.1, MeOH); ORD, see Figure 1; nmr (CDCl$_3$) 1.48 and 1.56 (s, 9, *tert*-BuO), 3.25 (d, 1, $J_{H.OH}$ = 5 Hz, C$_1$·OH), 3.7–4.4 (m, 5, C$_2$·, C$_3$·, C$_4$·, and C$_5$·H's), 5.10 (q, 1, $J_{1',2'}$ = 2.4 Hz, $J_{H.OH}$ = 5 Hz, C$_2$·H), 5.58 and 5.77 (s, 1, ArCHO$_2$), 7.4 (m, 10, arom), 8.35 ppm (s, 1, C$_6$H).

Anal. Calcd for C$_{31}$H$_{38}$N$_2$O$_7$: C, 67.62; H, 6.96; N, 5.09. Found: C, 67.79; H, 7.13; N, 4.99.

The more polar altro isomer 6a was obtained as a chromatographically homogeneous, but noncrystalline foam (7.04 g, 37%): λ_{max}^{MeOH} 266 mμ (ϵ 5700); $[\alpha]^{23}$D −66.7° (*c* 0.27, MeOH); ORD, see Figure 1; nmr (CDCl$_3$) 1.53 and 1.57 (s, 9, *tert*-BuO), 3.0 (m, 1, C$_1$·OH), 3.9–4.5 (m, 5, C$_2$·, C$_3$·, C$_4$·, and C$_5$·H's), 5.13 (br d, 1, $J_{1',2'}$ = 2 Hz, C$_1$·H), 5.69 and 5.76 (s, 1, ArCHO$_2$), 7.4 (m, 10, arom), 8.30 ppm (s, 1, C$_6$H).

Anal. Calcd for C$_{31}$H$_{38}$N$_2$O$_7$: C, 67.62; H, 6.96; N, 5.09. Found: C, 67.71; H, 7.12; N, 4.91.

(27) H. Zinner and H. Schmandke, *Chem. Ber.*, **94**, 1304 (1961).

(28) M. Prystasz and F. Šorm, *Collect. Czech. Chem. Commun.*, **31**, 1035 (1966).

5-(1-*p*-Iodobenzoyl-2,4:3,5-di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)uracil (7a).—A solution of 5a (400 mg, 0.72 mmol) and *p*-iodobenzoyl chloride (450 mg, 1.7 mmol) in pyridine (2 ml) was kept for 3 hr at 23°. It was then diluted with ether and extracted several times with aqueous sodium bicarbonate. The dried ether solution was purified by preparative tlc using carbon tetrachloride–acetone (19:1) to give 5b (411 mg) as a homogeneous, noncrystalline foam. This material (390 mg) was treated at room temperature for 7 min with 80% acetic acid giving a partially crystalline precipitate that was collected and washed with 80% acetic acid and then water. Crystallization from chloroform–ethanol gave 7a as tiny needles with mp 222–224°; λ_{max}^{MeOH} 258 mμ (ϵ 22,300); nmr (DMSO-d_6) 3.8–4.7 (m, 5, C$_2$·, C$_3$·, C$_4$·, and C$_5$· H's), 5.95 (s, 1, ArCHO$_2$), 6.28 (d, 1, $J_{1',2'}$ = 4.5 Hz, C$_1$· H), 7.2–7.5 (m, 10, arom), 7.60 (s, 1, C$_6$ H), 7.60 and 7.88 (d, 2, J = 8 Hz, *p*-iodobenzoyl), 11.3 ppm (br s, 1, NH).

Anal. Calcd for C$_{30}$H$_{25}$N$_2$O$_8$I: C, 53.90; H, 3.77; N, 4.19; I, 18.99. Found: C, 53.74; H, 4.24; N, 4.16; I, 18.99.

5-(1-*p*-Iodobenzoyl-2,4:3,5-di-*O*-benzylidene-D-*altro*-pentahydroxypentyl)uracil (8a).—The altro compound 6a (400 mg) was treated with *p*-iodobenzoyl chloride as above giving 396 mg of the noncrystalline ester 6b which was treated with 80% acetic acid for 15 min at 23°. In this case, precipitation did not occur and the product was isolated by dilution with chloroform and washing with aqueous sodium bicarbonate. After evaporation of the organic phase and crystallization from methylene chloride–ethanol, 8a (205 mg) was obtained as tiny crystals with mp 239–240° (mixture melting point with 7a 207–218°); λ_{max}^{MeOH} 258 mμ (ϵ 24,500); nmr (DMSO-d_6) 3.8–4.6 (m, 5, C$_2$·, C$_3$·, C$_4$·, and C$_5$· H's), 5.63 and 5.94 (s, 1, ArCHO$_2$), 6.24 (d, 1, $J_{1',2'}$ = 5 Hz, C$_1$· H), 7.2–7.5 (m, 10, arom), 7.51 (s, 1, C$_6$ H), 7.80 and 7.99 (d, 2, J = 8 Hz, *p*-iodobenzoyl), 10.92 and 11.23 (br s, 1, NH).

Anal. Calcd for C$_{30}$H$_{25}$N$_2$O$_8$I: C, 53.90; H, 3.77; N, 4.19; I, 18.99. Found: C, 53.93; H, 3.98; N, 4.29; I, 19.00.

5-(2,4:3,5-Di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)uracil (7b).—A solution of 5a (250 mg) in 80% acetic acid (4 ml) was kept at 23° for 2.5 hr while following the hydrolysis by tlc using chloroform–methanol (9:1). The mixture was then diluted with ethyl acetate and washed with saturated aqueous potassium carbonate. Evaporation of the organic phase and purification of the residue by preparative tlc using carbon tetrachloride–acetone (1:1) followed by crystallization from methanol gave 159 mg (80%) of 7b as fine needles of mp 247–248° as a methanol solvate: λ_{max}^{MeOH} 265 mμ (ϵ 8000); $[\alpha]^{23}$D +3.2° (*c* 0.1, MeOH); ORD (MeOH) positive Cotton effect with a peak at 257 mμ (Φ +15,900°), a trough at 234 mμ (Φ +2300°), and a peak at 223 mμ (Φ +7100°); nmr (DMSO-d_6) 3.17 (s, 3, MeOH), 3.9 (m, 3, OCH), 4.2 (m, 2, OCH), 4.78 (br d, 1, $J_{H.OH}$ = 5 Hz, C$_1$· H), 5.53 (d, 1, $J_{H.OH}$ = 5 Hz, C$_1$· OH), 5.62 and 5.75 (s, 1, ArCHO$_2$), 7.2–7.5 (m, 11, arom and C$_6$ H), 11.0 ppm (br s, 2, N$_1$ H and N$_3$ H).

Anal. Calcd for C$_{23}$H$_{22}$N$_2$O$_7$·MeOH: C, 61.27; H, 5.57; N, 5.97. Found: C, 61.15; H, 5.34; N, 6.00.

5-(2,4:3,5-Di-*O*-benzylidene-D-*altro*-pentahydroxypentyl)uracil (8b).—A solution of 6a (250 mg) in 80% acetic acid (4 ml) was kept at 23° for 2.5 hr and worked up exactly as above. Crystallization from methanol–ether gave 8b (148 mg, 74%) as short needles of mp 253–254° with gas evolution; λ_{max}^{MeOH} 262 mμ (ϵ 7700); $[\alpha]^{23}$D −100.8° (*c* 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 260 mμ (Φ −14,800°), crossover at 242 mμ, and a peak at 234 mμ (Φ +4700°); nmr (pyridine-d_5) 3.95–4.6 (m, 4, C$_3$·, C$_4$·, and C$_5$·H's), 4.68 (d, 1, $J_{1',2'}$ = 3 Hz, C$_2$· H), 5.77 (d, 1, $J_{1',2'}$ = 3 Hz, C$_1$· H), 5.81 and 5.98 (s, 1, ArCHO$_2$), 7.3–7.8 (m, 10, arom), 8.0 (s, 1, C$_6$ H).

Anal. Calcd for C$_{23}$H$_{22}$N$_2$O$_7$·MeOH: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.03; H, 5.20; N, 6.02.

After drying *in vacuo* at 100°, the free compound was obtained.

Anal. Calcd for C$_{23}$H$_{22}$N$_2$O$_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 63.54; H, 5.16; N, 6.48.

5-(D-*allo*-Pentahydroxypentyl)uracil (9a).—A solution of 5a (1.0 g) in 80% acetic acid (20 ml) was heated at 100° for 8 min and evaporated to dryness. Trituration of the residue with ethanol gave 252 mg (53%) of pure 9a. Retreatment of the evaporated mother liquors with 60% acetic acid at 100° for 5 min gave a further 105 mg of product and recrystallization from 90% ethanol gave a total of 292 mg (61%) of 9a with mp 191–192° (mixture melting point with 10a 184–186°); $\lambda_{max}^{H_2O}$ 264 mμ (ϵ 7500); $[\alpha]^{23}$D +55.8° (*c* 0.2, H$_2$O); ORD (MeOH) positive Cotton effect with a peak at 260 mμ (Φ +4000°), a trough at 233 mμ

(Φ +300°), and a peak at 219 mμ (Φ +1700°); nmr (DMSO-d_6) 3.2–5.1 (m, 11, all sugar CH and OH including 4.65 ppm, d, 1, $J_{1',2'} = 4.5$ Hz, C$_{1'}$ H), 7.26 ppm (s, 1, C$_6$ H).

Anal. Calcd for C$_9$H$_{14}$N$_2$O$_7$: C, 41.30; H, 5.35; N, 10.69. Found: C, 41.29; H, 5.51; N, 10.91.

5-(D-*allo*-Pentaacetoxypentyl)uracil (9b).—A mixture of 9a (300 mg), pyridine (5 ml), and acetic anhydride (1.0 ml) was stirred overnight at 23°. After evaporation of the solvent the residue was dissolved in chloroform, washed with bicarbonate and with water, dried, and evaporated. Preparative tlc using chloroform–methanol (9:1) gave a single band that was eluted giving 458 mg (85%) of the pentaacetate (9b) as a foam that could not be crystallized: λ_{max}^{MeOH} 262 mμ (ϵ 7900); [α]^{23}D +73° (c 0.2, MeOH); ORD (MeOH) positive Cotton effect with a peak at 264 mμ (Φ +7100°), crossover at 244 mμ, and a trough at 230 mμ (Φ −4100°); nmr (CDCl$_3$) 2.02, 2.05, and 2.10 (9 H) (s, 3, OAc), 4.1–4.6 (m, 2, C$_{5'}$ H$_2$), 5.35 (m, 2, C$_{3'}$ H and C$_{4'}$ H), 5.70 (t, 1, $J_{1',2'} = J_{2',3'} = 5.5$ Hz, C$_{2'}$ H), 5.99 (d, 1, $J_{1',2'} = 5.5$ Hz, C$_{1'}$ H), 7.58 ppm (s, 1, C$_6$ H).

Anal. Calcd for C$_{19}$H$_{24}$N$_2$O$_{12}$: C, 48.31; H, 5.12; N, 5.93. Found: C, 48.64; H, 5.24; N, 6.29.

5-(D-*altro*-Pentahydroxypentyl)uracil (10a).—A solution of 6a (0.75 g) in 60% acetic acid (20 ml) was heated at 100° for 6 min and evaporated to dryness. Trituration of the residue with methanol gave 243 mg of almost pure 10a. The mother liquors which contained some monobenzylidene derivative 11 were evaporated to dryness and retreated as above with acetic acid for 5 min giving a further 69 mg (total yield 87%) of almost pure 10a. Recrystallization from aqueous ethanol gave 255 mg (72%) of 10a with mp 197–199°; $\lambda_{max}^{H_2O}$ 263 mμ (ϵ 7400); [α]^{23}D −96.0° (c 0.1, MeOH); ORD (H$_2$O) negative Cotton effect with a trough at 252 mμ (Φ −10,600°) and a peak at 232 mμ (Φ −1700°); nmr (DMSO-d_6) 3.4–3.7 (m, 5, C$_{2'}$, C$_{3'}$, C$_{4'}$, and C$_{5'}$ H's), 4.3 (m, 1, OH), 4.6 (m, 3, OH), 4.78 (s, 1, C$_{1'}$ H), 7.20 (s, 1, C$_6$ H), 10.5–11.0 ppm (m, 2, N$_1$ H and N$_3$ H).

Anal. Calcd for C$_9$H$_{14}$N$_2$O$_7$: C, 41.30; H, 5.35; N, 10.69. Found: C, 41.46; H, 5.50; N, 10.63.

5-(2,4-*O*-Benzylidene-D-*altro*-pentahydroxypentyl)uracil (11).—During preparation of 10a a less polar by-product was usually detected by tlc. In one experiment on hydrolysis of 6a (650 mg) as above this product was isolated by preparative tlc on microcrystalline cellulose using 1-butanol–acetic acid–water (5:2:3). Crystallization from ethyl acetate–methanol gave 70 mg (17%) of 11 with mp 218–219°; λ_{max}^{MeOH} 262 mμ (ϵ 7700); [α]^{23}D −144° (c 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 255 mμ (Φ −16,900°), a peak at 235 mμ (Φ −11,500°), and a trough at 220 mμ (Φ −27,200°); nmr (CDCl$_3$) 3.6 (br s, 5, C$_{2'}$, C$_{3'}$, C$_{4'}$, and C$_{5'}$ H's), 4.95 (d, 1, $J_{1',6} = 1$ Hz, C$_{1'}$ H), 5.53 (s, 1, ArCHO$_2$), 7.40 (br s, 6, Ar and C$_6$ H). The compound did not reduce periodate.

Anal. Calcd for C$_{16}$H$_{18}$N$_2$O$_7$: C, 54.85; H, 5.18; N, 8.00. Found: C, 54.70; H, 5.71; N, 8.18.

5-(D-*altro*-Pentaacetoxypentyl)uracil (10b).—A suspension of 10a (310 mg) in pyridine (3 ml) and acetic anhydride (3 ml) was stirred at 23° for 45 hr. After addition of water, the mixture was extracted into chloroform, washed with bicarbonate, and evaporated leaving a crystalline residue that was recrystallized from methylene chloride–ether giving 471 mg (84%) of 10b with mp 181–182°. An analytical sample had mp 183–184°; λ_{max}^{MeOH} 262 mμ (ϵ 7500); [α]^{23}D −38.7° (c 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 265 mμ (Φ −14,500°), crossover at 250 mμ, and a peak at 233 mμ (Φ +15,600°); nmr (CDCl$_3$) 2.01, 2.04, 2.06, and 2.11 (6 H) (s, 3, OAc), 4.25 (m, 2, C$_{5'}$ H$_2$), 5.3 (m, 2, C$_{3'}$ H and C$_{4'}$ H), 5.55 (q, 1, $J_{1',2'} = 2.5$ Hz, $J_{2',3'} = 8$ Hz, C$_{2'}$ H), 5.99 (d, 1, $J_{1',2'} = 2.5$ Hz, C$_{1'}$ H), 7.37 (br d, 1, $J_{6,N_1H} = 4$ Hz, C$_6$ H), 9.93 (br s, 1, N$_3$ H), 10.25 ppm (br d, $J_{6,N_1H} = 4$ Hz, N$_1$ H).

Anal. Calcd for C$_{19}$H$_{24}$N$_2$O$_{12}$: C, 48.31; H, 5.25; N, 5.98. Found: C, 48.31; H, 5.25; N, 5.98.

5-β-D-Ribofuranosyluracil (1) and 5-α-D-Ribofuranosyluracil (2). A. From 6a in Hot Acid.—A solution of 6a (250 mg) in ethanol (4.5 ml) was heated under reflux on a boiling water bath. Concentrated hydrochloric acid (0.5 ml) was added and after 40 sec the mixture was chilled in ice and evaporated to dryness under high vacuum. The residue was repeatedly coevaporated with ethanol until the odor of hydrochloric acid was absent and was then partitioned between water and ether. Following evaporation of the aqueous phase the residue was crystallized from ethanol giving 62 mg (56%) of 1 that was pure by borate electrophoresis and had mp 222–223° (reported mp 222–224°,[5b]

223–224°[4]); $\lambda_{max}^{H_2O}$ 262 mμ (ϵ 7900); $\lambda_{max}^{pH\ 12}$ 287 mμ (ϵ 7800); A_{280}/A_{260} (pH 12) = 2.10; ORD (H$_2$O) negative Cotton effect with a trough at 284 mμ (Φ −700°), crossover at 274 mμ, and a peak at 253 mμ (Φ +2300°); nmr (pyridine-d_5) 4.13 (q, 1, $J_{gem} = 12$ Hz, $J_{4',5'a} = 3$ Hz, C$_{5'a}$ H), 4.32 (q, 1, $J_{gem} = 12$ Hz, $J_{4',5'b} = 3$ Hz, C$_{5'b}$ H), 4.61 (m, 1, C$_{4'}$ H), 4.85 (t, 1, $J_{2',3'} = J_{3',4'} = 4.5$ C$_{3'}$ H), 4.98 (t, 1, $J_{1',2'} = J_{2',3'} = 4.5$ Hz, C$_{2'}$ H), 5.43 (q, 1, $J_{1',2'} = 4.5$ Hz, $J_{1',6} = 1$ Hz, C$_{1'}$ H), 8.16 ppm (d, 1, $J_{1',6} = 1$ Hz, C$_6$ H). Acetylation with acetic anhydride and pyridine quantitatively gave the 2',3',5'-tri-*O*-acetate that was isolated by preparative tlc using chloroform–2-propanol (9:1): nmr (pyridine-d_5) 1.99, 2.03, and 2.08 (s, 3-OAc), 4.95–5.15 (m, 3, C$_{4'}$ H and C$_{5'}$ H$_2$), 5.26 (d, 1, $J_{1',2'} = 4.5$ Hz, C$_{1'}$ H with slight allylic coupling), 5.86 (t, 1, $J_{2',3'} = J_{3',4'} = 6$ Hz, C$_{3'}$ H), 6.13 (q, 1, $J_{1',2'} = 4.5$ Hz, $J_{2',3'} = 6$ Hz, C$_{2'}$ H), 7.90 ppm (s, 1, C$_6$ H).

B. From 6a at Room Temperature.—A solution of 6a (250 mg) in methanol (2.25 ml) and concentrated hydrochloric acid (0.25 ml) was kept at 23° for 24 hr during which time some pure 1 crystallized from solution. The mixture was evaporated to dryness and worked up as in A giving 62 mg (56%) of pure 1 with mp 222–223°.

C. From 5a.—A solution of 5a (550 mg, 1 mmol) in methanol–hydrochloric acid (10 ml, 9:1) was treated as in A above. The aqueous solution following ether extraction was made 0.1 M in ammonium hydroxide and 0.05 M in boric acid and applied to a 3.5 × 35 cm column of Dowex-1 (HCO$_3^-$) resin. After a water wash the column was eluted with a linear gradient starting with 4 l. of 0.02 M boric acid, pH 9.3 in the mixing vessel, and 4 l. of 0.1 M ammonium bicarbonate in the reservoir. Following two very small peaks, two major, well-separated peaks emerged. The first peak (3500 OD units at 263 mμ) was evaporated to dryness, repeatedly coevaporated with methanol, and then passed through a 1 × 15 cm column of Dowex 50 (H$^+$) resin. The eluate was evaporated to dryness and coevaporated three times with methanol. The final residue was crystallized from ethanol giving 98 mg (40%) of electrophoretically pure α-pseudouridine (2) with mp 218–219° (reported[5b] mp 207–210°); $\lambda_{max}^{H_2O}$ 263 mμ (ϵ 7500); $\lambda_{max}^{pH\ 12}$ 288 mμ (ϵ 5600); A_{280}/A_{260} (pH 12) = 1.51; ORD (H$_2$O) positive Cotton effect with a peak at 283 mμ (Φ +3200°), crossover at 275 mμ, a trough at 255 mμ (Φ −13,100°), crossover at 234 mμ, and a peak at 230 mμ (Φ +1200°); nmr (pyridine-d_5) 4.16 (q, 1, $J_{gem} = 12$ Hz, $J_{4',5'a} = 4.5$ Hz, C$_{5'a}$ H), 4.37 (q, 1, $J_{gem} = 12$ Hz, $J_{4',5'b} = 3$ Hz, C$_{5'}$, H), 4.67 (m, 1, C$_{4'}$ H), 5.0 (m, 2, C$_{2'}$ H and C$_{3'}$ H), 5.62 (q, 1, $J_{1',2'} = 3$ Hz, $J_{1',6} = 1.5$ Hz, C$_{1'}$ H), 7.98 ppm (d, 1, $J_{1',6} = 1.5$ Hz, C$_6$ H). Acetylation (acetic anhydride, pyridine) gave the 2',3',5'-tri-*O*-acetate that was isolated by preparative tlc using chloroform–2-propanol (9:1) with mp 175–177°; nmr (pyridine-d_5) 1.99 (s, 9, 2'-, 3'-, and 5'-OAc), 4.4–4.8 (m, 3, C$_{4'}$ H and C$_{5'}$ H$_2$), 5.75 (q, 1, $J_{1',2'} = 3$ Hz, $J_{1',6} = 1.5$ Hz, C$_{1'}$ H), 5.92 (q, 1, $J_{2',3'} = 5$ Hz, $J_{3',4'} = 4$ Hz, C$_{3'}$ H), 6.25 (q, 1, $J_{1',2'} = 3$ Hz, $J_{2',3'} = 5$ Hz, C$_{2'}$ H), 7.99 (d, 1, $J_{1',6} = 1.5$ Hz, C$_6$ H).

The second major peak (2500 OD units at 263 mμ) was worked up in an identical way giving 67 mg (27%) of β-pseudouridine (1) with mp 222–223° from ethanol.

D. From 5a and 6a with Sulfuric Acid.—A roughly equal mixture of 5a and 6a (0.8 mmol) was dissolved in methanol-4 N sulfuric acid (3:1) and heated at 100° for 6 min. It was then diluted with water, extracted with ether, and brought to pH 8 with barium hydroxide. After centrifugation the supernatant liquid was separated by ion exchange chromatography as in C giving traces (total of 1.6%) of pyranosyl pseudouridines followed by 1 and 2 which were isolated crystalline as above in yields of 29 and 22%.

E. From 10a.—A suspension of 10a (50 mg) in 1 N hydrochloric acid was stirred at room temperature for 22 hr, a clear solution resulting after 3 hr. The solution was carefully evaporated to dryness and coevaporated several times with ethanol giving a white residue that was crystallized from ethanol giving 35 mg (75%) of pure 1 identical with that above.

5-(2,4:3,5-Di-*O*-benzylidene-1-keto-D-*ribo*-tetrahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (13). A.—A solution of 5a (300 mg) in DMSO (2 ml) and acetic anhydride (1.3 ml) was kept at 23° for 24 hr. After addition of chloroform, the solution was extracted several times with aqueous sodium bicarbonate, dried (MgSO$_4$), and evaporated. Preparative tlc using carbon tetrachloride–acetone (9:1) gave 274 mg (92%) of crystalline 13 with mp 250–252° from ethanol;[29] λ_{max}^{MeOH} 252 mμ (ϵ 10,900), 283

(29) In some experiments a lower melting form (mp 154–156°) was obtained. Recrystallization of this compound with seeding by the higher melting form gave mp 252–254°.

(11,000); $[\alpha]^{23}$D −44.2° (c 0.2, MeOH); ORD (MeOH) multiple Cotton effect with a peak at 335 mμ (Φ +8300°), crossover at 307 mμ, a trough at 290 mμ (Φ −7500°), crossover at 277 mμ, a shoulder at 265 mμ (Φ +5100°), and a peak at 238 mμ (Φ +30, 500°); nmr (CDCl₃) 1.60 and 1.62 (s, 9, *tert*-BuO), 3.9–4.5 (m, 4, C₃', C₄', and C₅' H's), 5.45 (d, 1, $J_{2',3'}$ = 8 Hz, C₂' H), 5.67 and 5.82 (s, 1, ArCHO₂), 7.3–7.6 (m, 10, arom), 8.40 ppm (s, 1, C₆H).

Anal. Calcd for C₃₁H₃₆N₂O₇: C, 67.86; H, 6.61; N, 5.11. Found: C, 67.73; H, 6.76; N, 4.92.

The same compound was obtained by oxidation of 6a in a similar way.

B.—A crude mixture of 5a and 6a (500 mg) in acetonitrile (30 ml) was stirred for 1 hr at room temperature with activated manganese dioxide (9 g). After filtration through Celite, the filtrates were evaporated to dryness leaving a chromatographically homogeneous, crystalline residue. Recrystallization from ethanol gave 219 mg (45%) of 13 identical with that above.

Metal Hydride Reduction of 13. A. Using Sodium Borohydride.—Sodium borohydride (7 mg) was slowly added to a slurry of 13 (45 mg) in methanol (2 ml). After 10 min the solvent was evaporated and the residue was partitioned between benzene and water. Evaporation of the benzene left a crystalline residue of almost pure 5a. Quantitative tlc using carbon tetrachloride–acetone (85:15) showed the product to contain 94% 5a and 6% 6a with quantitative recovery.

B. Using LiAlH₄.—Lithium aluminum hydride (5 mg) was added to a solution of 13 (45 mg) in tetrahydrofuran (2 ml) and after 30 min the mixture was worked up as above giving crystalline, almost pure 5a that was shown by tlc to be 96% 5a and 4% 6a.

5-(2,4:3,5-Di-O-benzylidene-1-keto-D-*ribo*-tetrahydroxypentyl)uracil (14).—A suspension of finely divided 13 (400 mg) in 80% acetic acid (5 ml) was stirred at 25° for 1.5 hr. During this time 13 dissolved and was replaced by fine needles of 14 (283 mg) which were removed by filtration. Addition of water to the filtrate gave a further 17 mg (total yield), 300 mg (94%) of 14 which was recrystallized from ethanol with mp 269–271° dec; λ_{max}^{MeOH} 290 mμ (ϵ 7400), 227 (sh, 5700); $[\alpha]^{23}$D −91.4° (c 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 296 mμ (Φ −9000°), crossover at 278 mμ, and a peak at 262 mμ (Φ +4800°);

nmr (pyridine-d₅) 4.0–4.6 (m, 3, C₄' H and C₅' H₂), 4.68 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 9 Hz, C₃' H), 5.92 and 6.23 (s, 1, ArCHO₂), 6.48 (d, 1, $J_{2',3'}$ = 9 Hz, C₂' H), 7.2–7.8 (m, 10, arom), 8.21 ppm (s, 1, C₆H).

Anal. Calcd for C₂₃H₂₀N₂O₇: C, 63.30; H, 4.62; N, 6.42. Found: C, 63.15; H, 4.45; N, 6.04.

5-(D-*altro*-1-Acetamido-2,3,4,5-tetrahydroxypentyl)uracil (17).—A solution of 10b (350 mg, 0.71 mmol) in methanol (5 ml) and concentrated ammonium hydroxide (5 ml) was kept at 23° for 5 hr and then evaporated to dryness *in vacuo*. Preparative tlc on three Avicel plates using 1-butanol–acetic acid–water (5:2:3) gave a major band moving just slower than α-pseudouridine. Elution with water and evaporation gave a syrup (4250 OD units at 260 mμ, 81%) that was dissolved in hot 90% methanol to remove some insoluble material, evaporated, and crystallized from 90% ethanol giving 122 mg (57%) of 17 with mp 223–224°; λ_{max}^{MeOH} 262 mμ (ϵ 7400); $[\alpha]^{23}$D +52.4°; ORD (H₂O) negative Cotton effect with a trough at 258 mμ (Φ −11,600°), crossover at 242 mμ, and a peak at 230 mμ (Φ +6100°); nmr (DMSO-d₆–D₂O) 1.91 (s, 3, C₁' NAc), 3.2–3.7 (m, 5, C₂', C₃', C₄', and C₅' H's), 5.15 (br, s, 1, C₁' H), 7.29 ppm (s, 1, C₆H). The compound consumed 3.0 equiv of periodate[22] with release of 1.0 equiv of formaldehyde.[23]

Anal. Calcd for C₁₁H₁₇N₃O₇: C, 43.56; H, 5.65; N, 13.86; O, 36.93. Found: C, 43.68; H, 5.84; N, 13.34; O, 36.91.

Reactions of Diaryl Disulfides with Active, Nonnucleophilic Alkylating Agents[1]

BERNARD MILLER* AND CHUNG-HWA HAN

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01002

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Reaction of diphenyl disulfide with triethyloxonium fluoroborate or diethoxycarbonium fluoroborate gave diethylphenylsulfonium fluoroborate and S-ethylsulfonium salts of ethyl p-thiophenoxyphenyl sulfide (5) and of a product assigned the structure of ethyl p-(p-thiophenoxyphenyl)thiophenoxyphenyl sulfide (6). Recovered diphenyl disulfide, thianthrene (3), and the S-ethylsulfonium salt of ethyl o-thiophenoxyphenyl sulfide (4) were also obtained in smaller amounts. The products obtained from alkylation of mixtures of diphenyl disulfide with diphenyl disulfide-d₁₀ or anisole showed that formation of all products proceeded through intermolecular steps. Formation of all products of these reactions, as well as the reaction of di-β-naphthyl disulfide with trimethyloxonium fluoroborate to give dibenzothianthrene (8), could be explained as proceeding by S-alkylation of the disulfides, followed by nucleophilic attack upon the unalkylated sulfur atom by another disulfide molecule or by anisole.

The structural similarities between *sym*-diphenylhydrazines and diphenyl disulfides have prompted several research groups to react diphenyl disulfide with strong protonic acids[2,3] or with boron trifluoride,[2] in attempts to obtain rearrangements similar to the benzidine rearrangements of diphenylhydrazines.[4] These attempts have been unsuccessful, resulting either in no reaction[2] or in formation of ill-characterized polymers.[3] It has

been suggested[3] that the polymeric materials may arise by oxidation and sulfonation of a 4,4′-dimercaptobiphenyl resulting from rearrangements of the benzidine type, but no concrete support for this proposal has been offered.

There are indeed excellent reasons why reactions analogous to the benzidine rearrangement are unlikely to occur during the reactions of diphenyl disulfides with proton acids. Benzidine rearrangements of most *sym*-diphenylhydrazines have been found to proceed from the diprotonated forms.[4] The very low basicity of disulfides, as compared to hydrazines, requires that much stronger acids must be used even for monopro-

(1) Part of this work has been published as a preliminary communication: B. Miller and C.-H. Han, *Chem. Commun.*, 623 (1970).

(2) H. H. Szmant and R. L. Lapinski, *J. Org. Chem.*, **21**, 847 (1956).

(3) H. J. Shine and J. L. Baer, *Chem. Ind.* (*London*), 565 (1957).

(4) D. V. Banthorpe in "Topics in Carbocyclic Chemistry," D. Lloyd, Ed., Logos Press, Ltd., London, 1969, pp 1–63.

tonation to occur, while diprotonation seems unlikely to occur at all. The use of very high concentrations of acid, particularly of sulfuric acid,[2,3] greatly increases the possibility of obtaining products of ring substitution or of oxidative cleavage of the S–S bond. The well-known susceptibility of the S–S bond to nucleophilic attack (presumably due to availability of d orbitals on sulfur for attack by the nucleophile)[5] should be greatly enhanced in a protonated disulfide, so that reactions such as that in eq 1 (which have analogies in the acid-catalyzed exchange reactions of disulfides)[5]

$$\overset{\text{H}}{\underset{+}{\text{PhSSPh}}} + X^- \longrightarrow PhSH + XSPh \qquad (1)$$

must be avoided. Finally, and perhaps most important, the very low bond strength of a C=S double bond[6] makes it appear highly improbable that a sulfur analog of 1, which presumably is an intermediate in the benzidine rearrangement (regardless of its detailed mechanism),[4] could form from a diphenyl disulfide.

1

Despite these difficulties, the great interest in expanding our knowledge of the class of reactions represented by the benzidine rearrangement (which includes not only reactions leading to semidines and diphenylines[4] but also the acid-catalyzed rearrangements of quinamines[7] and, probably, of O,N-diphenylhydroxylamines[8]) encouraged us to reinvestigate the possibility of such rearrangements occuring.

Although divalent sulfur atoms are poor hydrogen bases, they are usually excellent carbon bases.[9] We therefore decided to employ "carbon acids" (alkylating agents) as the reagents for our attempted rearrangements. To minimize the possibility of bimolecular cleavage of an alkylated disulfide occurring, we decided to employ alkylating agents with as poorly nucleophilic leaving groups or counterions as possible. Trialkyloxonium salts, as well as the less common dialkoxycarbonium salts, were therefore chosen to react with diaryl disulfides.

Results

Reaction of diphenyl disulfide with triethyloxonium fluoroborate in refluxing chloroform proceeded slowly, requiring from 6 to 24 hr, depending on the concentration of the solution and the amount of alkylating agent employed. A large excess of the alkylating agent was necessary to obtain reasonably complete reaction, due to partial decomposition of the oxonium salts in the refluxing reaction mixture. Evaporation of the solvent at the end of the reaction left gummy mixtures which appeared to consist largely of sulfonium salts. Thin layer chromatography of the alkylation products on silica in a large variety of solvent systems showed the

presence of several components which could not be completely separated. Attempts to isolate the products by column chromatography failed. However, careful extraction and preparative tlc procedures (see Experimental Section) resulted in the isolation of two crystalline products which were identified as diethyl phenylsulfonium fluoroborate and diethyl p-thiophenoxyphenylsulfonium fluoroborate (2), as will be discussed below. No other products could be isolated by these means.

We therefore decided to convert the mixture of sulfonium salts to neutral sulfides, which we felt would be easier to isolate. Either pyrolysis of the crude alkylation product at 175° for 10 hr or hydrolysis in refluxing aqueous alkali yielded a product mixture which did not give a test for sulfonium salts.[10] Vpc analysis showed the pressure of seven components in this mixture. Essentially identical vpc analyses were obtained for the neutral mixtures obtained from pyrolysis and from hydrolysis of the sulfonium salts. Direct vpc analysis of the crude alkylation product showed the presence of the same seven peaks, but several of these peaks were much smaller when analysis was carried out before cleavage of the sulfonium salts. Apparently the sulfonium salts were only partially cleaved on the vpc column.

The first five components were isolated by preparative vpc on a 6 ft, 30% SE-30 column. The final two components, one of which appeared as a shoulder preceding the other, were obtained at much higher retention times than the other components. They could not be separated from one another but were collected as a mixture in approximately a 1:5 ratio.

The first three components isolated were identified as ethyl phenyl sulfide, recovered diphenyl disulfide, and thianthrene (3). The fourth and fifth components were separated with appreciable difficulty, since the fourth component was a minor product which appeared at a retention time very close to that of the fifth component. Both compounds had analyses corresponding to the formula $C_{14}H_{14}S_2$. The two isomers had very similar nmr spectra, each showing the presence of an ethyl group on sulfur and of nine aromatic protons. The mass spectrum of each showed a parent peak at m/e 246 and a base peak at m/e 215, corresponding to loss of an ethyl group. The ir spectrum of each showed strong peaks at 690 and 740–750 cm^{-1}, indicating the presence of unsubstituted or ortho-substituted phenyl groups.[11] The spectrum of the major (fifth) component, but not that of the minor component, had, in addition, a medium intensity absorption at 820 cm^{-1}, suggesting the presence of a para-substituted benzene ring.[11] The major product was therefore tentatively assigned the structure ethyl p-thiophenoxyphenyl sulfide (5) and the minor product the structure ethyl o-thiophenoxyphenyl sulfide (4). The two isomers were independently synthesized by reaction of o- and p-thio-

(5) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(6) H. Mackle, *Tetrahedron*, **19**, 1159 (1963).

(7) B. Miller, *J. Amer. Chem. Soc.*, **86**, 1127 (1964).

(8) J. R. Cox, Jr., and M. F. Dunn, *Tetrahedron Lett.*, **No. 15**, 985 (1963).

(9) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, pp 159–162.

(10) H. Potratz and J. Rosen, *Anal. Chem.*, **21**, 1276 (1949).

(11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, Chapter 5.

phenoxyphenyldiazonium chlorides with ethanethiol. The ir and nmr spectra and vpc retention times of the products were identical with those of **4** and **5**, respectively.

4

5

The sixth and seventh components of the mixture, as was mentioned above, could not be separated from one another, but were isolated as a mixture in the approximate ration 1:5. Although neither could be obtained in a pure state, we believe that a reasonable structural assignment for the major component, at least, can be based on the information given below. The mass spectrum showed a parent peak at m/e 354 (corresponding to the formula $C_{20}H_{18}S_3$) and a base peak at m/e 325. The nmr spectrum of the mixture showed the presence of one ethyl group attached to sulfur and of 13 aromatic protons. No other peaks could be detected. These facts suggest that the two compounds are isomers containing one S-ethyl group and three aromatic rings linked together by sulfide bonds. The ir spectrum of the mixture shows peaks at 685 and 735 cm^{-1}, characteristic of phenyl or ortho-substituted aromatic rings, and a strong peak (the most intense in the spectrum) at 813 cm^{-1}, characteristic of para-substituted aromatic compounds.[11] The intensity of the 813-cm^{-1} peak, compared to the peaks at lower frequency, suggests that two of the three rings are para substituted. We therefore propose that the structure of the main component in the mixture of high retention time isomers is **6**. The minor component is presumably an isomer with one ortho-substituted ring.

6
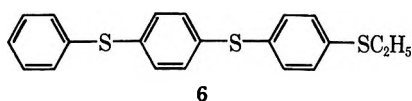
Synthetic mixtures of the compounds isolated from the reaction were prepared, and the mole fraction/area relationship for these components was determined. The mole ratios of the products of the reaction were obtained from the areas of peaks in the chromatogram of the reaction mixture after hydrolysis or pyrolysis. The number of moles of each product obtained from reaction of 1.00 mol of diphenyl disulfide is given in eq 2. Beneath these values, in parentheses, are listed the number of equivalents of phenyl groups (based on 2.00 phenyl equivalents in the starting diphenyl disulfide) in each product of the reaction. The number of phenyl equivalents obtained from this reaction adds up to 1.97. Although there is some uncertainty in this value, due to the impurity of the **6** obtained from the reaction, it does appear that we have isolated almost all the products of the reaction.

Thioethers **4** and **5** closely resemble the *o*- and *p*-thiosemidines obtained from benzidine rearrangements. In hope of determining whether these products are obtained by *intra*- or *inter*molecular reaction paths,

(2)
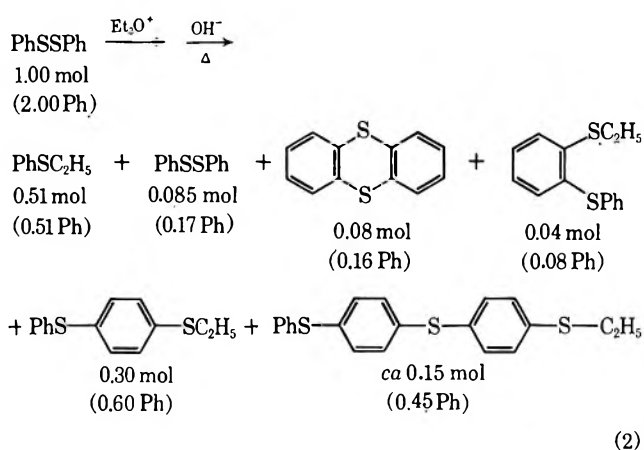
we reacted triethyloxonium fluoroborate with a mixture of phenyl disulfide and diphenyl disulfide-d_{10}. (Diphenyl disulfide-d_{10} was prepared by reacting phenyl-d_{10} magnesium bromide with sulfur and oxidizing the thiol thus prepared to the disulfide.) No apparent change in the course of reaction with the Meerwein reagent was observed when deuterated diphenyl disulfide was substituted for diphenyl disulfide. The products of the reaction were again isolated by preparative vpc, and the deuterium distribution in the products was determined from their mass spectra.

As can be seen from the results recorded in the Experimental Section, the mass spectra of all the products showed good agreement with the 1:2:1 undeuterated–half-deuterated–perdeuterated patterns expected for intermolecular rearrangements, if allowance is made for some exchange with the partially deuterated fluoroboric acid produced in the reaction. However, it can also be seen that the diphenyl disulfide recovered from the reaction had undergone complete exchange of phenyl groups between the deuterated and undeuterated species. Since exchange of phenyl groups in diphenyl disulfide under these conditions is therefore at least as fast as the rearrangements to **3**, **4**, and **5**, no conclusion can be drawn as to whether the formation of these products involves a second intermolecular step (other than that involved in exchange of phenyl groups among diphenyl disulfide molecules).

We then attempted to obtain indirect evidence that the major reaction product **5**, at least, can be formed intermolecularly by demonstrating that similar products can be obtained from clearly intermolecular electrophilic substitution processes. When anisole was added to the reaction mixture of diphenyl disulfide and triethyloxonium fluoroborate in chloroform, formation of the normal reaction products was almost entirely inhibited. Instead, a single new product was obtained, along with an equimolar amount of diethyl phenylsulfonium fluoroborate. The product was isolated by vpc and shown to be *p*-thiophenoxyanisole (**7**) by comparison with an authentic sample.[12]

7
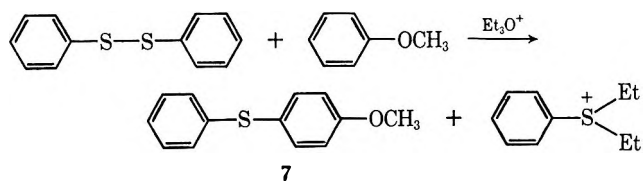
(12) (a) O. Hinsberg, *Chem. Ber.*, **36**, 107 (1903); (b) W. E. Truce, D. P. Tate, and D. N. Burdge, *J. Amer. Chem. Soc.*, **82**, 2872 (1960).

In view of the exceptional reactivity of dinaphthyl-hydrazines in benzidine rearrangements,[4] we decided to examine the reactions of dinaphthyl disulfides with Meerwein reagents. However, we could discern no reaction between triethyloxonium fluoroborate or di-ethoxycarbonium fluoroborate and di-8-naphthyl di-sulfide even after long reaction times. Trimethyl-oxonium fluoroborate, on the other hand, did react with the disulfide in a reasonable time. Analogy with the corresponding benzidine rearrangement[4] suggested that the two α positions might become linked during the reaction. However, no evidence for formation of any compound with a new C–C bond could be obtained. Instead, a mixture of dimethyl naphthylsulfonium fluoroborate and a solid (mp 182–185°) with the formula $C_{20}H_{12}S_2$ was obtained. This product showed no evidence for the presence of a disulfide link, and its nmr spectrum showed only aromatic absorption. On this basis, the product was assigned the structure of one of the isomeric benzothianthrenes **8a** or **8b**, and, indeed,
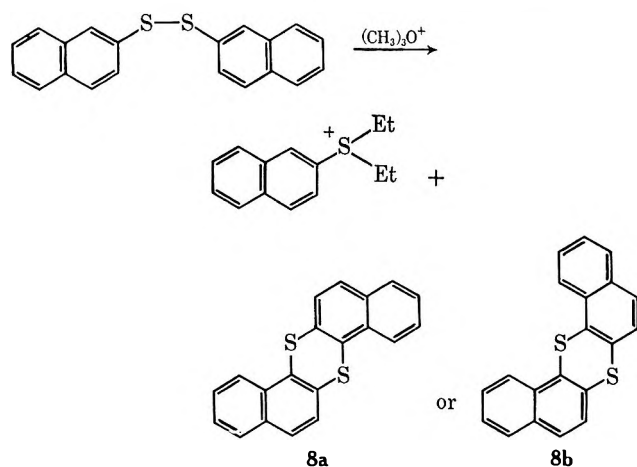
was found to be identical with the compound (mp 184°) previously assigned structure **8b** by Fries and Volk.[13] Although the gross structure of the product is established however, the stereochemistry (which seems to have been assigned arbitrarily[13]) is still uncertain. Our attempts to determine the stereochemistry of the product by synthesis of one of the stereoisomers by un-equivocal methods failed. However, on the basis of the presumed mechanism for its formation (see below), we favor structure **8a** for this product.

In contrast to the reaction of di-β-naphthyl disulfide, the reaction of di-α-naphthyl disulfide with trimethyl-oxonium fluoroborate gave a complex mixture from which no pure products could be isolated.

Discussion

Reaction of diphenyl disulfide with triethyloxonium fluoroborate gives products which closely resemble those of the semidine rearrangement of *sym*-diphenylhydra-zines.[4] It is clearly of great interest to determine whether formation of these products proceeds by inter-molecular or intramolecular paths. (It may be noted, by the way, that there is no direct evidence that semi-dine rearrangements actually proceed by intramolecular pathways, although it is commonly assumed that they do.[4]) The most direct attempt to demonstrate the

(13) K. Fries and W. Volk, *Chem. Ber.*, **42**, 1170 (1909).

nature of the pathways involved in formation of prod-ucts **3–5**—the mixed rearrangement of deuterated and undeuterated diphenyl disulfide—failed, due to the fact that the disulfide itself undergoes exchange of the two aromatic rings during the reaction. The exchange is clearly catalyzed by triethyloxonium fluoroborate, since no exchange takes place in the absence of this reagent. A simple chain mechanism can be written for the exchange reaction, which has analogy in the proton-catalyzed exchanges observed in dialkyl disul-fides.[5] This mechanism is outlined in eq 3. (O:
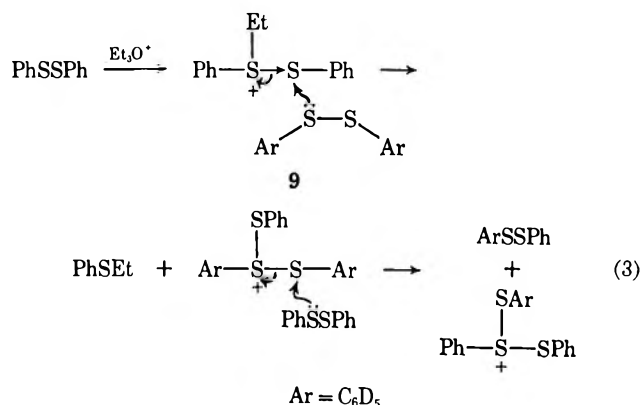
course, initial alkylation of deuterated disulfide would also occur.) We have written the actual exchange step as involving displacement on a sulfur atom in the alkyl-ated disulfide **9**, in order to minimize the number of postulated intermediates in the reaction. The possi-bility that the actual electrophilic reagent is the phe-nylsulfenium cation, however, has not been eliminated. (It has been suggested[14] that sulfenium cations are in-termediates in proton-catalyzed exchange reaction.)

Although no conclusion about the intermolecular or intramolecular nature of the "rearrangement" steps leading to **4** and **5** can be drawn from the mixed reaction experiment, other evidence provides strong argument that these products are formed by intermolecular paths. Clearly, formation of at least one of the diaryl sulfide links in **6** must proceed by an intermolecular path. Since exactly the same sort of linkage is char-acteristic of each of the other products of the reaction, it seems superfluous to postulate a second, intramolec-ular path to form those bonds. A similar argument holds for formation of the diaryl sulfide linkage in **7**. The formation of **7**, to the essential exclusion of the normal reaction products of diphenyl disulfide with triethyloxonium fluoroborate, or of the meta or ortho isomers of **7**, is completely consistent with the reactivity expected of anisole in electrophilic substitution reac-tions[15] but quite different from its reactivity patterns in homolytic substitution reactions.[16] In all respects, formation of **7** appears to be a typical electrophilic aromatic substitution. It does not, of course, neces-sarily follow that formation of products **3–6** similarly follow electrophilic paths, but in view of the basic simi-larities of these products to **7**, there again seems no point in postulating very different reaction mechanisms to explain their formation.

(14) R. E. Benesch and R. Benesch, *J. Amer. Chem. Soc.*, **80**, 1666 (1958).
(15) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, N. Y., 1960.
(16) P. B. D. De la Mare and J. H. Ridd, "Aromatic Substitution–Nitration and Halogenation," Academic Press, New York, N. Y., 1959.

(4)

(5)
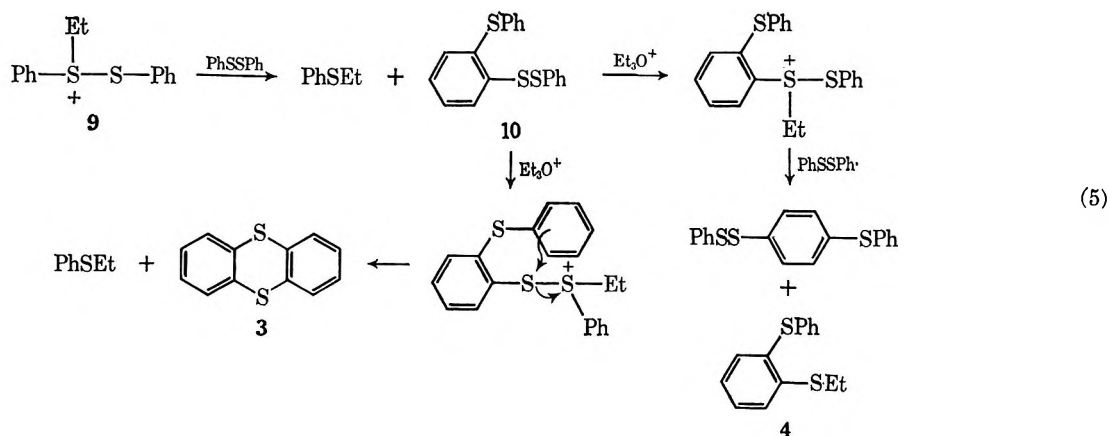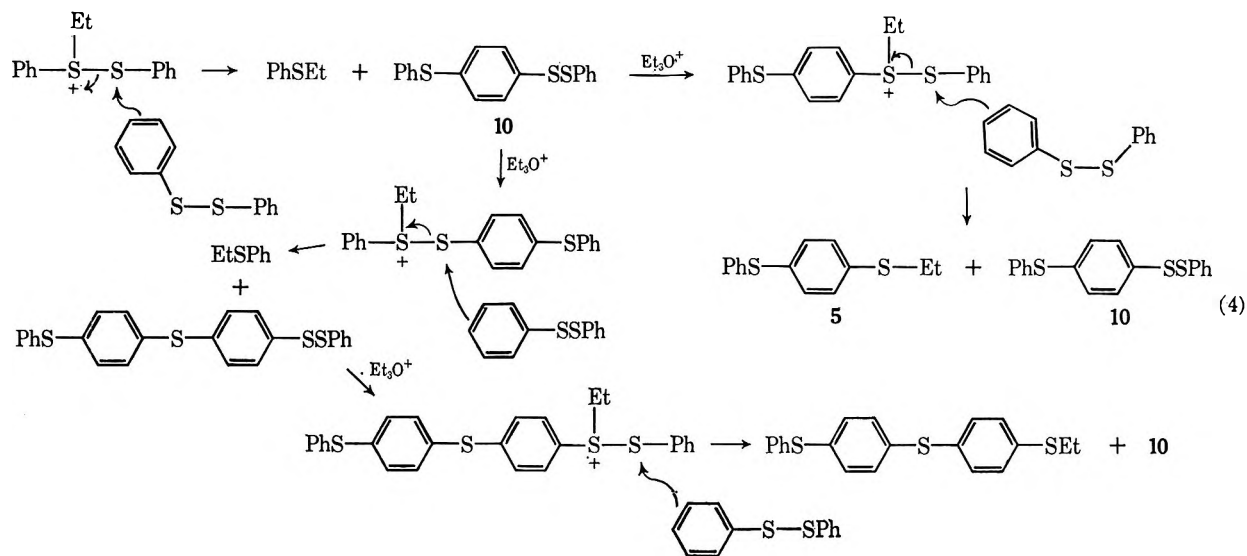
All the products of the reaction of diphenyl disulfide with triethyloxonium fluoroborate can be accounted for by electrophilic attack by the alkylated diphenyl disulfide 9 upon a diphenyl disulfide molecule. This mechanism is outlined in eq 4 for the formation of the major reaction products 5 and 6, and in eq 5 for the formation of 3 and 4.

In writing these mechanisms, we have assumed that the electrophilic agents were alkylated diaryl disulfides rather than free sulfenium ions. Some justification for this choice can be found in the high para/ortho ratios in the products of the reaction of phenyl disulfide with triethyloxonium fluoroborate. If the number of times reaction occurs at a para position to give 5 and 6 (counting two para attacks to form a molecule of 6) is compared to the number of times attack occurs at an ortho position to give 3 and 4, a para/ortho ratio of approximately 5:1 is obtained. This is quite a high ratio, particularly since the directing atom is a divalent sulfur. High para/ortho ratios are often characteristic of substitution upon rings bearing substituents with unshared electrons but high electronegativities, e.g., fluorine.[16] In these instances, the inductive effect of the substituent reduces the reactivity of the ortho positions. A similar high para/ortho ratio would not be expected to result from substitution upon a ring bearing a divalent sulfur. Aromatic rings substituted with bromine and chlorine atoms, which have higher electronegativities than sulfur,[17] typically give para/ortho ratios of *ca.* 2:1 in

halogenation and nitration reactions.[16] It is true that the ortho/para ratio can vary greatly with the nature of the attacking electrophile. Use of more reactive electrophiles, *e.g.*, the bromonium ion in place of molecular bromine, results in more indiscriminate attack at both ortho and para positions, while use of bulkier electrophiles results in more selective attack at the para position, presumably due to steric repulsions by the existing substituent.[16] On both grounds, the *S*-ethyl-sulfonium salt 9 seems more likely to give a high para/ortho ratio in attack upon a diphenyl disulfide molecule than does a simple sulfenium cation.

Finally, we may note that application of the mechanism in eq 5 to di-β-naphthyl disulfide gives rise to the intermediate 11. Cyclization of 11, in the manner suggested for formation of 3, should give rise to the "trans" dibenzothianthrene 8a. As has been mentioned above,
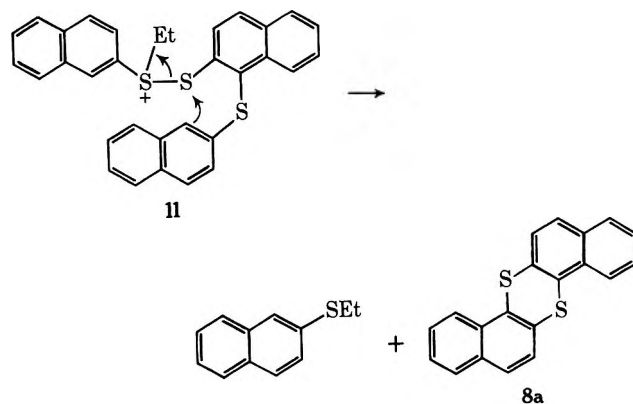
(17) L. Pauling, "The Nature of the Chemical Bond," 2nd ed, Cornell University Press, Ithaca, N. Y., 1948.

11

8a

however, experimental confirmation for the geometry of this molecule has not yet been obtained.

Experimental Section

Unless otherwise noted, all nmr spectra were recorded in CDCl$_3$ solution. Melting points are corrected and boiling points are uncorrected. Mass spectra were taken on A.E.I. MS-9 mass spectrometers with probe inlets at 100–125°.[18] Coupling constants (J) are given in hertz.

Reaction of Diphenyl Disulfide with Triethyloxonium Fluoroborate.—A solution of diphenyl disulfide (6.39 g, 0.030 mol) and triethyloxonium fluoroborate (8.55 g, 0.044 mol) in 20 ml of chloroform was heated at reflux for 16 hr. The mixture was then cooled to room temperature and washed several times with small portions of water. The chloroform layer was dried over magnesium sulfate and the solvent evaporated to give 1.68 g of yellow oil. This could not be crystallized on standing. Tlc on silica plates showed the presence of several components which were not well resolved. A sample of the chloroform-soluble material was applied to a preparative tlc plate (silica, 20 × 20 cm) and the plate developed with a 9:1 mixture of acetone and ethyl acetate. The only well-developed spot appeared at R_f 0.9, with appreciable tailing. This was scraped off the plate and extracted with acetone. Evaporation of the acetone left a small amount of solid, which had ir spectra and tlc retention times identical with those of diethyl *p*-thiophenoxyphenylsulfonium fluoroborate (2).

The combined aqueous washes were extracted several times with chloroform. The chloroform extract was dried and the solvent evaporated to give a yellow oil, which partially crystallized on standing. The crystals were isolated and identified by melting point, mixture melting point, and ir spectra as diethyl phenylsulfonium fluoroborate.

In another urn, using 0.05 mol of diphenyl disulfide and 0.15 mol of triethyloxonium fluoroborate, the reaction was followed by vpc on a 5 ft, 3% SE-30 on Chromosorb W column at 200°. Essentially identical chromatograms were obtained after reaction times of 6, 12, and 17 hr. Significant peaks were observed at retention times of 0.7, 1.5, 2.3, 2.9, 3.5, 22 (shoulder), and 26.8 min. The reaction product was refluxed for 19 hr with 50 ml of 10 *N* sodium hydroxide solution. The same peaks as before hydrolysis were observed on vpc, but the relative areas of the peaks were somewhat different. The first five products eluted were isolated by preparative vpc on a 5 ft, 20% SE-30 on Chromosorb W column, at temperatures ranging from 150–250°, and were identified (in order of elution) as ethyl phenyl sulfide, phenyl disulfide, thianthrene (3), ethyl *o*-thiophenoxyphenyl sulfide (4), and ethyl *p*-thiophenoxyphenyl sulfide (5) by comparison of their ir and nmr spectra and vpc retention times with those of authentic samples. The products with the highest retention times could not be obtained from the same column as the other products but were collected from vpc on an 18 in., 30% SE-30 on Chromosorb W column at 250°. The main peak could not be collected free of the component immediately preceding it which appeared as a shoulder even in an analytical column. The ratio of the two components was approximately 5:1. The nmr spectrum of the mixture showed a triplet (3 H, J = 7.5) at 1.30 ppm, a quartet (2 H, J = 7.5) at 2.84 ppm, and a multiplet (13 H) around 7.25 ppm. Its ir spectrum had peaks at 1570 (m), 1470 (s), 1440 (s), 1387 (m), 1310 (m), 1255 (m), 1145 (m), 1095 (m–s), 1010 (m), 960 (w), 815 (vs), 735 (s), and 685 cm^{-1} (m). Its mass spectrum had major peaks at m/e 354 (M$^+$) and m/e 325.

Reaction of Diphenyl Disulfide with Diethoxycarbonium Fluoroborate.—Diphenyl disulfide (4.35 g, 0.02 mol) and diethoxycarbonium fluoroborate[19] (11.4 g, 0.06 mol) were dissolved in 20 ml of chloroform and the mixture was stirred at room temperature for 5.5 hr. Water was added and the mixture stirred for 0.5 hr, the layers were separated, and the chloroform layer was dried and evaporated to give 3.54 g of recovered diphenyl disulfide. In another run, using the same quantities of materials, the mixture was refluxed for 4 hr and then worked up in the manner described for the reaction of diphenyl disulfide with triethyloxonium fluoroborate. A gummy residue (3.79 g) was obtained, whose ir spectrum was identical with that of the crude

product from the reaction with triethyloxonium fluoroborate. Part of the product (1.65 g) was refluxed with 5 ml of 10 *N* sodium hydroxide solution for 10 hr. The ir spectrum and vpc analysis of the product showed it to be essentially identical with that obtained from the reaction of diphenyl disulfide with triethyloxonium fluoroborate.

Ethyl *p*-Thiophenoxyphenyl Sulfide (5).—Phenyl *p*-aminophenyl sulfide[20] (6.6 g, 0.0328 mol) was dissolved in 95 ml of an 11% solution of sulfuric acid in water. The solution was kept at 0–5° while a solution of sodium nitrite (2.55 g, 0.037 mol) in 10 ml of water was added. The greenish-brown diazonium salt solution was then added to an ice-cold solution prepared by addition of ethanethiol (2.16 g, 0.0348 mol) to a solution of sodium hydroxide (4.2 g, 0.104 mol) in 25 ml of water. The reaction mixture was stirred for 4 hr at room temperature and extracted with three 50-ml portions of ether. The combined ether extract was washed with sodium carbonate solution and then with water and dried over magnesium sulfate. Evaporation of the ether gave an oil which was distilled under vacuum to give ethyl *p*-thiophenoxyphenyl sulfide (3.0 g, 37.0%), bp 144–145° (2.7 mm). Its ir spectrum showed absorptions at 1580 (m), 1480 (s), 1140 (m), 1390 (m), 1260 (m), 1100 (m), 1080 (m), 1020 (m), 1010 (m), 810 (m), 740 (s), and 690 cm^{-1} (s). Its nmr spectrum showed a triplet (J = 7.0) at 1.30 ppm (3 H), a quartet (J = 7.0) at 2.90 ppm (2 H), and a broad absorption at 7.3 ppm (9 H). Its molecular weight (mass spectrum) was 246.

Anal. Calcd for C$_{14}$H$_{14}$S$_2$: C, 68.3; H, 5.73; S, 26.0. Found: C, 68.0; H, 5.51; S, 26.3.

Diethyl *p*-Thiophenoxyphenylsulfonium Fluoroborate (2).—Ethyl *p*-thiophenoxyphenyl sulfide (1.25 g, 5.08 × 10^{-3} mol) was added to triethyloxonium fluoroborate (1.45 g, 7.63 × 10^{-3} mol) in 5 ml of chloroform. The mixture was refluxed for 16 hr and cooled, and 5 ml of water added to the reaction mixture. The aqueous layer was separated and washed with three 3-ml portions of chloroform. The combined chloroform layer was dried over magnesium sulfate and the solvent evaporated. The residue was twice recrystallized from ethanol, giving 1.0 g (54.5%) of diethyl *p*-thiophenoxyphenylsulfonium fluoroborate as pale yellow rods, mp 104–106°. Its ir spectrum (Nujol mull) had peaks at 1570 (s), 1480 (s), 1440 (s), 1400 (m), 1290 (m), 1210 (w), 1050 (s), 820 (m), 750 (s), and 690 cm^{-1} (m). Its nmr spectrum showed a triplet (6 H, J = 7.0) at 1.30 ppm, a quartet (4 H, J = 7.0) at 3.70 ppm, and multiplets (*ca.* 7 H and 2 H, respectively) at 7.25–7.7 and 7.7–8.1 ppm.

Anal. Calcd for C$_{16}$H$_{19}$S$_2$BF$_4$: C, 53.0; H, 5.29; S, 17.7. Found: C, 53.3; H, 5.48; S, 17.5.

Ethyl *p*-Phenylsulfonylphenyl Sulfone.—Hydrogen peroxide (30% solution, 1.8 g) was added drop by drop to a solution of ethyl *p*-thiophenoxyphenyl sulfide (1.23 g, 0.005 mol) in 2 ml of glacial acetic acid. The mixture was heated under reflux for 3 hr and was then poured into 10 ml of water. The mixture was extracted with three 5-ml portions of chloroform and the chloroform extract dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from ethanol gave ethyl *p*-phenylsulfonylphenyl sulfone as white plates, mp 114–116°. Its ir spectrum (Nujol mull) had strong peaks at 1160 and 1320 cm^{-1}.

Anal. Calcd for C$_{14}$H$_{14}$O$_4$S$_2$: C, 54.2; H, 4.55; S, 20.7. Found: C, 54.5; H, 4.64; C, 20.8.

Ethyl *o*-thiophenoxyphenyl sulfide (4) was prepared by a procedure similar to that used for the preparation of ethyl *p*-thiophenoxyphenyl sulfide, starting with 7.0 g (0.0348 mol) of phenyl *o*-aminophenyl sulfide.[20] Distillation of the product gave ethyl *o*-thiophenoxyphenyl sulfide as a yellow oil, bp 141–142° (3 mm), in 43% yield. Its ir spectrum had peaks at 1570 (m), 1480 (s), 1440 (s), 1370 (w), 1250 (m), 1100 (w), 1040 (m), 1420 (m), 750 (s), and 690 cm^{-1} (s). Its nmr spectrum showed a triplet (3 H, J = 7.0) at 1.30 ppm, a quartet (2 H, J = 7.0) at 2.90 ppm, and a broad absorption (9 H) around 7.3 ppm. Its molecular weight (mass spectrum) was 246.

Anal. Calcd for C$_{14}$H$_{14}$S$_2$: C, 68.3; H, 5.73; S, 26.0. Found: C, 67.8; H, 5.80; S, 26.1.

Diethyl *o*-thiophenoxyphenylsulfonium fluoroborate was prepared in the same manner as diethyl *p*-thiophenoxyphenylsulfonium fluoroborate, starting with 1.25 g (5.08 × 10^{-3} mol) of ethyl *o*-thiophenoxyphenyl sulfide. The product (obtained in 66% yield) was recrystallized from ethanol and melted at 99–101°. Its ir spectrum (Nujol mull) had peaks at 1580 (m), 1290

(18) We wish to express our thanks to Mr. Thomas Mead, American Cyanamid Co., Stamford, Conn., and Dr. Arthur Kluge, Cornell University, for the mass spectroscopic analyses.

(19) R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

(20) E. Bourgeois and P. Huber, *Recl. Trav. Chim. Pay-Bas*, **31**, 30 (1912).

(m), 1260 (m), 1050 (s), 800 (w), 770 (s), 730 (w), 710 (w), and 700 cm^{-1} (m). Its nmr spectrum showed a triplet (3 H, $J = 7.0$) at 1.30 ppm, a quartet (4 H, $J = 7.0$) at 3.75 ppm, and multiplets at 7.25–7.65 (8 H) and 7.7–8.1 (1 H) ppm.

Preparation of Diphenyl Disulfide-d_{10}.—Phenyl-d_5-magnesium bromide was prepared in the usual manner from 10.0 g (0.063 mol) of bromobenzene-d_5[21] and 1.66 g (0.0693 g-atom) of magnesium in 40 ml of ether. Sulfur powder (2.0 g, 0.0625 mol) was added slowly to the mixture, which was stirred at room temperature according to the procedure of Leuckart.[22] After completion of the addition, the mixture was stirred for an additional 6 hr. The reaction was then quenched by the addition of water and then of dilute hydrochloric acid, and the ether layer was separated, dried over magnesium sulfate, and evaporated under vacuum to give a yellow fluid residue. The residue was stirred while a solution of ferric chloride (3.55 g, 0.0219 mol) in 8 ml of water was slowly added. The mixture was stirred for 1 hr and filtered, and the collected solids were washed with water and with dilute hydrochloric acid. Recrystallization of the product from ethanol gave 2.67 g (40.5%) of diphenyl disulfide-d_{10} as small needles, mp 60–61°. It showed essentially no absorption in the proton nmr region. Its ir spectrum showed peaks at 1550 (m), 1340 (s), 1320 (m), 1030 (m), 870 (w), and 820 cm^{-1} (m). Its mass spectrum showed peaks at m/e 228 and 227 in the ratio 95.2:4.8.

Reaction of Diphenyl Disulfide-d_{10} with Triethyloxonium Fluoroborate.—A mixture of diphenyl disulfide-d_{10} (0.5 g, 0.0022 mol) and triethyloxonium fluoroborate (0.00876 mol) in chloroform was refluxed and worked up as described for the undeuterated disulfide. The vpc retention times of the products were identical with those of the undeuterated products. Ethyl p-thiophenoxyphenyl sulfide-d_9 was isolated by vpc. Its mass spectrum showed the following parent peaks.

m/e	Mol %
255 (C$_{14}$H$_5$D$_9$S$_2$)	81
254 (C$_{14}$H$_6$D$_8$S$_2$)	16
253 (C$_{14}$H$_7$D$_7$S$_2$)	3

Reaction of Diphenyl Disulfide and Diphenyl Disulfide-d_{10} with Triethyloxonium Fluoroborate.—A mixture of diphenyl disulfide (0.25 g, 0.00115 mol) and diphenyl disulfide-d_{10} (0.25 g, 0.00110 mol) was allowed to react with 1.76 g of triethyloxonium fluoroborate and worked up as usual. The ethyl p-thiophenoxyphenyl sulfide fraction was isolated by vpc. Parent peaks of the mass spectrum are shown in Table I. The reaction was repeated using

TABLE I

m/e	Mol %	m/e	Mol %
255 (C$_{14}$H$_5$D$_9$S$_2$)	13.6	250 (C$_{14}$H$_{10}$D$_4$S$_2$)	21.6
254 (C$_{14}$H$_6$D$_8$S$_2$)	6.1	249 (C$_{14}$H$_{11}$D$_3$S$_2$)	4.4
253 (C$_{14}$H$_7$D$_7$S$_2$)	2.7	248 (C$_{14}$H$_{12}$D$_2$S$_2$)	1.7
252 (C$_{14}$H$_8$D$_6$S$_2$)	3.1	247 (C$_{14}$H$_{13}$DS$_2$)	4.7
251 (C$_{14}$H$_9$D$_5$S$_2$)	22.0	246 (C$_{14}$H$_{14}$S$_2$)	20.1

0.5 g of diphenyl disulfide (0.00231 mol) and 0.54 g (0.00237 mol) of diphenyl disulfide-d_{10}. Recovered diphenyl disulfides, **3**, and **4** were isolated by vpc. The parent peaks of their mass spectra are shown in Table II.

Reaction of Diphenyl Disulfide with Triethyloxonium Fluoroborate in the Presence of Anisole.—A mixture of diphenyl disulfide (2.18 g, 0.01 mol), anisole (2.16 g, 0.02 mol), and triethyloxonium fluoroborate (8.02 g, 0.05 mol) in 10 ml of chloroform was refluxed for 2.5 hr. It was then washed with water, the chloroform layer dried, and the solvent evaporated. The residue was refluxed with 10 ml of 10 N sodium hydroxide solution for 10 hr and (after cooling in ice) extracted with chloroform. The chloroform layer was washed with water, dried, and evaporated to give 4.4 g of yellow oil. The components of the product mixture were isolated by vpc on a 5 ft, 20% SE-30 on Chromosorb W column and identified by their vpc retention times and ir spectra as recovered anisole, ethyl phenyl sulfide, and p-thiophenoxyanisole.[12] A sample of p-thiophenoxyanisole was prepared for comparison by the method of Truce.[12b] Comparison

with synthetic mixtures showed that ethyl phenyl sulfide and p-thiophenoxyanisole were present in a 1:1 molar ratio.

Reaction of Di-β-naphthyl Disulfide with Trimethyloxonium Fluoroborate.—Di-β-naphthyl disulfide (5.0 g, 0.0158 mol) was added slowly to a suspension of trimethyloxonium fluoroborate[23a] (11.6 g, 0.0785 mol) in 50 ml of a 3:1 mixture of methylene chloride and nitromethane. The mixture was then heated under reflux for 24 hr, first becoming dark green and then changing to dark blue. The mixture was washed with water, the organic layer dried over magnesium sulfate, and the solvent evaporated. The residue was triturated with chloroform, and the insoluble solids (2.85 g) were extracted with acetone. The acetone-insoluble solids (0.49 g) could not be dissolved in any solvent tested and were not further investigated. Partial evaporation of the acetone resulted in precipitation of a solid, which was recrystallized from acetone–chloroform to give 1.76 g (0.0078 mol, 49%) of dimethyl-β-naphthylsulfonium fluoroborate, mp 126–128°, as colorless prisms. It was identified by comparison with a synthetic sample (see below). Further evaporation of the acetone mother liquors gave a second solid which was recrystallized from chloroform–acetone and then sublimed under vacuum to give 0.76 g (38%) of **8a** as colorless needles, mp 184–186°. Its nmr spectrum showed a multiplet from 7.50–7.75 ppm.

Anal. Calcd for C$_{20}$H$_{12}$S$_2$: C, 76.0; H, 3.80; S, 20.2. Found: C, 75.8; H, 3.98; S, 20.1.

Preparation of Dimethyl β-Naphthylsulfonium Fluoroborate.— Methyl β-naphthyl sulfide[23b] (2.0 g, 0.015 mol) was added slowly to a refluxing suspension of trimethyloxonium fluoroborate in 3:1 methylene chloride–nitromethane. After 3 hr, the mixture was washed with water, dried with magnesium sulfate, and evaporated. The residue was recrystallized twice from acetone–ether to give 1.5 g (0.0055 mol, 37%) of dimethyl β-naphthylsulfonium fluoroborate, mp 126–128°. Its nmr spectrum (in deuterioacetone) showed a singlet (6 H) at 2.85 ppm and a multiplet (7 H) at 7.0–8.2 ppm.

TABLE II
Diphenyl Disulfide

m/e		Mol %	m/e		Mol %
228	(C$_{12}$D$_{10}$S$_2$)	16.1	222	(C$_{12}$H$_6$D$_4$S$_2$)	3.8
227	(C$_{12}$HD$_9$S$_2$)	3.4	221	(C$_{12}$H$_7$D$_3$S$_2$)	2.0
226	(C$_{12}$H$_2$D$_8$S$_2$)	2.1	220	(C$_{12}$H$_8$D$_2$S$_2$)	3.8
225	(C$_{12}$H$_3$D$_7$S$_2$)	3.8	219	(C$_{12}$H$_9$DS$_2$)	6.3
224	(C$_{12}$H$_4$D$_6$S$_2$)	7.2	218	(C$_{12}$H$_{10}$S$_2$)	18.6
223	(C$_{12}$H$_5$D$_5$S$_2$)	32.6			

Thianthrene (3)

m/e		Mol %	m/e		Mol %
224	(C$_{12}$D$_8$S$_2$)	18.7	219	(C$_{12}$H$_5$D$_3$S$_2$)	8.2
223	(C$_{12}$HD$_7$S$_2$)	6.3	218	(C$_{12}$H$_6$D$_2$S$_2$)	3.7
222	(C$_{12}$H$_2$D$_6$S$_2$)	3.2	217	(C$_{12}$H$_7$DS$_2$)	5.6
221	(C$_{12}$H$_3$D$_5$S$_2$)	4.6	216	(C$_{12}$H$_8$S$_2$)	16.4
220	(C$_{12}$H$_4$D$_4$S$_2$)	33.3			

Ethyl o-Thiophenoxyphenyl Sulfide (4)

m/e	Mol %	m/e	Mol %
255	16.7	250	18.7
254	7.4	249	5.4
253	1.7	248	4.0
252	2.1	247	2.8
251	23.3	246	17.7

(21) Obtained from Diaprep, Inc., Atlanta, Ga.
(22) R. Leuckart, *J. Prakt. Chem.*, **41**, 179 (1890).

(23) (a) H. Meerwein, *Org. Syn.*, **46**, 120 (1966); (b) J. Jacques, *Bull. Soc. Chim. Fr.*, 231 (1955).

A Novel Rearrangement of Methyl 2-Mercaptobenzoate.
Oxygen → Sulfur Migration of the Methyl Group

JOHN C. GRIVAS* AND KRISHNA C. NAVADA

The Sherwin-Williams Company, Pigments Laboratory, Chicago, Illinois 60628

Methyl 2-mercaptobenzoate (1) formed solid adduct 2a with benzylamine and 2b with dodecylamine. Heating 2a or 1 in excess of benzylamine at 130° for 5 hr afforded N-benzyl-2-mercaptobenzamide (6a) in good yield. On the other hand, heating 2a or 1 in excess of benzylamine at 170–200° for 1–2 hr gave N-benzyl-2-methylthiobenzamide (3a) in 52% yield. Under similar conditions 2b gave N-dodecyl-2-methylthiobenzamide (3b). Evidence was presented to explain the reaction of 1 with primary aliphatic amines in terms of a two-step process involving migration of the methyl group from the oxygen to the sulfur atom, followed by dehydration of the intermediate amine salt of 2-methylthiobenzoic acid (9) formed. Aniline failed completely to react with 1. Heating of 1 in tributylamine or the sodium salt of 1 in methanol at 200–210° for 16 hr yielded 2-methylthiobenzoic acid (5). It is proposed that the rearrangment takes place *via* an intramolecular SNi type mechanism.

In connection with broader studies aimed at the synthesis of biologically active amides of 2,2′-dithiodibenzoic acid (7), the reaction of methyl 2-mercaptobenzoate (1) with primary amines at elevated temperatures was investigated. The expected amides 6 are conventionally prepared by reduction[1] of their corresponding disulfides which, in turn, can be obtained from the diacid 8 (8 → 7 → 6). Although primary and secondary amines normally react by displacement of an alkoxide group, one sterically hindered methyl ester has been reported to react[2] by an SN2 displacement at the methyl group. On the other hand, certain aliphatic tertiary amines are known[3] to cause solely a reversible alkyl–oxygen cleavage. A similar behavior

$$RCOOR' + NR_3'' \rightleftharpoons RCOO^- R'\overset{+}{N}R_3''$$
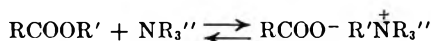
of amines toward methyl salicylate has been reported[4] recently. The irreversible alkyl–oxygen cleavage by sulfide and mercaptide ions has also been demonstrated.[5,6] We wish now to report that heating of

$$RCOOR' + R''S^- \longrightarrow RCOO^- + R'SR''$$
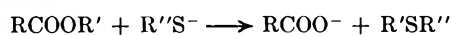
methyl 2-mercaptobenzoate in basic media at 170–210° results in the migration of the methyl group from the oxygen to the sulfur atom.

Results and Discussion

Addition of benzylamine to an equimolar amount of 1 in the absence of solvent or in ether gave crystalline adduct 2a in 90% yield. As expected, heating of 1 in excess of benzylamine at 130° for 5 hr gave amide 6a, which could be best isolated after its oxidation to the known[1] disulfide 7a by methanolic iodine. The overall yield was 70% (1 → 2a → 6a → 7a) (Scheme I). On the other hand, when adduct 2a was heated in the absence of solvent at 175° for 1 hr, it was converted completely (tlc) into products other than the expected

SCHEME I

a, R = benzyl
b, R = dodecyl

6a. Chromatography of the reaction mixture yielded N-benzyl-2-methylthiobenzamide (3a) in 52% yield. Unequivocal proof was provided with the independent synthesis of 3a by methylation of 6a with dimethyl sulfate–sodium hydroxide. Compound 6a, in turn, was prepared[1] from 8 (8 → 7a → 6a).

The reaction 1 → 2 → 3 also occurred in ethylene glycol, glycerine, or excess of benzylamine at 175–195° (1–2 hr) and appeared to be generally for primary aliphatic amines. For example, heating equimolar amounts of 1 and dodecylamine in a nitrogen atmosphere gave N-dodecyl-2-methylthiobenzamide (3b) in 25% yield. Under the same conditions, aniline

(1) (a) F. Gialdi, R. Ponci, and A. Baruffini, *Farmaco, Ed. Sci.*, **15**, 856 (1960); (b) R. G. Bartlett and E. W. McClelland, *J. Chem. Soc.*, 818 (1934).

(2) H. E. Zaugg, P. F. Helgren, and A. D. Schaefer, *J. Org. Chem.*, **28**, 2617 (1963).

(3) (a) M. S. Newman and H. A. Lloyd, *J. Amer. Chem. Soc.*, **74**, 2672 (1952); (b) E. L. Eliel and R. P. Anderson, *ibid.*, **74**, 547 (1952); (c) A. C. Pierce and M. M. Joullié, *J. Org. Chem.*, **27**, 3968 (1962).

(4) (a) T. Kametani, K. Kigasawa, and T. Hayasaka, *Yakugaku Zasshi*, **87**, 265 (1967); *ibid.*, **88**, 445 (1968); (b) T. Kametani, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, T. Iwata, and H. Ishimary, *Chem. Pharm. Bull.*, **15**, 613 (1967).

(5) (a) J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 99 (1953); (b) W. R. Vaughan and J. B. Baumann, *J. Org. Chem.*, **27**, 739 (1962).

(6) J. C. Sheehan and G. D. Daves, Jr., *ibid.*, **29**, 2006 (1964).

failed to react with **1**, since the recovery of both starting materials was better than 90%.

The moderate yield of **3** is not surprising because of two side reactions occurring concurrently, *i.e.*, the amidation of the ester group to **6**, and the relatively less known[5a,7] alkylation of the mercapto group by aliphatic amines. Although small amounts of **6** and
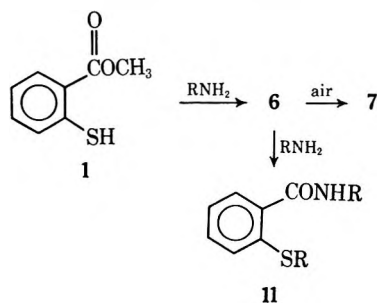
7 always accompany the rearrangement products, by-product **11** could not be isolated. The alkylation of pure **6** to **11** (R = benzyl) by benzylamine, however, has been reported[8] and corroborated in our laboratory.

These results are explained in terms of a two-step process involving migration of the methyl group from the oxygen to the sulfur atom (**2 → 9**) followed by de-

hydration. The feasibility of the dehydration step was proven by reacting 2-methylthiobenzoic acid (**5**, prepared from **4**) with excess of benzylamine at 175–180° for 4 hr. Amide **3a**, identical in all respects with the product obtained by heating **2a**, was isolated in 18% yield.

In order to avoid the amidation step and shed more light, a solution of **1** in tributylamine was heated at 210° for 5 hr. The rearrangement product, 2-methyl-thiobenzoic acid (**5**), was isolated in 54% yield, which was lower than expected due to possible concurrent alkylation of **1** by tributylamine. For example, tributylamine was allowed to react with **6a** to yield *N*-benzyl-2-butylthiobenzamide (**11**, mp 84–84.5°, –SR = –SCH₂CH₂CH₂CH₃, NHR=NHCH₂C₆H₅) in fair yield. The fact that the product of this reaction was not the other known isomer,[1a] *N*-butyl-2-benzylthiobenzamide (mp 91–92°), was established unequivocally by nmr studies. Thus, compounds **3a**, **6a**, *N*-benzyl-2-butylthiobenzamide, and *N*-benzyl-2-benzylthiobenzamide exhibited a doublet at 4.49–4.57 ppm, which is characteristic of the two methylene protons of the benzylbenzamido (PhCONHCH₂Ph) moiety. As expected, this doublet collapsed to a singlet upon deuterium exchange at the amido hydrogen. On the other hand, the SCH₂ signal for *N*-benzyl-2-butylthiobenzamide (triplet) and the SCH₂Ph signal for *N*-benzyl-2-benzylthiobenzamide (singlet) appeared at 2.78 and 4.00 ppm and were unchanged, as expected, upon deuteration.

(7) L. N. Nikolenko and V. A. Koptyug, *Zh. Obshch. Khim.*, **25**, 1757 (1955); *Chem. Abstr.*, **50**, 5557 (1956).

(8) W. Baker, A. S. El-Nawawy, and W. D. Ollis, *J. Chem. Soc.*, 3163 (1952).

Indeed, in view of the side reactions the isolation of the rearrangement products **3** or **5** in 25–55% yield was significant. Despite the possibility that amines could participate in the rearrangement of **1** by either rupturing or weakening the methyl–oxygen bond, their major role appeared to be the provision of mercaptide ions. This was supported by (a) the complete failure of neat **1** to rearrange at 200° for 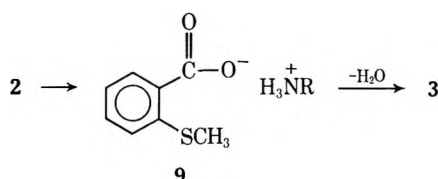16 hr, (b) the same failure of **1** in the weakly basic aniline, and (c) the rearrangement of the sodium salt of **1** in methanol (**1 → 5**) under the same conditions with the highest yield (72%). This rearrangement[9] should proceed by the way of an intramolecular SNi type mechanism, in which the migration of the methyl group is facilitated by the lower energy requirement of a six-membered transition state. However, a competitive intermolecular mechanism which is initiated by the nucleo-

philic attack of a mercaptide ion on the ester methyl group of another molecule is also possible. The fact that the intermolecular mechanism operated only to a small extent, if at all, was shown by competitive experiments, in which the sodium salt of **1** was heated in the presence of an equimolar amount of sodium thiophenoxide. Acid **5** was isolated in about 60% yield along with some (8–9%) 2,2′-dithiodibenzoic acid (**8**). The small drop in yield of **5** from 72% to 60%, partly compensated by the appearance of diacid **8**, could be attributed to the intermolecular attack of the thiophenoxide ion on **1**. The product of this attack, 2-mercaptobenzoic acid, could then easily be oxidized by air to give **8**. Since the mercaptide ion in **1** is sterically more hindered by the carbomethoxy group, as compared to the thiophenoxide ion, the reaction between two molecules of **1** becomes even less significant. We can thus conclude that the SNi mechanism is predominant at least.
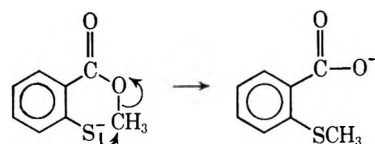
Experimental Section[10]

Bis(2-benzylcarbamylphenyl) Disulfide (7a).—A solution of ester[11] **1** (5 g, 0.03 mol) in excess of benzylamine (10 ml) was stirred at 130° for 5 hr, diluted with water (250 ml), acidified with hydrochloric acid, and extracted with benzene (100 ml). The benzene extract was evaporated to dryness *in vacuo* to yield crude **6a** (7 g, 90%). A portion of crude **6a** (3.6 g) was dissolved in methanol (50 ml) and oxidized by methanolic iodine to yield very pure **7a**, mp 211–213°, 2.5 g (69%) (lit.[1b] mp 206°). This compound was identical (mixture melting point, ir, and nmr) with an authentic sample (mp 208–209.5°) prepared in a manner similar to that described[1b] in the literature (**8 → 7a**).

(9) This reaction is an *aliphatic rearrangement* which differs from the *Smiles rearrangement* in two important aspects: (1) the migrating group is aliphatic not aromatic, and (2) the nucleophile attacks a contiguous aliphatic carbon atom and not a contiguous aromatic ring. For a comprehensive review of the Smiles rearrangement, see H. J. Shine in "Reaction Mechanisms in Organic Chemistry," C. Eaborn and N. B. Chapman, Ed., Elsevier, New York, N. Y., 1967. p 307.

(10) Melting points were determined with a Thomas-Hoover melting point apparatus and were not corrected. Microanalyses were performed at Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were recorded on a Varian HA-100 spectrometer using tetramethylsilane as internal reference. Infrared spectra were determined with a Perkin-Elmer 221 spectrophotometer.

(11) L. Gatterman, *Chem. Ber.*, **32**, 1150 (1899); Schenley Industries, Inc., British Patent 767,027 (Jan 30, 1957); *Chem. Abstr.*, **51**, 17998 (1957).

Methyl 2-Mercaptobenzoate–Benzylamine Adduct (2a).—A solution of benzylamine (1.1 g, 0.01 mol) in ether (25 ml) was added dropwise to a stirred solution of methyl 2-mercaptobenzoate (1.7 g, 0.01 mol) in ether (25 ml) at 10°. The reaction mixture was stirred at room temperature for 1 hr, and the precipitated pure 2a was filtered off, mp 84–85°, yield 2 g (71%). The melting point did not change after one recrystallization from ether: ir (KBr) 3400 (NH₂), 2670 (NH), 2575 cm⁻¹ (SH); nmr (CDCl₃) δ 3.87 (s, 3, CH₃O), 3.82 (s, 2, CH₂), 2.54 (s, 3, SH + NH₂).

Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.45; H, 6.18; N, 5.09; S, 11.64. Found: C, 65.28; H, 6.3; N, 5.02; S, 11.77.

N-Benzyl-2-methylthiobenzamide (3a). **A. From Methyl 2-Mercaptobenzoate (1 → 2a → 3a).**—Addition of benzylamine (2.15 g, 0.02 mol) to methyl 2-mercaptobenzoate (1, 3.4 g, 0.02 mol) resulted in an exothermic reaction yielding an oil which solidified upon standing. The adduct 2a so obtained was heated in an oil bath at 175° for 1 hr, and the main portion of the reaction mixture (5 g) was chromatographed on alumina (150 g). Elutions with benzene and benzene–chloroform solutions (9:1 to 6:4 v/v) yielded pure 3a, after one recrystallization from hexane: mp 129–130°; yield 2.6 g (52%); ir (CHCl₃) 3450 (NH), 1658 cm⁻¹ (C=O); nmr (CDCl₃) δ 2.38 (s, 3, CH₃S), 4.60 (d, 2, NHCH₂C₆H₅), 6.7 (broad, 1, NH).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44; S, 12.46. Found: C, 70.05; H, 5.88; N, 5.45; S, 12.26.

This sample was identical (mixture melting point, tlc, ir, and nmr) with the samples prepared by the following routes B and C.

B. From 2-Methylthiobenzoic Acid (5 → 3a).—A mixture of 2-methylthiobenzoic acid (3.4 g, 0.02 mol) and benzylamine (8.7 ml, 0.08 mol) was stirred and heated under a nitrogen atmosphere at 175–180° for 4 hr. The reaction mixture was cooled to room temperature and diluted with water (100 ml) to precipitate solid 3a, mp 131.5–132.5°, 0.9 g (17.5%). Recrystallization from acetone–hexane did not change the melting point. Unreacted 5 was also recovered (35%) from the mother liquor.

C. From *N*-Benzyl-2-mercaptobenzamide (6a → 3a).—Amide 6a (2.4 g, 0.01 mol) was dissolved in 10% sodium hydroxide (5 ml) by warming on a steam bath and then cooled. To this solution dimethyl sulfate (1.26 g, 0.01 mol) was added, and the mixture was heated on a steam bath for 15 min, diluted with water (5 ml), made strongly alkaline with 10% sodium hydroxide (2 ml), heated for an additional 30 min, and extracted with benzene (three 100-ml portions). The combined extracts were washed with dilute sodium hydroxide and water and evaporated to dryness to yield 3a, mp 129–130°, yield 2.2 g (84%). One recrystallization from benzene gave pure 3a, mp 130–131°.

N-Dodecyl-2-methylthiobenzamide (3b).—Dodecylamine (5.6 g, 0.03 mol) was added to ester 1 (5.1 g, 0.03 mol) with stirring. An exothermic reaction took place giving adduct 2b as an oil, which solidified upon standing and was not characterized further. It was heated in a nitrogen atmosphere at 170–180° for 2 hr, cooled, dissolved in benzene, and chromatographed on alumina (300 g). Elutions with benzene, benzene–chloroform (9:1 to 1:9), and chloroform gave a total of 3.6 g of the product. The analytical sample was prepared by one crystallization from hexane (50 ml): mp 65–66°; 2 g (20%); ir (Nujol) 3280 (NH), 1630 cm⁻¹ (C=O); nmr (CDCl₃) δ 0.87 (t, 3, CCH₃), 1.27 (m, 20, (CH₂)₁₀), 2.44 (s, 3, CH₃S), 3.44 (m, 2, CH₂NH), 6.4 (broad, 1, NH).

Anal. Calcd for $C_{20}H_{33}NOS$: C, 71.59; H, 9.91; N, 4.17; S, 9.56. Found: C, 71.75; H, 9.76; N, 4.00; S, 9.30.

2-Methylthiobenzoic Acid (5). A. By Rearrangment of 1 in Tributylamine.—Ester 1 (5.1 g, 0.03 mol) in tributylamine (28 g, 0.15 mol) was heated in an oil bath in a nitrogen atmosphere at 175–180° for 6 hr and at 205–210° for an additional 5 hr. Upon cooling the reaction mixture separated into two layers. The top layer was diluted with water, acidified with hydrochloric acid, stirred, and cooled giving crude 5 (1.1 g, mp 164–168°). The bottom layer was treated similarly to yield additional 5 which was recrystallized from ethanol (20 ml), mp 164–168°, 1.4 g. A second crop (0.8 g, mp 164–168°) was also obtained by evaporation of the mother liquor to dryness and crystallization of the residue from acetone–hexane. The three samples were combined (3.3 g, 66%) and purified by recrystallization from acetone–hexane: mp 168.5–170° (lit.¹² mp 169°), 2.1 g (47%); second crop mp 166–168°, 0.6 g (12%); nmr (acetone-d₆) δ 2.42 (s, 3,

SCH₃) 5.5 (broad, 1, (COOH)). The compound was identical (mixture melting point, tlc, ir, and nmr) with an authentic sample obtained by usual methylation of 4 to 5.

B. By Methylation of 4.—To a stirred solution of 4 (30.8 g, 0.2 mol) in aqueous sodium hydroxide (16 g, 0.4 mol in 150 ml of water), dimethyl sulfate was added dropwise in 30 min. The solution was heated on a steam bath for 2 hr, filtered, and acidified with 10% hydrochloric acid. The precipitated solid was filtered off and purified by one crystallization from aqueous ethanol and one from ethanol, mp 169–171° (lit.¹² mp 169°), 15.3 g (45%).

C. By Rearrangment of the Sodium Salt of 1 in Methanol.—A solution of 1 (5 g, 0.03 mol) in methanol (16 ml) containing an equivalent amount of sodium methoxide (1.6 g, 0.03 mol) was heated in a 45-ml stainless steel Parr bomb at 200–210° for 16 hr. The reaction mixture was cooled, evaporated to dryness under vacuum, taken up in water (100 ml), acidified with hydrochloric acid, and stirred for 1 hr. The precipitated crude produce (4 g, mp 164–170°) was purified by crystallization from acetone–hexane (mp 169–170°, 3.2 g, 64%). Mixture melting point and ir and nmr spectra showed that this sample was identical with those obtained by the aforementioned rearrangement of 1 in tributylamine (A), and methylation of 4 (B). A second crop (mp 168–169°, 0.4 g, 8%) was also obtained.

D. By Rearrangement of the Sodium Salt of 1 in Methanol in the Presence of Sodium Thiophenolate.—A solution of 1 (5 g, 0.03 mol), thiophenol (3.3 g, 0.03 mol), and sodium methoxide (3.2 g, 0.06 mol) in methanol (20 ml) was heated in a 45-ml stainless steel Parr bomb at 200–210° for 16 hr, cooled, and filtered.

The solid obtained was dissolved in water and acidified with dilute hydrochloric acid to give a precipitate, which was dissolved in hot acetone (200 ml) and clarified by gravity filtration. Upon standing at room temperature overnight, the acetone solutone solution deposited diacid 8 which was identified by the mixture melting point and ir spectrum, mp 295–298° (lit.¹³ mp 288.5°), yield 0.4 g (8.7%). The filtrate was concentrated, diluted with hexane, and cooled to yield 2-methylthiobenzoic acid (1.8 g, mp 168–169°, 36%).

The methanolic filtrate was evaporated to dryness, and the residue was taken up in water (50 ml) and extracted with chloroform. The aqueous phase was then acidified with dilute hydrochloric acid yielding additional 5 (1.2 g, mp 167–169°, 24%).

N-Benzyl-2-benzylthiobenzamide (11, R = Benzyl).—Amide 6a (1.2 g, 0.005 mol) in benzylamine (4.5 ml, 0.04 mol) was stirred under nitrogen at ca. 190° for 10 hr. The reaction mixture was dissolved in chloroform, extracted with water (50 ml), 5% hydrochloric acid (two 50-ml portions), 5% sodium hydroxide (two 50-ml portions), and water (50 ml), and evaporated to dryness to yield an oil which solidified upon standing. The crude product was purified by crystallization from acetone–hexane: mp 98–100° (lit.¹,⁸ mp 97–98°, 102–103°); yield 1.2 g (72%); ir and nmr spectra are in agreement with the structure.

N-Benzyl-2-butylthiobenzamide.—A solution of 6a (1.2 g, 0.005 mol) in tributylamine (3.7 g, 0.02 mol) was heated in a nitrogen atmosphere at 185–190° for 10 hr. The reaction mixture was diluted with water (10 ml), acidified with dilute hydrochloric acid, and extracted with carbon tetrachloride (10 ml). This layer was filtered from disulfide 7a (0.2 g, mp 206–208°), extracted with aqueous sodium hydroxide (0.4 g in 20 ml of water) and water (two 20-ml portions), dried (MgSO₄), and evaporated to dryness to yield an oil which partially crystallized. This crude product was taken up in hexane (10 ml), filtered off, and purified by column chromatography through silica gel and recrystallization from acetone–hexane: mp 84–84.5°; yield 0.3 g (20%); nmr (CDCl₃) δ 0.9 (t, 3, CH₃), 1.2–1.7 (m, 4, CH₂CH₂), 2.85 (t, 2, SCH₂), 4.67 (d, 2, NHCH₂).

Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68; S, 10.71. Found: C, 72.05; H, 7.02; N, 4.68; S, 10.81.

The aqueous extracts were combined and acidified to give crude starting material 6a, 0.4 g (25%), mp 95–105°. The other isomer, *N*-butyl-2-benzylthiobenzamide, has been reported¹ᵃ to have mp 91–92°.

(12) O. Hinsberg, *Chem. Ber.*, **43**, 653 (1910).

(13) K. W. Rosenmund and H. Harms, *ibid.*, **53**, 2237 (1920).

Anodic Oxidations. III.[1] Controlled Potential Cyanomethoxylation of 2,5-Dimethylfuran

KUNIHISA YOSHIDA* AND TAKAYUKI FUENO

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan

The anodic oxidation of 2,5-dimethylfuran in methanolic solution of sodium cyanide at 1.0–1.3 V gave a 2:1 isomeric mixture of *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofurans. The current efficiency ranged from 61 to 95% in the potential region studied. Small amounts of *cis*- and *trans*-2,5-dimethoxy-2,5-dimethyl-dihydrofurans and traces of 2-methoxymethyl-5-methylfuran and 2,5-bis(methoxymethyl)furan were also formed as by-products. Coulometric data showed that on an average two electrons were lost per 2,5-dimethyl-furan molecule. It was concluded that the overall reaction involves the initial oxidation of 2,5-dimethylfuran and proceeds nonstereospecifically.

There are already several reports available concerning anodic cyanation of aromatic compounds.[2] In most of these published examples, however, the reactions were conducted in methanol, thus leading to the competitive formation of methoxylated products which were often predominant in quantity over the cyanation products. An improved method of cyanation has recently been proposed by Andreades and Zahnow,[3] who electrolyzed various aromatic compounds in the presence of tetra-ethylammonium cyanide in acetonitrile.

In a previous communication of this series,[4] we have briefly described that a methanolic sodium cyanide solution containing 2,5-dimethylfuran provides a cis-trans isomeric mixture of 2-cyano-5-methoxy-2,5-di-methyldihydrofuran in high current efficiency, when electrolyzed under a controlled anode potential.
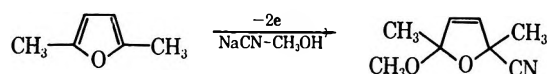
The purpose of the present paper is to examine the nature of the above reaction in more detail under various experimental conditions. It has been found that the reaction involves an initial oxidation of the furan and that the overall reaction is nonstereospecific.

Results

Controlled Potential Electrolysis.—First of all, current–potential measurements were carried out on an 0.8 M sodium cyanide solution in methanol at 25°, both in the presence and absence of 2,5-dimethylfuran. The measurements are not only useful for selecting the potentiostat setting at which the controlled potential electrolysis may efficiently be conducted but also provide a preliminary knowledge of the mechanistic features of the overall reactions. The current–potential curves observed are graphically shown in Figure 1.[5]

As can be seen in Figure 1, a methanolic solution of sodium cyanide alone is not discharged unless the anode potential exceeds 1.4 V, whereas a solution containing 2,5-dimethylfuran allows current to pass through it at a

potential as low as 1.0 V. Clearly, 2,5-dimethylfuran is oxidizable at a relatively low anode potential.[6]

Electrolytic oxidation of 2,5-dimethylfuran was conducted at anode potentials controlled to within 0.01 V at a voltage between 1.0 and 1.3 V. Coulometric data showed an average of two electrons lost per 2,5-di-methylfuran molecule. The oxidation products comprized mainly *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofuran (I_c and I_t).[4] Small amounts of *cis*- and *trans*-2,5-dimethoxy-2,5-dimethyldihydrofuran (II_c and II_t) with traces of 2-methoxymethyl-5-methyl-furan (III) and 2,5-bis(methoxymethyl)furan (IV) were also formed as minor products. Identifications of these products will be the subject of the next subsection.
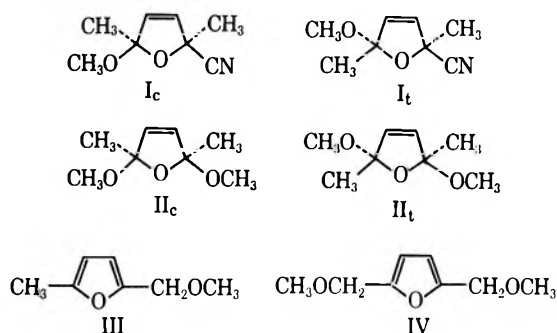
Table I summarizes the results of electrolysis conducted at various anode potentials. The initial concentrations of sodium cyanide and 2,5-dimethylfuran were both fixed at 0.8 M.

TABLE I
ANODIC OXIDATIONS CONDUCTED AT VARIOUS POTENTIALS AT 25° [a]

Anode potential, V	Conversion, %	Current efficiency for I, %	Molar ratios II/I	I_c/I_t
1.0	3	95	0.05	2.1
1.1	5	87	0.08	2.2
1.2	17	70	0.09	1.9
1.3	31	61	0.09	2.0
35[b]	~60	49	0.10	2.0

[a] [NaCN] = [2,5-dimethylfuran] = 0.8 M; reaction time, 6 hr. [b] Nonpotentiostatic oxidation at an overall voltage of 35 V. See the Experimental Section.

(1) Part II: K. Yoshida and T. Fueno, *Chem. Commun.*, 711 (1970).

(2) (a) K. Koyama, T. Susuki, and S. Tsutsumi, *Tetrahedron Lett.*, 627 (1965); (b) V. D. Parker and B. E. Burgert, *ibid.*, 4065 (1965); (c) K. Koyama, T. Susuki, and S. Tsutsumi, *Tetrahedron*, **23**, 2675 (1967); (d) T. Susuki, K. Koyama, A. Omori, and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **41**, 2663 (1968); (e) L. Eberson and S. Nilsson, *Discuss. Faraday Soc.*, **45**, 242 (1968); (f) S. Tsutsumi and K. Koyama, *ibid.*, **45**, 247 (1968); (g) V. D. Parker and B. E. Burgert, *Tetrahedron Lett.*, 2415 (1968).

(3) S. Andreades and E. W. Zahnow, *J. Amer. Chem. Soc.*, **91**, 4181 (1969).

(4) K. Yoshida and T. Fueno, *Bull. Chem. Soc. Jap.*, **42**, 2411 (1969).

(5) All potentials were measured against sce.

(6) It has been known that the half-wave potential of 2,5-dimethylfuran in acetic acid is 1.20 V: L. Eberson and K. Nyberg, *J. Amer. Chem. Soc.*, **88**, 1686 (1966).
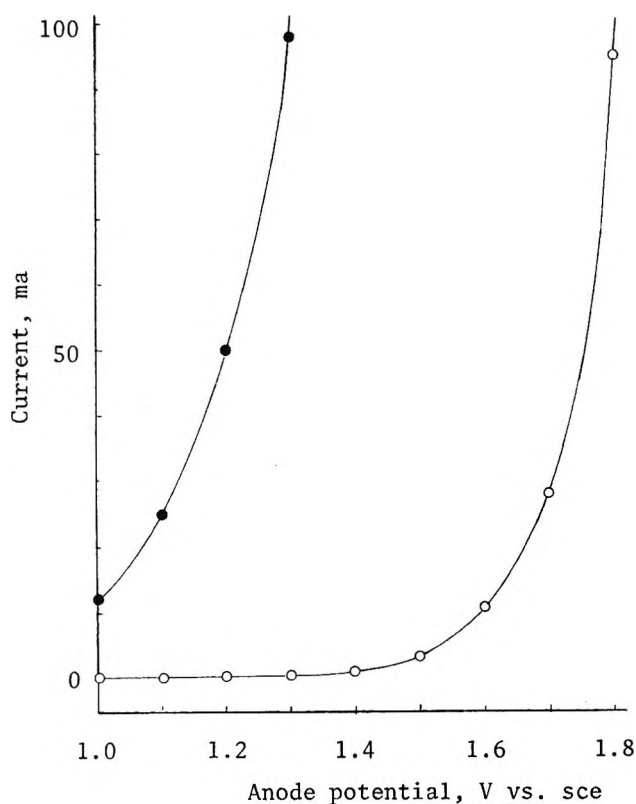
Figure 1.—Plots of current vs. anode potential for electrolyses of solutions containing 0.8 *M* sodium cyanide in methanol at 25°: O, without 2,5-dimethylfuran; ●, with 0.8 *M* 2,5-dimethylfuran.

It may be seen from Table I that, although the conversion of 2,5-dimethylfuran tended to decrease with the lowering in anode potential, the current efficiency for the formation of I steadily increased with the lowering potential until it reached a value as great as 95% (based on a 2e process) at 1.0 V. In contrast, there was no significant variation in distribution of the products I_c, I_t, and II ($II_c + II_t$). The trend remained the same in the nonpotentiostatic experiment (at 35 V). It thus appears that the anode potential plays no essential role in determining the product distribution.

Comparative experiments were also carried out with different initial concentrations of reactants at a given anode potential of 1.3 V. The results are shown in Table II.

TABLE II

ANODIC OXIDATIONS CONDUCTED WITH VARIOUS INITIAL CONCENTRATIONS OF SODIUM CYANIDE[a]

[NaCN]	Conversion, %	Current efficiency for I, %	Molar ratios II/I	I_c/I_t
0.1[b]	4	80	0.05	2.2
0.1	5	70	0.09	1.9
0.2	10	65	0.07	2.0
0.8	31	61	0.09	2.0

[a] [2,5-Dimethylfuran] = 0.8 *M*; anode potential, 1.3 V; reaction time, 6 hr; temperature, 25°. [b] [2,5-Dimethylfuran] = 2.0 *M*.

The data listed in Table II clearly show that the conversion increased with the increasing concentration of the cyanide used but that the current efficiency for the formation of I again ran antiparallel to the conversion. Here also, the product distribution was practically unaltered.

Identification of the Products.—Each product was isolated by fractional distillation or preparative vpc and identified by the infrared, mass, and nmr spectroscopies.

The structural assignments for the two isomers, I_c and I_t, were based on their nmr spectra.[7] The methoxy protons of I_c (τ 6.81) resonated at a magnetic field a little lower than did those of I_t (τ 6.92). It is apparent from molecular models that the methoxy protons in the cis isomer are located closer to the cyano group than those in the trans isomer, indicative of the lower-field shift[8] of the methoxy protons in the former compound. This implies that a cis configuration is assignable to the product I_c. Extensive nmr spectral data[9-11] of geometrical isomer pairs of 2,5-disubstituted furans lend support to the present structural assignments.

It was confirmed that neither of the isomers I_c and I_t undergoes interconversion under the present experimental conditions. Both of them also remained intact on vpc. The isomeric compositions determined from nmr spectroscopy and analytical vpc always agreed with each other, the ratio of I_c to I_t being 2.0 as has been shown in Tables II and III. However, a trace of sulfuric acid instantaneously converted either isomer into an equilibrium mixture of the two isomers ($I_c/I_t = 2.0$). When heated in carbon tetrachloride, the individual isomers suffered slow isomerization, eventually attaining equilibrium.

The minor products II_c, II_t, III, and IV were identified by comparisons with the authentic samples prepared by other routes. The ratio of II_c to II_t was ca. 1, a value which was essentially equal to the ratio already reported for the anodic methoxylation of 2,5-dimethylfuran.[12]

Discussion

As has already been described, a methanolic solution of sodium cyanide is not discharged at an anode potential between 1.0 and 1.3 V.[13] Because in the same potential range the solution containing 2,5-dimethylfuran is oxidizable, the primary electrode process in this latter case must be the oxidation of 2,5-dimethylfuran to a cationic species. By analogy with anodic aromatic substitution reactions,[14] a mechanism involving a cation radical intermediate as in Scheme I is conceivable. Probably, the anodically generated cation radical 1 is attacked by the cyanide ion (or methanol) to produce the radical 2 (or 4), followed by further anodic oxidation and successive nucleophilic attack by

(7) The proton peaks of both these isomeric products were of the ABM₃-P₃X₃ type (see Table III).

(8) This arises mainly from the local magnetic anisotropy effect of the cyano group. In addition, since the methoxy protons are more or less positively charged, a weak interaction may be expected between the methoxy protons and the electron-rich cyano group at a closer distance. The interaction is expected to be a kind of weak hydrogen bonding. Such an interaction is considered to cause a lower-field shift of the resonance signal of the proton involved in the interaction.[6]

(9) A. Aito, T. Matsuo, and C. Aso, *Bull. Chem. Soc. Jap.*, **40**, 130 (1967).

(10) D. Gagnaire and P. Vottero, *Bull. Soc. Chim. Fr.*, **12**, 2779 (1963).

(11) T. Hiraoka, T. Iwashige, and I. Iwai, *Chem. Pharm. Bull.*, **13**, 285 (1965).

(12) S. D. Ross, M. Finkelstein, and J. J. Uebel, *J. Org. Chem.*, **34**, 1018 (1969).

(13) Andreades and Zahnow reported that the cyanide ion dissolved in acetonitrile is oxidized at ca. 0.6 V.³ In methanol, however, the cyanide ion (or, more strictly, the ion pair of sodium cyanide) is apparently stabilized by strong solvation, thus surviving under the anode potential of even 1.3 V.

(14) (a) R. N. Adams, *Accounts Chem. Res.*, **2**, 175 (1969); (b) G. Manning, V. D. Parker, and R. N. Adams, *J. Amer. Chem. Soc.*, **91**, 4584 (1969).

SCHEME I
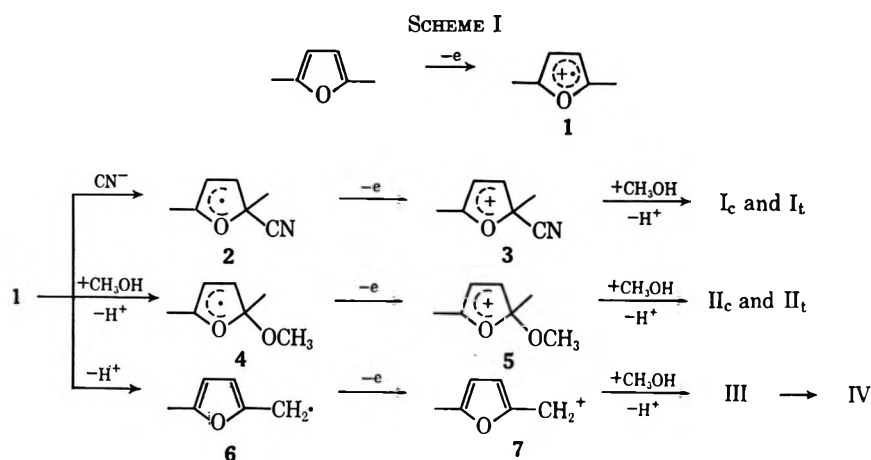
solvent, leading to the formations of I and II. Part of 1 should also undergo deprotonation to afford the 5-methyl-2-furylmethyl radical 6, which should finally give rise to III and IV.

It is to be expected that the carbon atoms of a higher positive charge in the cationic species 1 and 3 would
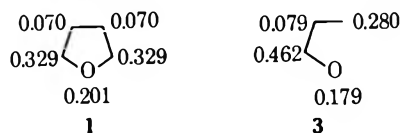
react more readily with a nucleophile. Net charge distributions calculated for these cationic species by the ω technique[15] as used in π-electron approximation indicated that in both these species the greatest positive charge is imparted on the 2 (and 5) position, in accord with the products obtained.

Stereochemical phase of the reactions leading to the formation of geometrical isomers deserves comment. We at first anticipated operation of some factor that might control the stereochemistry, assuming that the attack of nucleophiles on the cations 3 and 5 take place primarily on the electrode surface. In reality, however, the products were in all cases equilibrium mixtures of the cis and trans isomers. It must be concluded, therefore, that the intermediates 3 and 5 suffer the attack by solvent primarily in a homogeneous environment. Analogous results have recently been obtained in both the chemical and electrochemical methoxylation of 2,5-dimethylfuran.[12]

In conclusion, the cyanomethoxylation of 2,5-dimethylfuran proceeds *via* a polar mechanism involving initial oxidation of the furan ring to give an intermediate cation radical. The overall reaction proceeds nonstereospecifically.

Experimental Section

Materials.—Methanol used in the current–potential measurements was of optical pure grade. For the preparative runs, methanol was purified by fractional distillation from magnesium activated with iodine. Reagent grade sodium cyanide was used with no purification other than drying. 2,5-Dimethylfuran was prepared according to a known procedure[16] and the purity checked by vpc.

(15) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 115, 135. The parameters used were h_O = 2, k_{C-O} = 0.8, h_C = -0.5 (inductive model for the methyl group), δ = 0.1, ω = 1.4. Other reasonable choices of the parameter set did not alter the results materially.

(16) R. Gaertner and R. G. Tonkyn, *J. Amer. Chem. Soc.*, **73**, 5872 (1951).

Authentic samples of *cis*- and *trans*-2,5-dimethoxy-2,5-dimethyldihydrofurans were prepared by anodic methoxylation of 2,5-dimethylfuran.[12,17] 2,5-Bis(methoxymethyl)furan was prepared by the bromination of 2,5-dimethylfuran with N-bromosuccinimide, followed by treatment with sodium methoxide.[12] 2-Methoxymethyl-5-methylfuran was obtained according to the same method as above except that 1 equiv of N-bromosuccinimide was used.

Analytical Method.—Reaction products and the furan recovered were determined by vpc (column, PEG 6000; column temperature, 120°; internal standard, tetralin). Infrared spectra of the products were recorded on a JASCO Model IR-E infrared spectrophotometer. Nmr spectra were obtained with a JEOCO Model JNM-4H-100 spectrometer. Mass spectra were measured with a Hitachi Model RMS-4 instrument.

Current–Potential Measurements.—Current–potential curves (uncorrected for the internal resistance drop in the cell) were taken at 25° by using a two-compartment cell with a platinum wire electrode in the cathode compartment and the saturated calomel reference electrode, a platinum plate electrode having an area of 8 cm², and a magnetic stirrer bar in the anode compartment. Prior to use the electrodes were cleaned with a dichromate cleaning solution, rinsed with water, and dried. Nitrogen was bubbled through the cell before measurements. Anode potential was controlled by means of a YANACO Model VE-3 potentiostat.

Current was measured as a function of anode reference potential in the range of 1.0–1.8 V, using 0.8 M furan concentrations. The time required for the current and potential to reach steady-state values varied from solution to solution and depended on current. Most measurements took from 10 to 20 min per point, and during that time interval the current fell only slightly.

To examine the influence of cell resistance, measurements were also carried out by using an undivided cell. However, no significant difference was found between the two results.

Potentiostatic Oxidations.—Controlled potential electrolyses were performed by using the same cell that was used for current–potential measurements. The total electrolysis current was determined in two ways; one was by the gain in weight of the copper cathode while the other by a graphic current–time integration method. Replicate determinations of the total current by the two methods agreed to within 5%.

The electrolyses were carried out under an atmosphere of nitrogen pressure at 25°. In a typical experiment a methanolic solution (50 ml) of 2,5-dimethylfuran (3.85 g, 0.04 mol) and sodium cyanide (1.96 g, 0.04 mol) was electrolyzed for 6 hr, using an anode potential of 1.3 V. The catholyte was methanol, 0.8 M in sodium cyanide. The total electricity used amounted to 2430 C.

The electrolyzed mixture was treated with 150 ml of water and the organic material extracted with two 50-ml portions of ether. The combined ether extract was washed thoroughly with water, dried over anhydrous magnesium sulfate, and filtered. Vpc analysis showed that 1.27 g of 2,5-dimethylfuran had been consumed, corresponding to 1.9 electrons lost per 2,5-dimethylfuran molecule. The furan remaining unchanged as well as ether was then evaporated off under reduced pressure. Vacuum distillation of the residual liquid gave the following fractions:

(17) A. J. Baggaley and R. Brettle, *J. Chem. Soc. C*, 969 (1968).

fraction 1, bp 60–70° (14 mm), 0.2 g; fraction 2, bp 85–89° (14 mm), 1.1 g; fraction 3, bp 120–150° (14 mm), 0.4 g.

The infrared spectrum of the main fraction (fraction 2) showed absorption bands at 3115 (=CH), 2860 (OCH₃), 2260 (CN), 1635 (C=C), 1175, 1145, 1100, 1060, and 1045 cm⁻¹ (COCOC); mol wt (mass spectrum), 153. *Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.78; H, 7.30; N, 9.06. The nmr spectrum of this fraction (100 MHz, 10% in CCl₄) suggested that this material was a 2:1 isomeric mixture of *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofuran (I_c and I_t). The yield was 20% (based on 2,5-dimethylfuran used; current efficiency, 61%). Each isomer was then separated in pure form by preparative vpc, the column packing being PEG 6000. The cis isomer had a shorter retention time. The melting points were 31.5–32.5°, cis, and 49.5–50.5°, trans. The proton chemical shifts τ of these isomers are listed in Table III.

Fraction 1 was mainly a 1:1 mixture of 2-cyano-5-methoxy-2,5-dimethyldihydrofuran (I_c and I_t) and 2,5-dimethoxy-2,5-dimethyldihydrofuran (II_c and II_t), with trace quantities of 2-methoxymethyl-5-methylfuran (III) and 2,5-bis(methoxymethyl)furan (IV). Fraction 3 was a clear, viscous liquid. No attempt was made to identify it.

Nonpotentiostatic Oxidations.—Preparative-scale electrolysis was carried out in a two-compartment H-type cell with glass frit separating the compartments fitted with platinum foil electrodes (20 × 30 mm²). The anolyte was made up of 15.4 g (0.16 mol) of 2,5-dimethylfuran, 7.8 g (0.16 mol) of sodium cyanide, and 200 ml of methanol. The catholyte was a metha-

nolic solution of sodium cyanide. The electrolysis was carried out under a nitrogen atmosphere for 18 hr at 35 V until 18,900 C had passed through the electrolyte. During the electrolysis, the solution was kept stirred magnetically and cooled externally with ice (2–5°).

The electrolyzed mixture was treated as usual. Vacuum distillation afforded 7.4 g of I (30% yield based on 2,5-dimethylfuran used; current efficiency, 49%; cis/trans = 2.0) and 0.8 g of II (3% yield; current efficiency, 5%; cis/trans ≃ 1), with traces of III and IV. When the electrolysis was conducted in an undivided cell, the yield of I decreased considerably.

Registry No.—I_c, 28463-58-3; I_t, 28463-59-4; 2,5-dimethylfuran, 625-86-5.

TABLE III
PROTON CHEMICAL SHIFTS (τ VALUES) IN *cis*- AND *trans*-2-CYANO-5-METHOXY-2,5-DIMETHYLDIHYDROFURAN[a,b]

Compd	Vinyl proton	Methoxy proton	Methyl proton
I_c	3.92 (1 H, d, J = 5.6 cps)	6.81 (3 H, s)	8.38 (3 H, s)
	4.18 (1 H, d, J = 5.6 cps)		8.55 (3 H, s)
I_t	3.99 (1 H, d, J = 5.8 cps)	6.92 (3 H, s)	8.34 (3 H, s)
	4.13 (1 H, d, J = 5.8 cps)		8.49 (3 H, s)

[a] Measured at 100 MHz in CCl₄. [b] Abbreviations: d, doublet; s, singlet.

Homolytic Arylation of Pyridine and Pyridine *N*-Oxide and the Effect of Localization Energy and Temperature on Arylation Patterns

R. M. ELOFSON,* F. F. GADALLAH, AND K. F. SCHULZ

Contribution No. 508 from the Research Council of Alberta, Edmonton, Canada

Pyridine and pyridine *N*-oxide have been phenylated by electrolytic reduction of benzenediazonium tetrafluoroborate in aprotic media giving high yields of phenylated products. Nonelectrolytic reduction systems were also investigated, leading to a new mechanism for diazonium salt–pyridine reactions. Partial rate factors and total rate ratios for pyridine *N*-oxide are reported for the first time. Experimental results are related to theoretical values calculated from molecular orbital theory by Brown and Barnes.

Previously this laboratory reported the polarographic reduction in aprotic solvents of substituted benzenediazonium tetrafluoroborates in which the most positive wave is produced by a reversible one-electron step.[1a] The phenyl radical formed in this system has been used to phenylate benzene, toluene, anisole, benzonitrile, nitrobenzene, bromobenzene, and naphthalene with most encouraging results.[1b]

Therefore, it seemed of interest to examine the electrochemical arylation of heteroaromatic nitrogen compounds. Pyridine was chosen because the abundant available data concerning the homolytic arylation of pyridine would provide a way to evaluate our method. Pyridine *N*-oxide was chosen for precisely the opposite reason: the few and conflicting data might be elucidated by our study.

Homolytic arylation of pyridine has been achieved using benzoyl peroxide, lead tetrabenzoate, phenyl iodobenzoate, and electrolysis of benzoic acid as sources of the free radical.[2–6] Abramovitch and coworkers,[7,8] using an equimolar mixture of pyridine and benzene-

diazonium tetrafluoroborate, reported production of phenyl radicals, but no results for the phenylation of pyridine were given.

Data on homolytic phenylation of pyridine *N*-oxide are scarce. Dyall and Pausaker[9] treated pyridine *N*-oxide with phenyl radical generated from diazoaminobenzene and succeeded in separating the three phenylpyridine *N*-oxides. The isomer ratio they observed agrees qualitatively with ratios predicted by Barnes[10] from molecular orbital theory. The actual ratios differed from one run to the next and no total rate ratio was measured. On the other hand, Abramovitch and Koleoso,[8] phenylating pyridine *N*-oxide at room temperature to 60°, with an equimolar mixture of benzenediazonium tetrafluoroborate and pyridine, obtained 0.9% of isomeric phenylated oxides and 6% of phenylated pyridines with isomer ratios qualitatively similar to theory, but no attempt was made to obtain the total rate ratio $_{C-H}^{N-O}K$ or partial rate factors. Since the total rate ratio we obtained is high, we have pursued

(1) (a) R. M. Elofson and F. F. Gadallah, *J. Org. Chem.*, **34**, 854 (1969); (b) F. F. Gadallah and R. M. Elofson, *ibid.*, **34**, 3335 (1969).

(2) R. O. C. Norman and G. K. Radda, *Advan. Heterocycl. Chem.*, **2**, 131 (1963).

(3) R. A. Abramovitch and J. G. Saha, *ibid.*, **6**, 229 (1966).

(4) G. H. Williams, "Homolytic Aromatic Substitution," Pergammon Press, London, 1960.

(5) D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.*, 3963 (1955).

(6) P. J. Bunyan and D. H. Hey, *ibid.*, 3787 (1960).

(7) R. A. Abramovitch and J. G. Saha, *Tetrahedron*, **21**, 3297 (1965).

(8) R. A. Abramovitch and O. A. Koleoso, *J. Chem. Soc. B*, 1292 (1968).

(9) L. K. Dyall and K. H. Pausaker, *ibid.*, 18 (1961).

(10) R. A. Barnes, *J. Amer. Chem. Soc.*, **81**, 1935 (1959).

Table I

Phenylation of Pyridine by Different Methods[a]

Reaction	Radical source	Temp, °C	Yield, %	r	Isomer ratio %	$^x_H K$[b]	Fr[c]	Other products	Ref
1	Elect. redn of PhN₂BF₄			α	56		1.93		
	in C₅H₅N + CH₃CN	0	35	β	27	1.15	0.93	1.2% biphenyl	
				γ	17		1.17		
2	(PhCO₂)₂	105	62	α	54		1.7		
				β	32	1.04	1	PhCOOH	4,5
				γ	14		0.87		
3	(PhCO₂)₄Pb	105	42	α	52				
				β	32.5			PhCOOH	5
				γ	15.5				
4	Electrolysis of	10–20		α	56				
	PhCOOH in C₅H₅N			β	35				6
				γ	9				
5	Elect. redn of			α	57				
	PhN₂BF₄ in C₅H₅N only	0	81	β	24			0.7% biphenyl	
				γ	19				
6	PhN₂BF₄ in C₅H₅N			α	54				
	over Hg pool	15	87	β	28			0.7% biphenyl	
				γ	18				
7	PhN₂BF₄ in C₅H₅N only			α	57				
		15	92	β	27			0.7% biphenyl	
				γ	16				
8	Calcd from exptl			α	52		1.62		
	data of eq 1	105		β	30	1.04	0.95		
				γ	18		1.12		

[a] Experimental isomer ratios, total rate ratios, partial rate factors, yields, and calculated rates and isomer ratios. [b] $^x_H K$ = total rate ratio of pyridine relative to benzene (ref 4). [c] Fr = partial rate factor for position r ($α$, $β$, or $γ$) compared to any position in benzene (ref 4).

theoretical calculations to show quantitative correlations as described below.

Results

Electrolytic Reductions.—The method developed in our laboratory[1] of producing phenyl radical by the electrolytic reduction of benzenediazonium tetrafluoroborate was applied to the phenylation of pyridine in the presence of acetonitrile to give 35% (based on the diazonium salt) and in the absence of acetonitrile to give 81% yields (Table I). Both of these reactions consume for completion much less than the stoichiometric amount of current calculated for one-electron reduction of benzenediazonium tetrafluoroborate.

Using electrolytic reduction of benzenediazonium tetrafluoroborate in acetonitrile to phenylate pyridine N-oxide at 0°, relatively high yields of phenylated pyridine N-oxides (*ca.* 35%) have been obtained. Competitive reactions at 0° have resulted in total and partial rates close to the theoretically predicted values discussed below (Tables II and III).

Nonelectrolytic Reductions.—When it was found that fewer coulombs than calculated were required to complete the electrolysis of pyridine reactions, several nonelectrolytic systems were investigated. Benzenediazonium tetrafluoroborate in pyridine over mercury with stirring but without current and at 15° resulted in a vigorous reaction which was complete in about 15 min. About 0.7% biphenyl and 87% phenylpyridines were obtained. When mercury was absent, about 60 min was required for completion and 0.7% biphenyl and 92% phenylpyridines were obtained. The isomer ratios in nonelectrolytic and electrolytic reactions were virtually the same. Near-quantitative yields were

obtained in all reactions in the absence of acetonitrile (Table I).

Since our isomer ratios at 0° were different from those obtained by Dyall and Pausaker[9] for pyridine N-oxide at 131°, we repeated their work. Another set of reactions was performed to obtain the total rate ratio at 131°. Anisole was chosen as the reference compound because of its high boiling point.

Discussion

Abramovitch and coworkers[7,8] have suggested that aromatic diazonium tetrafluoroborates couple with pyridine giving complex 1 which decomposes on heating (eq 1). However, our decompositions of diazonium

$$\text{Ar—N=N—}\overset{+}{\text{N}}\!\!\bigcirc \xrightarrow{\Delta} \text{Ar} \cdot + \text{N}_2 + \cdot\overset{+}{\text{N}}\!\!\bigcirc \quad (1)$$
$$\underset{\text{BF}_4^-}{} \qquad\qquad\qquad \underset{\text{BF}_4^-}{}$$
$$\mathbf{1}$$
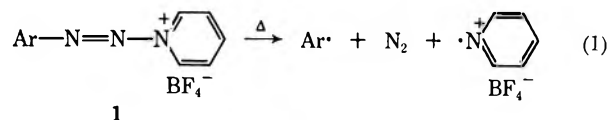
salts were performed at temperatures less than or equal to 15°. The yields were high and the isomer ratios very like those observed in benzoyl peroxide reactions. Therefore, if complex 1 is a significant intermediate, it must be rapidly formed and decomposed at one low temperature, which seems unlikely. Furthermore, when we phenylated pyridine N-oxide using benzenediazonium tetrafluoroborate and pyridine (100:2:4 molar ratio) at 20°, the predicted isomer ratios (Table II, f_1 and f_2), accompanied by traces of phenylpyridines, were obtained.

It seems reasonable to suggest the system used by Abramovitch and Koleoso[8] (1:1:1 molar ratio) produced high yields of polysubstituted phenylpyridine

TABLE II
PHENYLATION OF PYRIDINE N-OXIDE BY DIFFERENT METHODS[a]

	Reaction conditions	Temp, °C	Yield, %	r	Isomer ratio %	$^{N-O}_{C-H}K$[b]	Fr[c]	Other products and comments	Ref
a	Elect. redn of PhN₂BF₄ in PyN→O + CH₃CN (+PhH)	0	35	α	89		139	From isomer ratio and competitive reactions	
				β	<1	52	1.5		
				γ	10		31.2		
b	PhNHN₂Ph + PyN→O (+PhOCH₃)	131	45	α	82		50.7	From isomer ratio and competitive reactions; $^{OCH_3}_{H}K$ 1.43 calculated at 131° from 1.96 at 0°	
				β	4	20.6	2.5		
			·	γ	14		17.3		
c	PhNHN₂Ph + PyN→O (+PhOCH₃)	131	45	α	82		39.85	As in b but $^{OCH_3}_{H}K$ found experimentally at 131°	
				β	4	16.2	1.95		
				γ	14		13.6		
d	PhNHN₂Ph + PyN→O	131	27	α	76.2			Average of three runs	9
				β	7.8				
				γ	16				
e	PhNHN₂Ph + PyN→O	181	28	α	79			~6% phenylpyridines	9
				β	7.7				
				γ	13.3				
f₁	PhN₂BF₄ + C₅H₅N + PyN→O (0.02:0.04:1.0 mol) in CH₃CN	20	23	α	87			<1% of phenylpyridines	
				β	<1				
				γ	12				
f₂	PhN₂BF₄ + C₅H₅N + PyN→O (0.02:0.04:1.0) on Hg pool in CH₃CN	20	20	α	87			<1% of phenylpyridines	
				β	<1				
				γ	12				
g	PhN₂BF₄ + C₅H₅N + PyN→O (equimolar) + CH₃CN	rt-60	0.9	α	66.2			65.5⎫ Phenylpyridines	8
				β	2.5			11.8⎬ in 6%	
				γ	31.3			22.7⎭	

[a] Experimental isomer ratios, total rate ratios, partial rate factors, yields and isomer ratios.   [b] $^{N-O}_{C-H}K$ = total rate ratio of pyridine N-oxide relative to benzene.   [c] In a, b, and c, Fr calculated from isomer ratios and $^{N-O}_{C-H}K$.

TABLE III
PHENYLATION OF PYRIDINE N-OXIDE[a]

	Reaction conditions	Temp, °C	r	Isomer ratio %	$^{N-O}_{C-H}K$	Fr[b]	Comments
h	Calcd values from L.E.[c] at 0° taking β = 0.95	0	α	92.0		134	Calcd from Dickerman[21]
			β	1	48.5	1.2	
			γ	7.2		19.7	
i	Calcd from h	131	α	84.6		27.4	
			β	3.5	10.8	1.13	
			γ	11.6		7.49	
j	Calcd from exptl, 0° (a), eq 3	131	α	84		28.06	
			β	3.4	12.6	1.3	
			γ	13.6		10.23	

[a] Calculated isomer ratios, total rate ratios, and partial rate factors.   [b] In h, i, and j, Fr was calculated first considering no change in Lr or ΔH with temperature; then $^{N-O}_{C-H}K$ was calculated from $^{N-O}_{C-H}K$ = (2Fα + 2Fβ + 2Fγ)/6; then the isomer ratio was calculated from % r = Fr/3K for α and β and = Fr/6K for γ.   [c] L.E., localization energy.

N-oxides (not isolated) owing to the high reactivity of pyridine N-oxide. The reaction might have been further complicated by side reactions which occurred during heating in an acetonitrile solution and during reductions involving thiourea.

We suggest pyridine forms a coordination complex **2** analogous to the pyridine complex of positive iodine.[11] A one-electron reversible half-wave potential was obtained ($E_{1/2}$ = −0.16 V *vs.* sce).[12] We suggest −0.16 V is the value for reduction of complex **2**. A redox reaction could then follow in nonelectrolytic arylation in which the diazonium cation accepts one electron from pyridine giving a diazo radical and a

pyridyl radical according to Scheme I.[13] Pyridyl radical then abstracts hydrogen atoms from σ complex **3** giving pyridinium tetrafluoroborate; Hg⁰ apparently exerts a catalytic effect by facilitating the one-electron transfer from the nitrogen lone pair.[17] Hence the rate of decomposition is increased when mercury is present.

(11) (a) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Wiley, New York, N. Y., 1966, p 680; (b) N. W. Alcock and T. C. Waddington, *J. Chem. Soc.*, 2510, (1962).

(12) Polarography of benzenediazonium tetrafluoroborate. As described previously[1b] the polarogram was run for a solution of 6.0 × 10⁻⁴ M benzenediazonium tetrafluoroborate, 6 × 10⁻² M pyridine, and 0.1 M Bu₄NClO₄ in acetonitrile at 0°.

(13) This reaction is similar to the one between iodide ion and diazonium cation.[14–16]

(14) B. Chauncy and E. Gullert, *Aust. J. Chem.*, **22**, 993 (1969).

(15) R. M. Elofson and F. F. Gadallah, unpublished results.

(16) D. H. Hey, G. H. Jones, and M. J. Perkins, *Chem. Commun.*, 1375 (1969).

(17) Clearly the role of mercury as a catalyst in our reactions is more like the role of Cu₂Cl₂ in Meerwein reactions than that of zinc in related reactions. Hg⁰ may be oxidized by diazonium cations ($E^0_{(-N_2\cdot \rightarrow -N_2+)}$ = −0.541)[1a] to produce Hg⁺. Hg⁺ ($E^0_{(Hg^0 \rightarrow Hg^+)}$ = −0.789) facilitates oxidation of the σ complex to produce Hg⁰ + H⁺ and the reaction mixtures become acidic. As shown by Waters [*J. Chem. Soc.*, 864 (1939)], Zn⁰ can reduce diazonium salts to produce free radicals. But the resulting Zn²⁺ cannot oxidize the σ complex, the oxidizing potential is low ($E^0_{(Zn^0 \rightarrow Zn^{2+})}$ = +0.763), and zinc lacks an intermediate valence state to catalyze the necessary one-electron transfer. Therefore, Zn⁰ must be used in stoichiometric amounts.

SCHEME I[a]

$$ArN_2{}^+BF_4{}^- + nPy \longrightarrow [ArN_2(Py)_n]^+BF_4{}^- \longrightarrow$$

2

[a] *n* = number of pyridine molecules (presently under investigation) associated with a diazonium cation. This reaction is similar to the reaction between iodide ion and diazonium cation.[14-16]

The properties of this coordination complex **2** will be the subject of a subsequent paper.

If the diazonium cation is in fact reduced by pyridine, and the σ complex oxidized by pyridyl radical, it would most certainly occur during electrochemical reductions, hence making the short time and less than expected current required readily explicable.

Phenylation of pyridine *N*-oxide with benzenediazonium tetrafluoroborate at 0° produced a distribution of products quite different from that obtained by Dyall and Pausaker using diazoaminobenzene at 131°; so we were prompted to repeat their work. Good agreement was found with a single run (no. 3; α:β:γ as 80.9:5.6:13.5, respectively) of Pausaker's work,[9] especially considering Dyall and Pausaker used infrared spectral analysis, and in the work reported here glc and mass spectra analysis were used.

Moreover, the total rate factor proved to be remarkably large and was lower at 131° than at 0° (16.2 and 52, respectively). Coupled to the obvious shift in isomer ratio with the temperature change, this development alerted us to the necessity as well as the opportunity to compare the partial and total rates observed at two temperatures with the theory of rate processess, and also to compare these relative rates at any temperature with molecular orbital calculations by Barnes.[10]

Brown,[18] among others,[19,20] showed how this could be done. Rates of attack by trichloromethyl radical on several aromatic hydrocarbons at 91° were compared with atom localization energies according to eq 2,

$$2.303RT \log k_1/k_2 = a(L_2 - L_1) \tag{2}$$

where *a* is a constant characteristic of the attacking species, and L_1 and L_2 are the calculated localization energies of pairs of aromatic positions. By plotting *RT* log k_1/k_2 vs. localization energy differences, he obtained a good linear plot for this reaction expressed in β units, where β is the standard resonance integral for the C–C bond in benzene.

Brown[18] concluded that a similar value for *a* could be used for phenylation. Using experimental localization energies calculated from the experimental partial rates (k_1/k_2 = F*r*) for pyridine at 80° using eq 2, he

was able to perform molecular orbital calculations for pyridine to obtain satisfactory values for the parameters *h* (=0.5) and *k* (=1) for the coulomb integral $\alpha_N = \alpha_C + h\beta$ and the resonance integral $\beta_{C-N} = k\beta$. More recently Dickerman, *et al.*,[21] found a value of 17.8 for phenylation of naphthalene and anthracene. This value is used in our calculations.

Subsequently Barnes[10] calculated a series of localization energies for pyridine *N*-oxide wherein β_{N-O} was taken to be 0.5β, 1.0β, and 1.5β. From these and experimental results, he found β_{N-O} for electrophilic reactions to be greater than 0.5β and for nucleophilic reactions to be approximately 0.8β. No experimental data for free-radical reactions were available at the time. By interpolation of Barnes' calculations at 0.5β, 1.0β, and 1.5β, we obtained from experimental data for the phenylation of pyridine *N*-oxide at 0° the best fit value of β_{N-O} = 0.95β (see item h, Table III). Assuming, reasonably, that localization energies do not change with temperature and that they are the sole factor in controlling isomer ratios, calculations were made to obtain theoretical values for 131° (item i, Table III). A third set of values were obtained from eq 3,[4] where Δ*S** accounts for differences in the statistical weights of reactive positions and Δ*H** is the difference in activation energies here designated as differences in localization energies. This third set was designed to transform experimental results obtained at 0° to values for 131° (item j, Table III).

The agreement between calculated values for 131° (10.8; Table III, i), experimental results (16.2; Table II, c), and calculated values for 131° based on experimental 0° (12.6; Table III, j) is very close.[22] The total rate factor at 0° is clearly large and is considered accurate within the limits of the glc method. At 0° only substitution in the α and γ positions contributes significantly to the total rate. Because of its very low value, which made accurate experimental determination rather difficult, the isomer ratio for phenylation at the β position in pyridine *N*-oxide at 0° should be considered semiquantitative. At 131° all experimental values fall within the range permitting accurate estimation of isomer ratios.

$$2.303 \log \frac{k_1}{k_2} = \frac{\Delta S^*}{R} - \frac{\Delta H^*}{RT} \tag{3}$$

The actual value of total rate ratio for pyridine *N*-oxide at 131° ($\overset{N-O}{C-H}K$) was estimated experimentally against anisole. The total rate ratio for anisole was calculated to be 1.43 at 131° from the experimental result 1.96 obtained at 0°,[1b] which gave a value of 20.6 for $\overset{N-O}{C-H}K$. However, $\overset{OCH_3}{H}K$ was determined experimentally at 131° to be 1.13, giving a value of 16.2 for $\overset{N-O}{C-H}K$. The latter value was considered more accurate.

The effect of temperature on phenylation of pyridine at 105° (*K* = 1.04) agrees well with the value calculated from results at 0° (*K* = 1.15). However, the difference is probably too small (∼0.1) to be experimentally significant.

(18) R. D. Brown, *J. Chem. Soc.*, 272 (1956).

(19) D. A. Brown and M. J. S. Dewar, *ibid.*, 2406 (1953).

(20) J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, **84**, 3539, 3541, 3546, 3548 (1962).

(21) S. C. Dickerman, N. Milstein, and J. F. W. McOmie, *ibid.*, **87**, 5522 (1965).

(22) The overall difference between the calculated value of 12.6 and the observed value of 16.2 amounts to a total discrepancy in apparent energy of activation of about 200 cal for the total rate ratio of pyridine *N*-oxide or a discrepancy in the frequency factor of <10⁰·¹¹.

Clearly, our calculations are somewhat naive. Their validity is obviously limited by the assumption that either localization energies do not change with temperature or that the frequency factor is independent of temperature. Nevertheless, they do indicate trends quite satisfactorily.

For naphthalene, the only other highly active substance which has been intensively investigated, given $K = 16.6$ at $0°$,[1b] the calculated value at $80°$ is 9.1. Experimental results from benzoyl peroxide reaction at $80°$ give $K = 10$, in excellent agreement with calculations. The results presented in Table II demonstrate unequivocally that for pyridine oxide isomer distributions total rate ratios and partial rate factors can be related to localization energies as conceived by Wheland[23] and calculated by Barnes.[10]

Total rate ratios and partial rate factors do change with temperature. This was pointed out by Inukai, Kobayashi, and Simamura[24] regarding high values obtained for the phenylation of nitrobenzene at $20°$ $(K = 5)$,[25] compared with those found at $80°$ $(K = 2.9)$. However, nitrobenzene is not particularly satisfactory as an aromatic substrate compound because of the high yields of tars at high temperatures.

One of the difficulties recognized in determining the validity of partial rate factors is the possible effect of side reactions on the course of the reaction. In the case of reactions of benzoyl peroxide, the problem has been summarized and discussed by Hey.[25] The phenylation technique developed in our laboratory[1b] gives little, if any, dimerization or disproportionation products except, possibly, during reactions with nitrobenzene.[26] Acetonitrile in these reactions (at low temperatures) appears to behave similarly to oxygen or nitrobenzenes in the benzoyl peroxide reaction (Scheme II).[25] Hence

SCHEME II

total rate ratios and partial rate factors calculated from these reactions should be relatively free of the effect of side reactions. Furthermore, because our results agree generally with the results obtained using benzoyl peroxide,[1b] it is reasonable to agree with Morrison[27] that "side reactions have no significant effect on isomer

(23) G. W. Wheland, *J. Amer. Chem. Soc.*, **64**, 901 (1942).

(24) T. Inukai, K. Kobayashi, and O. Simamura, *Bull. Chem. Soc. Jap.*, **35**, 1576 (1962).

(25) D. H. Hey, *Advan. Free-Radical Chem.*, **2**, 41 (1967).

(26) The absence of significant quantities of disproportionation products, particularly dihydrobiphenyls was shown by the results of combined glc-mass spectra measurements. High yields of benzene (50–60%) and clear light-colored reaction mixtures indicated the absence of high molecular weight materials. That the σ complex is being efficiently oxidized is attested by the fact that electrolytic reductions in the presence of oxygen gave lower yields and dark-colored reaction mixtures, precisley opposite to results obtained in phenylations with benzoyl peroxide.[27] Presumably, oxygen interferes with the activity of H₂ĊCN and/or Hg,[17] resulting in high yields of dimerization, disproportionation, and polymerization products.

(27) R. T. Morrison, J. Cazes, N. Samkoff, and C. A. Howe, *J. Amer. Chem. Soc.*, **84**, 4152 (1962).

distribution or relative reactivities as measured by product analysis."

Finally, the results demonstrate that total and partial rates are subject to the laws of the theory of rate processes. Thus kinetic information not otherwise obtainable can be estimated by competitive reactions with a known standard at a single temperature. However, experimentally, temperature effects are probably not significant unless the total rate ratio at $0°$ is >10 and/or temperature differences are $>100°$.

Experimental Section

Reagents.—All liquid reagents and solvents were dried over anhydrous sodium sulfate, fractionally distilled, degassed by bubbling purified nitrogen through them, and stored in the dark in air-tight containers. Acetonitrile was treated as previously described.[1b] Solid reagents and reference compounds were recrystallized. Melting points agreed with literature values. Pyridine *N*-oxide was prepared from pyridine, glacial acetic acid, and hydrogen peroxide,[28] mp 65–66°. Benzenediazoniumtetrafluoroborate was prepared from the published method.[1a]

Reduction of Pyridine *N*-Oxides.—Reduction using thiourea[29] gave a tarry reaction mixture and low yields of deoxygenated products. A synthetic mixture of pyridine *N*-oxide and phenylpyridine *N*-oxide was added to 8 *N* hydrochloric acid. Zinc dust (100% molar excess) was added slowly over an hour and the mixture left for 16–24 hr with stirring. The mixture was filtered and made basic. After liquid–liquid extraction with benzene for 24 hr, the benzene extract was dried and concentrated to 10 ml for glc analysis. Yields of 96–98% of the corresponding deoxygenated compounds were consistently obtained. This technique was used to identify and estimate the products of pyridine *N*-oxide reactions.

Electrolytic Reductions.—Generally, the previously published method was used.[1b] All reactions were run under purified nitrogen. Control voltage *vs.* sce was 0.35 V for pyridine[13] and 0 V for pyridine *N*-oxide. In competitive reactions, the ratios of concentrations of aromatic substrates (*i.e.*, nitrogen compound: benzene or anisole) were 1:1 and 1:10 for pyridine and 1:10 and 1:20 for pyridine *N*-oxide. To avoid disubstituted products, diazonium salt concentration was kept not higher than $^1/_{50}$th (mol/mol) of that of the aromatic substrates.

Initial currents ranged from 80 to 200 mA. A reaction was considered complete when the current had fallen to less than 1 mA and the α-naphthol test for diazonium salt was negative. All reactions developed dark colors, but no attempt was made to identify the source.

Nonelectrolytic Reactions of Pyridine.—Benzenediazonium tetrafluoroborate (1.92 g, (0.01 mol) was added to dry pyridine (79 g, 1 mol) at 15 ± 1° under nitrogen. A reaction began at once which was complete in 60–70 min, at which time the α-naphthol test for diazonium salt was negative. Repeating the reaction over a mercury pool, a more vigorous reaction resulted which was complete in about 15 min. The reaction mixture was analyzed by glc.

Phenylation Using Diazoaminobenzene.—Diazoaminobenzene (1.97 g, 0.01 mol) was added to 95 g of pyridine *N*-oxide (1 mol) under nitrogen in an oil bath maintained at 131 ± 2°. After 24 hr the mixture was cooled to room temperature and sufficient benzene was added to bring the volume to 100 ml. A 20-ml aliquot was reduced with zinc and HCl as described above.

Phenylation of Pyridine *N*-Oxide Using Benzenediazonium Tetrafluoroborate and Pyridine.—Two systems were investigated, the only difference between them being that one contained a mercury pool and one did not. Pyridine *N*-oxide (9.5 g, 0.1 mol) and 0.3:6 g of pyridine (0.004 mol) were dissolved in 23 ml of CH_3CN at 20 ± 1°. Diazonium salt (0.384 g, 0.002 mol) was added to the clear, degassed solution. The solution was stirred under nitrogen and guarded with a drying tube.

Both reactions began immediately and darkened in color. The one with mercury was very vigorous and was complete in less than

(28) H. S. Mosher, L. Turner, and A. Carlsmith in "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., p 828, 1963.

(29) D. I. Relyea, P. O. Tawney, and A. R. Williams, *J. Org. Chem.*, **27**, 477 (1962).

2 hr. The reaction without mercury required *ca.* 10 hr for completion.

Half of each reaction mixture was taken to dryness under vacuum at room temperature, basified with 20 ml of 5% NaOH, and extracted with benzene. The dried benzene extract was concentrated and used for glc analysis. The other half of each mixture was reduced with zinc and HCl as described above.

Competitive Reactions at 131°. (a) **Pyridine *N*-Oxide.**— Diazoaminobenzene (3.94 g, 0.02 mol) was added to a mixture of 19 g of pyridine *N*-oxide (0.2 mol) and 216 g of anisole (2 mol) under nitrogen at 131 ± 2°. After 24 hr the mixture was cooled and evaporated under vacuum to 100 ml. Hydrochloric acid (50 ml, 0.5 *N*) was added to each of duplicated 10-ml aliquots of this solution, and the mixtures were extracted with ether. The ether extracts, containing methoxybiphenyls, were dried and concentrated for glc analysis. The aqueous phases, containing the phenylpyridines and phenylpyridine *N*-oxides, were reduced with zinc and HCl as above.

Two other 10-ml aliquots of the reaction mixture were acidified, washed with ether to remove methoxybiphenyls, basified, and extracted with benzene to give phenylpyridines in <1% yield. The isomer ratios were found to be between those for phenylation of pyridine and those found for phenylation of pyridine *N*-oxide. The authors therefore found it reasonable to overlook this insignificant amount in calculations.

(b) Anisole.—Diazoaminobenzene (3.94 g, 0.02 mol) was dissolved in a cold solution of 108 g of anisole (1 mol) and 78 g of benzene (1 mol) in a Carius tube. The solution was frozen in liquid nitrogen and the tube sealed. The tube and contents were allowed to come to room temperature and then agitated in an oil bath at 131° overnight. The tube was then frozen again; the contents were removed, concentrated to 25 ml and used directly for glc analysis.

Identification and Estimation of Products.—All reaction mixtures were analyzed by gas–liquid partition chromatography (glc). Phenylpyridines and biphenyls were identified by retention times and mass spectroscopy and were collected for verification from melting points and infrared spectra. After completion of reactions containing acetonitrile, the latter was distilled under vacuum at room temperature. In the pyridine reaction dry ether was added to precipitate tetrabutylammonium perchlorate. The ether solution was concentrated under vacuum and used directly for glc analysis. Yields, isomer ratios, total rate ratios, and partial rate factors are mean values of duplicate or triplicate runs.

Glc Columns Used and Retention Times.—It was found that any of the following stationary phases could be used for separation of biphenyl, methoxybiphenyls, and phenylpyridines: ethylene glycol adipate (10%), butanediol succinate (15%), Apiezon L (25%), and QF-1 (20%) [all weight/weight % on Chromosorb WNAW, 60–80 mesh].

QF-1, 6 ft × 3/16 in., temperature programming from 70 to 160°, was used to separate phenylpyridines. The retention times for biphenyl and 2-, 3-, and 4-phenylpyridines were 6.5, 16, 17, and 17.5 min, respectively. Apiezon L, 8 ft × 3/16 in., temperature programming from 70 to 250° and held at 250°, separated 2-, 3-, and 4-methoxybiphenyls with retention times 28, 30.5, and 31.5 min, respectively.

The Radical-Induced Decomposition of Aryliodine Dicarboxylates

T. T. WANG AND J. E. LEFFLER*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Benzoyl and substituted benzoyl peroxides induce the decomposition of phenyliodine dibenzoate or dianisate in C₆H₅Cl at 80°. The rate of decomposition of the peroxide is slightly diminished, and the yield of chlorobiphenyls from the peroxide is increased as compared to the values in the absence of the iodine compounds. The major products from the iodine compound are iodobenzene and the corresponding carboxylic acid. The product mixture from previously decomposed benzoyl peroxide also accelerates the decomposition of the iodine compound. It is suggested that phenylchlorocyclohexadienyl radicals induce the decomposition of the iodine compound. The catalytic effect of peroxide decomposition products is attributed to substituted tetrahydroquaterphenyls acting as chain-transfer agents.

The thermal decomposition of aryliodine dicarboxylates (1) is accelerated both by added radical initiators and by radical chain-transfer agents.[1,2]

The decomposition of phenyliodine dibenzoate[3] (1a, R = C₆H₅), accelerated by benzoyl peroxide, continues at an enhanced rate long after the peroxide concentra-

1a, R = C₆H₅
b, R = *p*-CH₃OC₆H₄

tion has been reduced to a negligible value, and indeed a chlorobenzene solution of benzoyl peroxide decomposition products also accelerates the decomposition.[1] Thus benzoyl peroxide not only produces radicals capable of attacking the dibenzoate, but also a chain-transfer agent that increases the effectiveness of the dibenzoate itself as initiator.

The chain-transfer agent is not benzoic acid, phenyl benzoate, biphenyl, iodobenzene, or any of the isomeric chlorobiphenyls, since these substances are produced in substantial amounts by the decomposition of the dibenzoate in the absence of added peroxide and the expected autocatalysis is not observed.

In the present paper we report the results of an investigation of the peroxide-accelerated decomposition of phenyliodine dibenzoate and dianisate in chlorobenzene at 80°. At this temperature the spontaneous decomposition of the phenyliodine dicarboxylate is extremely slow, and its decomposition products are almost exclusively those of the induced reaction.
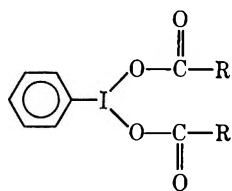
(1) J. E. Leffler, W. J. M. Mitchell, and B. C. Menon, *J. Org. Chem.*, **31**, 1153 (1966).
(2) J. E. Leffler and L. J. Story, *J. Amer. Chem. Soc.*, **89**, 2333 (1967).
(3) The *Chemical Abstracts* name is (dihydroxyiodo)benzene dibenzoate.

TABLE I

| Initial concn, M | | | | Yields, mol/mol[b] | | | | |
C6H5I-(OOCR)2[a]	(C6H5COO)2	C6H5I[h,d]	RCOOH[c]	Biphenyls			Esters	
0.005	0.005		1.74	0.44[e,f]	0.04[g,h]		0.016[h,i]	0.012[f,j,k]
	0.010		1.77	0.41[e,f]	0.042[g,h]		0.005[h,i]	0.016[f,j,k]
0.010	0.010	0.98	1.79	0.46[e,f]	0.45[f,l]	0.025[f,m,n]		
	0.020		1.51	0.40[e,f]	0.07[g,h]			0.016[f,j,k]
	0.030	0.97	1.78	0.34[e,f,o]				
0.010[p]	0.010	0.98	1.88[p,q]	0.56[e,f]	0.52[f,l]	0.025[f,m]		
None	0.010			0.23[e]	0.17[l]	0.021[m]		
None	0.010[r]			0.31[e]	0.22[l]	0.008[m]	0.01[j]	

[a] R = p-methoxyphenyl unless otherwise stated. [b] Per mole of the iodine compound or the peroxide, whichever is appropriate. [c] Anisic acid. [d] No iodoanisole was found. [e] o-Chlorobiphenyl. [f] Yield based on peroxide. [g] 2-Chloro-4'-methoxybiphenyl with traces of the 3- and 4-chloro isomers. [h] Yield based on the iodine compound. [i] Phenyl anisate. [j] Phenyl benzoate. [k] Accompanied by traces of o- and m-chlorophenyl benzoates. [l] m- plus p-chlorobiphenyl. [m] Biphenyl. [n] A yield of 0.029 of benzene, based on the peroxide, was also found. [o] A yield of 0.148 of benzene, based on the peroxide, was also found. [p] R = C6H5. [q] Includes an estimated 0.04 to 0.10 mol from the peroxide. [r] Data from ref 6.

Reaction Products.

—The major products from the phenyliodine dianisate or dibenzoate are iodobenzene (0.98 mol) and 1.5–1.9 mol of the corresponding carboxylic acid. The products from the benzoyl or substituted benzoyl peroxide are qualitatively similar to those formed in the absence of the iodine compound. However, the yield of chlorobiphenyls is considerably greater and increases with increasing relative initial concentration of the phenyliodine dianisate (Table I).

Various other oxidants have been observed to increase the yield of biphenyl from the decomposition of benzoyl peroxide in benzene,[4] probably by abstracting a hydrogen atom from some of the phenylcyclohexadienyl radicals[5] before they have an opportunity to dimerize to tetrahydroquaterphenyl.

The ratio of o- to (m- plus p-) chlorobiphenyls appears to be lower than that recently reported for benzoyl peroxide in chlorobenzene by itself.[6] Only traces of methoxychlorobiphenyls are formed. p-Iodoanisole, which would correspond to a product of the spontaneous ion-pair reaction observed at higher temperatures in the absence of peroxide or peroxide decomposition products,[1,7] is not a product of the induced decomposition.

Kinetics. The Peroxide.

—The rate law and first-order rate constant for the disappearance of benzoyl peroxide in the presence of phenyliodine dicarboxylate are very nearly the same as in the absence of the iodine compound. The first-order rate constant (k_{1p}, Table II) increases slightly with increasing initial peroxide concentration and decreases slightly during a run. For 0.01 M peroxide, k_{1p} in the absence of phenyliodine dicarboxylate is about 18% higher than in the presence of the iodine compound. This is to be expected if reaction with the phenyliodine dicarboxylate consumes radicals that would otherwise induce the decomposition of the peroxide. The data of Gill and Williams indicate about 19% induced decomposition at a peroxide concentration of 0.01 M in chlorobenzene, based on inhibition by galvinoxyl.[6]

The Iodine Compounds.

—The rate of the spontaneous decomposition of 0.01 M phenyliodine dianisate in chlorobenzene at 80° is about 10^{-10} M sec^{-1}, and most of this is probably the ion-pair reaction[1,7] leading

(4) G. R. Chalfont, D. H. Hey, Kathrine S. Y. Liang, and M. Perkins, *Chem. Commun.*, 367 (1967).
(5) D. F. DeTar, *J. Amer. Chem. Soc.*, **89**, 4058 (1967).
(6) G. B. Gill and G. H. Williams, *J. Chem. Soc.*, 7127 (1965).
(7) J. Y.-C. Chu, this laboratory.

TABLE II

PEROXIDE DECOMPOSITION RATE CONSTANTS IN C6H5Cl AT 79.8°

| Initial concn, M | | $10^5 \times k_{1p}$, | Initial concn, M | | $10^5 \times k_{1p}$, |
$\phi I(OOC$—$R)_2$[a]	$(ArCOO)_2$[b]	sec^{-1}	$\phi I(OOCR)_2$[a]	$(ArCOO)_2$[b]	sec^{-1}
0	0.0050	3.50[c]	0.0100	0.0103[d]	2.01
0	0.0103	3.59[c]	0.0102	0.0102[e]	10.1
0.0100	0.00345	2.92	0.0	0.0104[e]	10.1
0.0148	0.00509	2.92			
0.0100	0.0102	2.99			
0.0100	0.0301	3.17			

[a] R = p-CH3OC6H4 unless otherwise noted. [b] Ar = C6H5 unless otherwise noted. [c] Reference 6 (80.2°) gives k_{1p} = 2.98 × 10^{-5} sec^{-1}, initial concn 0.01 M, and 2.85 × 10^{-5} sec^{-1}, initial concn 0.0039 M. K. Nozaki and P. D. Bartlett, *J. Amer. Chem. Soc.*, **68**, 1686 (1946), report values near 3.7 × 10^{-5} in aromatic solvents at 0.01 M. [d] Bis(p-bromobenzoyl) peroxide at 78.5°. [e] Anisoyl peroxide.

to phenyl anisate and iodoanisole rather than a dissociation into radicals. At 130° the first-order rate constant for the spontaneous decomposition is 8.5 × 10^{-7} sec^{-1}.[7]

When a chlorobenzene solution of decomposition products from 0.01 M benzoyl peroxide is used as the solvent instead of pure chlorobenzene, the rate of decomposition of phenyliodine dianisate at 80° increases by about two orders of magnitude, to 4 × 10^{-8} M sec^{-1}.

The behavior of typical runs in which the solvent initially contains a low concentration of benzoyl peroxide rather than peroxide decomposition products is shown in Figure 1. The short induction period noticeable in the figure is somewhat longer in runs that have not been carefully degassed. After the induction period (1 or 2 hr), the disappearance of the phenyliodine dianisate becomes more rapid *and remains rapid for quite a few half-lives of the peroxide.* The half-life of benzoyl peroxide under these conditions is 6.0–6.5 hr depending on the initial concentrations.

Figure 2 summarizes the relationship between the maximum rate of dianisate decomposition attained in each run and the rate of decomposition of the added benzoyl peroxide. The peroxide decomposition rates were changed by varying the initial concentration of the peroxide. Since the peroxide decomposition rate decreases during the run (first-order rate law), the value at the end of the first peroxide half-life was chosen arbitrarily to represent the rate. As can be
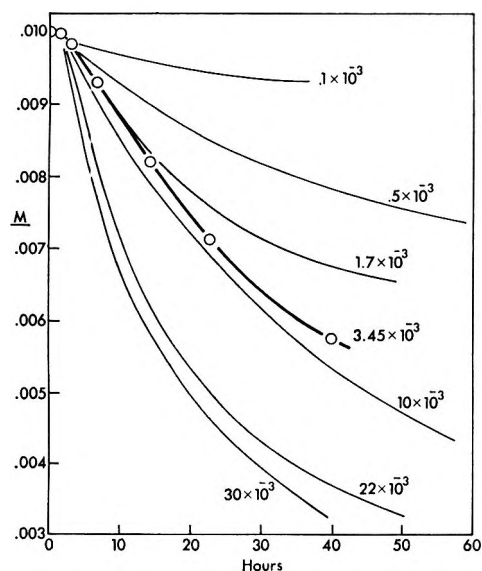
Figure 1.—Decomposition of 0.01 M phenyliodine dianisate in the presence of varying initial concentrations of benzoyl peroxide in C_6H_5Cl at 79.8°. For clarity, the experimental points are shown only for one run, and several runs at intermediate peroxide concentrations have been omitted.
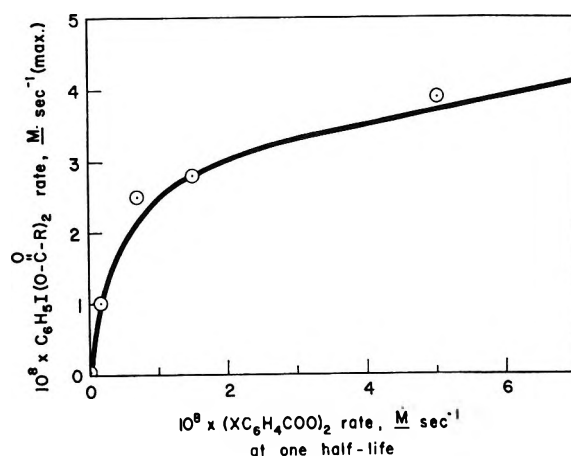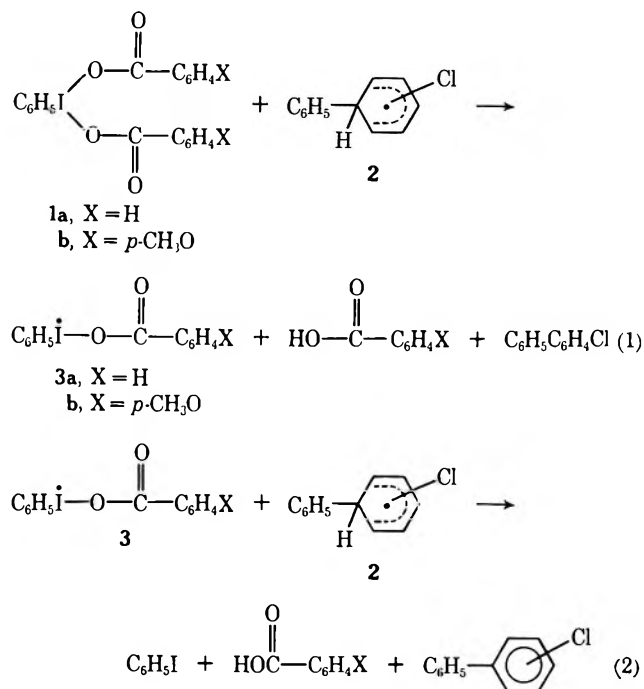

Figure 2.—The maximum rate of disappearance of phenyliodine dianisate, intially 0.01 M, in C_6H_5Cl at 78°, as a function of the rate of disappearance of benzoyl peroxide initiator. The latter rates were arbitrarily taken at the end of the first half-life and represent different initial peroxide concentrations.

seen from Figures 2 and 3 the induced decomposition of the dianisate is very sensitive to the first increments of added peroxide, but subsequent increments (above about 0.0005 M) have a much smaller effect. The induced decomposition rate at that point is about 2.5 × 10^{-8} M sec^{-1}, or comparable to that observed in runs *without* peroxide but *with* decomposition products corresponding to 0.01 M peroxide. At higher peroxide concentrations the rates of the two decomposition reactions appear to be linearly related.

Figure 3 also shows that the effects of bis(p-bromobenzoyl) peroxide (k_{1p} = 2.01 × 10^{-5}, point 1) and dianisoyl (k_{1p} = 10 × 10^{-5}, points 5 and 6) are similar to that of benzoyl peroxide (k_{1p} = 2.9 × 10^{-5}) if they are compared at equal decomposition rates rather than at equal concentrations.

Phenyliodine dibenzoate (points labeled 2 in Figure 3) decomposes at very nearly the same rate as the dianisate.

The effect of changing the initial concentration of dianisate (**1b**) at constant initial benzoyl peroxide concentration (0.01 M) can be seen by comparing points 3 (0.005 M dianisate) and 4 (0.015 M dianisate) and the line (0.010 M dianisate). Although the reproducibility of the maximum dianisate decomposition rates is only fair, they can be described roughly as a linear function of the product of the benzoyl peroxide and dianisate initial concentrations. The intercept of this function is nonzero and appears to be the same as the intercept of the straight-line portion of Figure 3. Both intercepts are close to the rates observed in solutions of benzoyl peroxide decomposition products, with no peroxide remaining at the beginning of the run.

In summary, the rate of decomposition of the phenyliodine dicarboxylate seems to have a constant contribution characteristic of a certain minimum amount of peroxide or peroxide decomposition products, and a variable contribution proportional to the dicarboxylate concentration and the rate of homolysis of the peroxide.

Discussion

The formation of iodobenzene and anisic acid as the major products of the induced decomposition suggests eq 1 and 2 as probable components of the mechanism. These reactions are closely analogous to in-

1a, X = H
b, X = p-CH$_3$O

3a, X = H
b, X = p-CH$_3$O

3

2

$$C_6H_5I + HOC\!-\!C_6H_4X + C_6H_5\!-\!\langle\bigcirc\rangle\!-\!Cl \quad (2)$$

duced decomposition and chain-breaking steps that have been proposed for the decomposition of benzoyl peroxide in benzene.[5] The fact that the induced decomposition of the peroxide is suppressed and the yield of monochlorobiphenyls is raised by the presence of the iodine compound is also explained by reactions 1 and 2, since these reactions divert phenylchlorocyclohexadienyl radicals from attacking the peroxide and decrease the dimerization to the corresponding tetrahydroquaterphenyls. The lower proportion of o-chlorobiphenyls in this reaction than in the decomposition of benzoyl peroxide by itself is not unexpected in view of the fact that the trivalent iodine compound
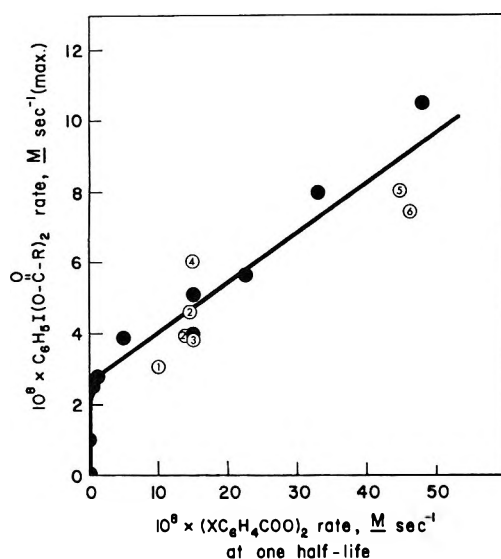
Figure 3.—The ordinate is the maximum rate of disappearance of the phenyliodine dianisate or dibenzoate. The abscissa is the rate of peroxide decomposition at the end of the first peroxide half-life. The solid circles represent 0.01 M dianisate with various concentrations of benzoyl peroxide. The open circles with numbers represent the following: (1) 0.01 M (p-BrC$_6$H$_4$COO)$_2$ and 0.01 M dianisate; (2) 0.01 M benzoyl peroxide and 0.01 M dibenzoate; (3) 0.01 M benzoyl peroxide and 0.005 M dianisate; (4) 0.015 M dianisate and 0.01 M benzoyl peroxide; (5) 0.01 M anisoyl peroxide and 0.01 M dibenzoate; (6) 0.01 M anisoyl peroxide and 0.01 M dianisate.

and the iodine radical (**3**) are more hindered than benzoyl peroxide and benzoyloxy radicals.

Since chlorine-substituted p-methoxybiphenyls are formed in only 4–7% yield, the dissociation of **3b** into iodobenzene and anisoyloxy radicals is not an important process, a conclusion that is also supported by the rate of decomposition of the benzoyl peroxide, which should be increased if extra aroyloxy radicals are formed.

However, even if eq 1 and 2 are accepted as contributors, the entire mechanism is far from being elucidated. The yield of anisic acid from **1b** requires more hydrogen atoms than can be balanced by the yield of biphenyls. One possible source is reaction with phenylchlorocyclohexadienyl dimers. These would be oxidized to a large number of involatile quaterphenyl isomers which would not appear in our isolated products.

A second problem is the nature of the chain-transfer agent that seems to be required by the kinetics. We suggest that this substance is formed by the decomposition of benzoyl peroxide by itself and to a lesser extent by the decomposition of benzoyl peroxide in the presence of phenyliodine dicarboxylates. An obvious candidate is the mixture of substituted tetrahydroquaterphenyls. A test of this hypothesis was attempted by means of model compounds. First it was ascertained that the chloro substituents are not essential by showing that the product mixture from the decomposition of benzoyl peroxide in *benzene* also accelerates the reaction. Then experiments were conducted with 1,3-cyclohexadiene and 1,4-dihydrobiphenyl. Cyclohexadiene appeared to accelerate the reaction, but the interpretation of this result is uncertain because of interference with the iodometric analysis for **1b**. The effect of 1,4-dihydrobiphenyl was

to *inhibit* the reaction, *i.e.*, to protect the iodine compound from the peroxide. On the other hand, a considerably enhanced acceleration was observed when the product mixture from benzoyl peroxide, previously decomposed in the presence of 1,4-dihydrobiphenyl, was added. That product mixture should contain an enhanced proportion of tetrahydroquaterphenyls, and the observed acceleration supports the hypothesis that compounds of this type act as chain-transfer agents.

Attempts were made to fit[8] the concentration–time curves with detailed mechanisms of the type suggested above, but none of these mechanisms was satisfactory for all three reaction conditions, pure solvent, peroxide decomposition products present, and peroxide present.[9]

Experimental Section

Chlorobenzene (Eastman Organic Chemical or Matheson Coleman and Bell) was purified by stirring vigorously with sulfuric acid until the acid layer was no longer colored. It was distilled over phosphorus pentoxide through a 35-in. column packed with glass helices after washing with water and sodium bicarbonate solution and successive 24-hr periods of drying with calcium chloride and phosphorus pentoxide. The middle fraction (bp 131.5°) was collected, kept in a ground-stoppered round-bottom flask, and sealed with Parafilm.

Benzoyl peroxide (Fisher Scientific Co.) was purified twice by dissolving it in a minimum amount of chloroform and then precipitated by dropwise addition of two volumes of methanol at room temperature. The white crystalline precipitate was collected on a fritted-glass filter, air-dried, and ground to powder with a glass spatula before further drying over calcium chloride or Drierite under vacuum. It had a purity of about 99% by iodometric titration.

p-Bromobenzoyl peroxide and **p-anisoyl peroxide** were prepared by the reactions of the corresponding benzoyl chlorides (prepared from acids and thionyl chloride) with lithium peroxide[10] (Alfa Inorganics, Inc.). Both compounds could be purified either by crystallization from hot dry toluene (80°) or by the chloroform-methanol procedure described above for the purification of benzoyl peroxide.

p-Bromobenzoyl peroxide[10] [mp (explodes) 144°] had a purity of 99.4% (iodometric titration).

p-Anisoyl peroxide [mp (explodes) 123–124°, lit.[10] 126–127°] had a purity of 99.6% (iodometric titration).

Phenyliodine diacetate was prepared by the reaction of iodobenzene with peractic acid.[11]

Phenyliodine dianisate was prepared by the exchange reaction of phenyliodine diacetate with anisic acid. Finely powdered phenyliodine diacetate (4.0 g, 0.0124 mol) was stirred in a solution of anisic acid (4.5 g, 0.0296 mol) in anhydrous ether (500 ml). (This is close to the solubility of anisic acid in ether.) The reaction mixture became homogeneous in about 15 min,[12] after which phenyliodine dianisate gradually separated from the clear solution during about 2 min. Stirring was continued for 5 hr. The yield of the crude product was 54% (3.8 g).

About 2.0 g of phenyliodine dianisate (mp 180–181°) was obtained after two recrystallizations from chloroform-n-pentane following the procedure described above for the purification of benzoyl peroxide. It had a purity of 98–99% (iodometric titration).

(8) Using REMECH; *cf.* D. F. DeTar and C. E. DeTar, *J. Phys. Chem.* **70**, 3842 (1966).

(9) A spontaneous initiation rate adequate to fit the results under the latter two conditions predicts excessively rapid decomposition in the pure solvent It may be that an intermediate such as the dimer of radical **3** accumulates and extends the duration of the rapid induced decomposition. It was not considered worthwhile to devote additional computer time to testing this hypothesis, however.

(10) "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y. 1955, p 649.

(11) H. Saltzman and J. G. Sharefkin, *Org. Syn.*, **43**, 60 (1963).

(12) Phenyliodine diacetate is only slightly soluble in ether. An ether-soluble intermediate was presumably formed at this stage.

Phenyliodine dibenzoate[13] was prepared by the reaction of phenyliodine oxide (prepared from phenyliodine diacetate and sodium hydroxide)[11] with benzoic acid in chloroform.[14] The crude product was crystallized twice from chloroform–*n*-pentane, mp 160–161°, purity 101.2% (iodometric titration).

Kinetic Procedure.—The ampoules were cleaned and dried as described previously.[2] For runs requiring 20-ml aliquots, the ampoules consisted of 25-ml round-bottom flasks with 18 × 250 ml necks terminating in 19/38 ground-glass joints. A tube containing P_2O_5 was connected to a vacuum manifold and to a side arm fitted with a joint for attachment of the kinetic ampule. Both necks of this apparatus were plugged with glass wool to prevent any accidental transfer of P_2O_5 while the solvent was distilled onto the P_2O_5 for drying, and then returned to the kinetic ampoule. It was found that the P_2O_5 could be used for three runs without reloading, if it was kept evacuated after the kinetic tube had been sealed off.

All ampoules were degassed to better than 5×10^{-6} mm and the solvent was carefully dried by means of the P_2O_5 tube unless otherwise stated. Normally, one of the eight tubes used in each run was used to determine the inital concentration. Other tubes were quenched in ice–water as soon as they were removed from the thermostat.

Effect of Peroxide Decomposition Products.—Ampoules containing degassed chlorobenzene (or in one case, benzene) solutions of 0.01 *M* benzoyl peroxide were heated for at least 15 half-lives of the peroxide, either at 80 or 127°. The ampoule containing the solution of peroxide decomposition products was put into a larger ampoule continuing the phenyliodine dianisate, or a solution of the dianisate, and the outer ampoule was degassed and sealed. The inner ampule was then broken open by shaking and the resulting solution used to obtain one point of a kinetic run.

Method of Following the Decomposition. Procedure A.—(1) Add two pieces of Dry Ice to 10 ml of phenyliodine dianisate–benzoyl peroxide solution in a 125-ml erlenmeyer flask; (2) add 20 ml of carbonated glacial acetic acid; (3) add 30 ml of carbonated, deionized water and swirl for 1–2 min; and (4) add 2 ml of saturated potassium iodide solution in carbonated water, swirl for 3–5 min, and titrate the liberated iodine with thiosulfate. Benzoyl peroxide is not reduced by iodide ion under these conditions. Benzoyl peroxide can be determined from the difference between the total oxidant titer (procedure B) and the trivalent iodine compound titer (procedure A).

Procedure B consists of steps 1 and 2 of procedure A; then add 3 ml of saturated potassium iodide and swirl for 15–20 min; add 30 ml of water and titrate. Dry Ice was added from time to time throughout the titration.

The rate of the first-order decomposition of benzoyl peroxide determined by following the peak height of the ir absorption at 998 cm^{-1} agrees with the titrimetric rate only during the first 5 hr.

Usually, 20.5 or 10.5 ml of solution was placed in the tube before degassing so that two exactly equal aliquots (10.0 or 5.0 ml) could be removed by pipet. Precisely measured amounts of solution were placed in the tube when only one component was to be titrated, in which case the tube was rinsed with carbonated acetic acid.

The concentration of sodium thiosulfate solution used in the present work was 0.01 ± 0.00030 *N*. The carbonated water and glacial acetic acid showed a negative blank test.

Product Analysis.—The decrease of ir absorptions of both phenyliodine dianisate [1610.0 ($\nu_{>C=O}$), 1250.5 and 1170.0 cm^{-1} (ν_{-OCO-})] and benzoyl peroxide [1775.0 ($\nu_{>C=O}$) and 998.0 cm^{-1} (ν_{-OCO-})] was observed during the course of reaction. There was no uv absorption in the wavelength region near 500 mμ, indicating that no iodine was formed.

The last tube of a kinetic run after a long period of time was used for product analysis. The content was first treated with a small amount of ethereal diazomethane to convert acid products to methyl esters, and was then subjected to gas chromatography, using an F & M Model 700, a flame ionization detector, and either column A (10% SE-30 on Chromosorb W, $^1/_8$ in. × 6 ft) or column B [5% poly(*m*-phenyl ether) (5-ring) on silanized Chromosorb W, $^1/_8$ in. × 8 ft]. Iodobenzene and methyl benzoate were determined on column A at 100° (internal standard, *p*-iodoanisole) and on column B at 70° (internal standard, *m*-bromochlorobenzene). Biphenyl, methyl anisate, and *o*-chlorobiphenyl were determined on column A at 130° and on column B at 135° (internal standard, *p*-iodoanisole). The yields of *m*- and *p*-chlorobiphenyls were determined by measuring the ratio of the integration counts of the area of the unresolvable peaks to that of *o*-chlorobiphenyl.

After the solvent had been removed under high vacuum, the residue was dissolved in a small amount of acetone and used for determination of the high-boiling products, phenyl benzoate, 1-chloro-4′-methoxybiphenyl, and phenyl anisate on column A at 150° (internal standard, *p*-iodophenyl benzoate). Gas and low-boiling products were not determined quantitatively.

Registry No.—1a, 6597-18-8; 1b, 28237-96-9; benzoyl peroxide, 94-36-0; anisoyl peroxide, 849-83-2.

(13) The convenient procedure for the preparation of phenyliodine dianisate described above is not a satisfactory method of the preparation of phenyliodine dibenzoate.

(14) D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.*, 1475 (1956).

Photochemically Generated Benzyne[1]

Maitland Jones, Jr.,* and Mark R. DeCamp[2]

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Photolysis of phthaloyl peroxide through Pyrex yields benzyne. The intermediate generated undergoes a stereospecific 2 + 4 and nonstereospecific 2 + 2 cycloaddition and is thus identical in symmetry properties with that formed by conventional decomposition of benzenediazonium-2-carboxylate. Reaction with low-boiling compounds is facilitated by this method and higher yields of products often are obtained. Benzyne reacts with methylacetylene, allene, and cyclopropane in ene fashion to give phenylallene, benzylacetylene, and allylbenzene, respectively.

Remarkable indeed is the relative absence from the chemical literature of references to the photochemical generation of benzyne. Flash photolysis of benzene-diazonium-2-carboxylate by Berry and coworkers has been reported[3-6] and a variety of precursors has been briefly mentioned in Hoffmann's book.[7] It is notable, however, that only two–three pages are required for a description of the "Generation of Dehydrobenzene by Photolytic Methods."[7] Of the 155 Diels–Alder reactions tabulated in ref 7, only three involve photochemically generated benzyne.

We were drawn to find a photochemical source of benzyne for several reasons. First, we hoped to detect reactions of either the excited singlet or triplet state and, second, it seemed to us that a photochemical method of generating benzyne would facilitate the investigation of reactions with low-boiling hydrocarbons. We hoped both to achieve better yields in the few reactions that had been done and to find new reactions.
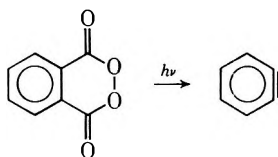
Here we amplify earlier reports[8,9] on the photolysis of phthaloyl peroxide. (*Caution*—see Experimental Section.) The main difficulty in this reaction is the insolubility of phthaloyl peroxide in most hydrocarbon solvents. Wittig and Ebel[9] used benzene as solvent but were able to isolate only a 7.4% yield of Diels–Alder adduct from tetracyclone. We find that the use of acetone or tetrahydrofuran allows formation of homogeneous solutions of phthaloyl peroxide in hydrocarbons. Using this modification of the earlier procedure,[9] reasonable yields can usually be achieved.

Stereochemical Studies.—We chose first to examine the 2 + 2 cycloaddition reaction. For the same reasons given earlier[10] (largely lack of ene reaction), the substrate used was *cis*- or *trans*-1,2-dichloroethylene. Irradiation, followed by analytical and preparative

(1) Support of this work by the National Science Foundation is gratefully acknowledged (Grant GP-12759).

(2) University Fellow, 1969–1970.

(3) R. S. Berry, G. N. Spokes, and R. M. Stiles, *J. Amer. Chem. Soc.*, **82**, 5240 (1960).

(4) R. S. Berry, G. N. Spokes, and M. Stiles, *ibid.*, **84**, 3570 (1962).

(5) R. S. Berry, J. Clardy, and M. E. Schafer. *ibid.*, **86**, 2738 (1964).

(6) M. E. Schafer and R. S. Berry, *ibid.*, **87**, 4497 (1965).

(7) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.

(8) L. Horner and H. Brüggemann, *Ann.*, **635**, 22 (1960).

(9) G. Wittig and H. F. Ebel, *ibid.*, **650**, 20 (1961).

(10) M. Jones, Jr., and R. H. Levin, *J. Amer. Chem. Soc.*, **91**, 6411 (1969).

gas–liquid partition chromatography (glpc) on a 2-m, 10% DC-710 silicone oil column gave, in addition to dimers, oligomers, and polymers of the dichloroethylenes, *cis*- and *trans*-1,2-dichlorobenzocyclobutene in 18–35% yield, depending upon the concentration of olefin and length of irradiation (Table I). After some hours of irradiation, glpc analysis revealed that, even though phthaloyl peroxide remained, the only reaction taking place was dimerization of the dichloroethylene.

TABLE I
STEREOCHEMISTRY OF THE 2 + 2 CYCLOADDITION OF BENZYNE

Mode[a]	Olefin	% cis adduct	% trans adduct
Δ	trans	19	81
Δ	cis	68	32
hν	trans	17[b]	83
hν	cis	69[b]	31

[a] Thermal source was benzenediazonium-2-carboxylate hydrochloride.[10] [b] Independent of choice of acetone or tetrahydrofuran as solvent.

The stereochemistry of the 2 + 4 reaction was also tested, and here too agreement with earlier work[10] was found. Irradiation of phthaloyl peroxide in *trans,-trans*-hexadiene-2,4 gave, as nearly as we can tell, the single dimethyldihydronaphthalene previously identified as cis.[10] The cis and trans isomers do not separate on glpc, but time-average scans of the vinyl region of the nmr spectrum allow the detection of very small amounts of the trans isomer. Under conditions where 2% of the trans material would be detected with ease, we see none. The combination of a nonstereospecific (and therefore very probably nonconcerted) 2 + 2 reaction with a stereospecific (and thus probably concerted) 4 + 2 reaction makes the intermediacy of the same, symmetric singlet state found in the thermal reaction highly probable. The question is, what is such

a species doing in a photochemical reaction? Several answers to this question are possible. Perhaps the

reactions of S[1] and S[0] benzyne are the same, or we are gaining entry to S[0] directly or through internal conversion from S[1]. The first of these possibilities appears unlikely to us, as the control of orbital symmetry over the stereochemical details of reactions seems sufficiently well established[11] to warrant confidence in the proposition that the excited and ground states will differ in their addition reactions. We have not observed an excited state of benzyne.

Other Known Reactions.—In this section we would like to demonstrate the utility of the photolytic reaction. When phthaloyl peroxide rather than a more conventional benzyne precursor is used, higher yields of products often can be obtained. Sometimes the increased yields allow the isolation of new products. For instance, butadiene was found to give a Diels–Alder adduct in 10% yield.[12] A later article reported 9%,[13,13a] and some years ago traces were probably obtained through photolysis of benzenediazonium-2-carboxylate.[3] Photolysis of phthaloyl peroxide in butadiene gives a 20% yield[14] of two products in the ratio of 4:1. We isolate, in addition to the Diels–Alder adduct, the product of the 2 + 2 cycloaddition. 1,4-Dihydronaphthalene is known[12] but 1-vinylbenzocyclobutene was not. Mass spectral analysis confirmed the elemental composition as $C_{10}H_{10}$, and examination of the nmr and uv spectra left no doubt as to the detailed structure. The crucial features of the nmr spectrum are the signals for the vinyl group at τ 3.70–4.25 (1 H) and 4.68–5.17 (2 H), a doubly allylic proton at 5.80–6.17 (1 H), and a multilined pattern at 6.45–7.35 (2 H). The uv spectrum [$\lambda_{max}^{cyclohexane}$ 272, 266, 261, 253 (sh) nm] is most similar to that of the vinylbenzocyclobutene isolated by Wittig and Dürr[12] from the 2 + 2 cycloaddition of benzyne and 2,3-dimethylbutadiene (272, 266, 260 nm).

The ene reaction[15] is very common in benzyne chemistry and we have discovered several, including some new types, on photolysis of phthaloyl peroxide. *cis*-Butene-2 gives a single major product, 3-phenylbutene-1 in *ca.* 9% yield.[14] The yield is not spectacularly high but should be compared with 4% reported for reaction
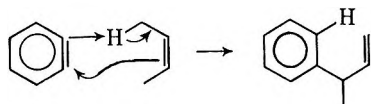
with isobutylene[12] and 13% for 2,3-dimethylbutene-2.[16] Similarly, propylene gives *ca.* 10% of the ene product, allylbenzene.

Previously Unknown Reactions.—While all of the examples mentioned above are known, many (but not all) are significantly easier to run using the photochemical method than the thermal. In this section we describe some new reactions with low-boiling hydro-

carbons. We suspect that they have not previously been reported at least partially because of the inconvenience of the usual thermal sources of benzyne.

Perhaps our first example, the reaction with methylacetylene, does not really qualify as new, since a similar reaction is mentioned in Hoffmann's book.[17] No details have appeared, however, and our yield is substantially greater. We find a 16% yield[14] of phenylallene
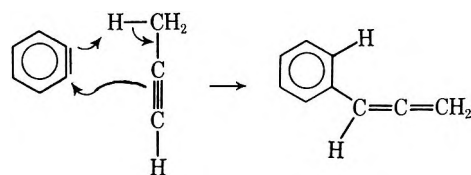
on irradiation of phthaloyl peroxide in methylacetylene Identification was by comparison with an authentic sample, and the mechanism of formation presumably involves an ene reaction.

A different kind of ene reaction appears in the reaction with allene. Again a single major product, benzylacetylene, is formed in 15% yield.[14] An ene reaction is implicated, but it is not of the usual sort. The or-

bitals involved are well aligned for such a reaction, although proof of concertedness is lacking. No evidence
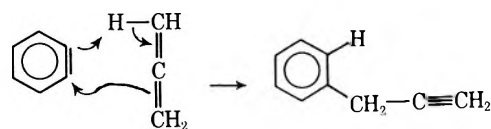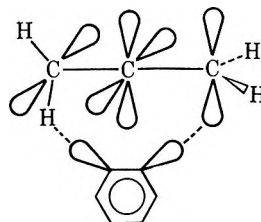
could be found for the product of a 2 + 2 cycloaddition, although Wasserman and Fernandez[18] have postulated such a process in the reaction of benzyne with phenylethoxyallene, generated *in situ* from 1-ethoxypropyne and benzyne.[18a]

Although a number of reactions with single bonds of strained hydrocarbons have been reported,[19-21] the parent of these, the reaction with cyclopropane, has escaped detection. We find that benzyne adds in ene fashion to cyclopropane to give, along with a large amount of polymer, 3–4% of allylbenzene. Indan was specifically sought and not found.
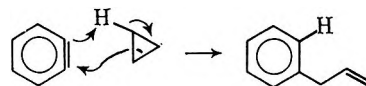
(11) R. Hoffmann and R. B. Woodward, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

(12) G. Wittig and H. Dürr, *Ann.*, **672**, 55 (1964).

(13) L. F. Hatch and D. Peter, *Chem. Commun.*, 1499 (1968).

(13a) NOTE ADDED IN PROOF.—See, however, footnote † in R. W. Atkin and C. W. Rees, *Chem. Commun.*, 152 (1969).

(14) Our yields do not generally reflect the fact that peroxide remains at the end of our reaction times. In a typical case, 20% of the peroxide was found remaining; a general upward correction by a factor of 1.25 is perhaps warranted.

(15) For a review of the ene reaction, see H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

(16) G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718 (1962).

(17) A private communication from M. Stiles and A. Haag (ref 7, p 198) reports a <4% yield of phenyl-*n*-propylallene from benzyne and hexyne-1).

(18) H. H. Wasserman and J. M. Fernandez, *J. Amer. Chem. Soc.*, **90**, 5322 (1968).

(18a) NOTE ADDED IN PROOF.—While this article was in press a communication on the reaction of benzyne with allenes appeared: H. H. Wasserman and L. S. Keller, *Chem. Commun.*, 1483 (1970).

(19) M. Pomerantz, G. W. Gruber, and R. N. Wilke, *J. Amer. Chem. Soc.*, **90**, 5040 (1968).

(20) P. G. Gassman and G. D. Richmond, *ibid.*, **90**, 5637 (1968).

(21) P. G. Gassman and G. D. Richmond, *ibid.*, **92**, 2090 (1970).

In summary, photolysis of phthaloyl peroxide yields a benzyne with the same symmetry properties as those generated in more conventional ways.[10] Reactions with low-boiling hydrocarbons are easy to run and often give higher yields than those of thermally generated benzyne. New reactions of benzyne with methylacetylene, allene, and cyclopropane are described. We hope in the future to report on their mechanisms.

Experimental Section

General.—Nuclear magnetic resonance spectra were recorded at 60 MHz on a Varian A-60A spectrometer. Nmr data of all products trapped from the vpc were obtained in capillary tubes with CCl$_4$ as solvent and tetramethylsilane added as an internal standard. Samples are collected directly from the gas chromatograph in Pyrex tubes slightly smaller than an ordinary melting point capillary. Solvent is added and the sealed tube mounted in a sawed-off nmr tube. Mounting techniques vary, but a current favorite involves wrapping the capillary in Scotch tape until it just fits the nmr tube. We heartily recommend the microtube technique as it allows analysis of samples as small as 1 mg. Mass spectra were measured on an AEI MS-9 mass spectrometer.[22] Uv spectra were run on a Cary 14 recording spectrophotometer. Gas chromatographic analyses and collections were performed on an Aerograph A90P chromatograph with the following columns: (A) 2 m, 10% DC-710 on 60–80 mesh Chromosorb W; (B) 1 m, 10% DC-550 on 60–80 mesh Chromosorb P. Yields were determined gas chromatographically and were not corrected for thermal conductivities. All photolyses were carried out with a Hanovia 450-W medium-pressure mercury arc shielded with Pyrex filters.

Phthaloyl Peroxide.—(*Caution*—see below.) Phthaloyl peroxide (PPO) was prepared in 40% yield by a slight modification of the method of Russell.[23] To an ice-chilled solution of 16 g each of K$_2$HPO$_4$ and KH$_2$PO$_4$ in 400 ml of water was added 8.3 g (0.11 *M*) of Na$_2$O$_2$. This solution was stirred vigorously in an ice bath during the addition of a chilled solution of 20.3 g (0.1 *M*) of *o*-phthaloyl dichloride in 300 ml of chloroform. The two-phase system was stirred for 15 min in an ice bath. The layers were separated and the organic portion dried over MgSO$_4$ and evaporated to dryness at the water pump. The white solid which remained was collected and washed repeatedly with hexane. After drying *in vacuo* overnight, the yield of white powder [mp 124.5–125° dec (lit.[23] 126°)] was 6–7 g. The product was not recrystallized and was stored in the freezer until use.

Warning. Upon melting a small sample of the peroxide in a capillary tube, there was a sharp, explosive report at 123°. PPO could also be detonated by striking with a hammer or by ignition. We experienced no trouble with phthaloyl peroxide during ordinary laboratory operations, but as with any peroxide it should be handled with utmost respect.

Photolysis of PPO in *trans*-Dichloroethylene (TDCE) and *cis*-Dichloroethylene.—PPO (300 mg) was dissolved in 5 ml of acetone and a large excess (*ca.* 10 ml) of TDCE. Irradiation in a Pyrex tube for 5 hr provided two products in the ratio 1:5 in addition to a number of olefinic photoproducts. The course of the photolysis was monitored by gas chromatography on column A at 150°. After *ca.* 3 hr the increase in cycloaddition products was negligible, although unreacted peroxide remained; *cis*- and *trans*-dichlorobenzocyclobutene were isolated by preparative gas chromatograph on column A with retention times of 16.5 and 7 min, respectively. They were identified by comparison with authentic samples. The overall yield of cycloaddition products ranged from 18 to 35% as determined by gas chromatography through addition of biphenylene as an internal standard.

The irradiation of PPO was also performed in *cis*-dichloroethylene (CDCE). PPO (320 mg) was dissolved in 10 ml of CDCE and 5 ml of acetone and irradiated for 6 hr in a Pyrex tube. Monitoring the progress of the reaction by gas chromatography indicated the rate of cycloaddition was very slow relative to the reaction in the trans olefin. The two cycloaddition products were obtained in a 7:3 ratio in very low yield.

Photolysis of *trans*-Dichlorobenzocyclobutene.—A sample of this material in TCDE was irradiated for 2 hr in an nmr tube and no isomerization could be observed.

Photolysis of PPO in *trans,trans*-Hexadiene-2,4.—PPO (300 mg) was dissolved in 5 ml of acetone and a 20-fold excess of *trans,trans*-hexadiene-2,4 (Chem Samples Co.) and sealed under nitrogen in a Pyrex tube. The solution was irradiated for 6.5 hr, after which it was concentrated and injected into the gas chromatograph (column B). In addition to a multitude of higher boiling products (retention times up to 30 min at 180°), *cis*-1,4-dimethyl-1,4-dihydronaphthalene was isolated by preparative gas chromatography (retention time 4.5 min at 130°) and identified by comparison with a known sample. The vinyl region of the spectrum was swept 60 times with a Varian Associates C-1024 Computer of Average Transients. No *trans*-1,4-dimethyl-1,4-dihydronaphthalene could be detected by the peak due to its vinyl protons, which appear *ca.* 15 Hz upfield from the peak for the vinyl hydrogens of the cis compound. Two per cent could easily have been seen under these conditions. This analytical method was made necessary because the two isomers were inseparable by gas chromatography in our hands.

Photolysis of PPO in *cis*-Butene.—Into a solution of 292 mg of PPO in 5 ml of acetone in a thick-walled Pyrex tube cooled to −78° was condensed 15 ml of *cis*-butene. The tube was carefully sealed under nitrogen and irradiated at room temperature for 10 hr. After irradiation the yellow solution was concentrated and injected into the gas chromatograph. 3-Phenyl-1-butene was isolated by preparative gas chromatography (retention time 4.5 min at 100°, column B). The yield was estimated to be 3.5% using gas chromatography with amylbenzene as an internal standard.

Photolysis of PPO in Propylene.—Into a thick-walled Pyrex tube cooled to −78° containing a solution of 300 mg of PPO in 5 ml of acetone was condensed 20 ml of propylene. The tube was carefully sealed under nitrogen and irradiated for 10 hr at room temperature. The yellow solution was filtered, concentrated, and analyzed by gas chromatography on column B at 85°. A single large product was isolated (retention time 4 min) and shown to be allylbenzene by comparison with an authentic sample.

Photolysis of PPO in Butadiene-1,3.—Into a solution of 295 mg of PPO in 5 ml of acetone in a thick-walled Pyrex tube cooled to −78° was condensed 15 ml of butadiene. The tube was sealed carefully under nitrogen and irradiated at room temperature for 8 hr. The yellow solution was concentrated and analyzed by gas chromatography. Two products in the ratio 4:1 were collected and identified as 1,4-dihydronaphthalene (retention time 13 min, 90°, column B) and 1-vinylbenzocyclobutene (retention time 5.5 min). The precise mass measurement for 1-vinylbenzocyclobutene was found to be 130.19243 (calcd for C$_{10}$H$_{10}$, 130.19126).

Using amylbenzene as an internal standard, the yield of cycloaddition products was found to be 20% by gas chromatography. The irradiation was run identically using tetrahydrofuran in place of acetone as the solvent. The same two products were observed in 4:1 ratio, in addition to the product of reaction of benzyne and tetrahydrofuran.

Photolysis of PPO in Allene.—Into a thick-walled Pyrex tube, cooled to −78°, containing a solution of PPO in 5 ml of acetone was condensed 15 ml of allene. The tube was carefully sealed under nitrogen and irradiated for 8 hr at room temperature. The yellow solution was concentrated and analyzed by gas chromatography. 3-Phenylpropyne (retention time 7 min at 85°, column B) was isolated by preparative gas chromatography and identified by comparison with an authentic sample. Using amylbenzene as an internal standard the yield was determined to be 15%.

Photolysis of PPO in Propyne.—Into a thick-walled Pyrex tube cooled to −78° containing 290 mg of PPO in 5 ml of acetone was condensed 15 ml of propyne. The tube was carefully sealed under nitrogen and irradiated for 10 hr at room temperature. The yellow solution was concentrated and analyzed by gas chromatography. The major component (retention time 8 min at 90°, column B) was identified as phenylallene by comparison with an authentic sample. The yield was determined to be 16% using amylbenzene as an internal standard. An estimated 20% PPO remained.

Photolysis of PPO in Cyclopropane.—Into a thick-walled Pyrex tube, cooled to −78°, containing a solution of 290 mg of

(22) We thank the National Science Foundation for providing funds for the purchase of this instrument through Grant GP-5200.

(23) K. E. Russell, *J. Amer. Chem. Soc.*, **77**, 4814 (1955).

PPO in acetone was condensed a large excess of cyclopropane. The tube was carefully sealed under nitrogen and irradiated for 10 hr at room temperature. There was a large amount of polymer so the yellow solution was filtered before concentration and analysis by gas chromatography. Two products in the ratio ~4:1 (retention times 4 and 9 min at 85°, colum B) were observed in addition to several higher boiling components. The major component was identified as allylbenzene by comparison with an authentic sample. It was obtained in 3-4% yield, as determined by using *tert*-butylbenzene as an internal standard. The minor product has not been isolated in sufficient quantity for identification, although it has been established that it is *not* indan.

Registry No.—Benzyne, 462-80-6; PPO, 4733-52-2.

Linear Free-Energy Relationships between Partitioning Solvent Systems[1]

A. LEO* AND CORWIN HANSCH

Department of Chemistry, Pomona College, Claremont, California 91711

The relationships between the octanol–water partitioning system and 20 others are examined from the viewpoint of the relative contribution of both hydrophobic bonding and hydrogen bonding forces. A classification of solute functional groups according to relative hydrogen-bond donating and accepting ability is presented. Fifty-eight new values for log *P* octanol–water are reported.

Information on how organic solutes are distributed between water and an immiscible solvent has been of primary interest to chemists working in two different fields: the physical chemist can use the data to help define the intramolecular forces acting between the solute and each of the solvents, and the biochemist can employ it in an approach to structure–activity relationships.[2] In this paper, the relationships between 21 partitioning systems are examined and discussed in reference to their application to both the physical and biological disciplines.

Since, in essence, partition coefficients are equilibrium constants, it should not be surprising that one can find extrathermodynamic relationships[3] between partition coefficients measured in different solvent systems. Certainly such an assumption was implicit in the work of Meyer[4] and Overton[5] who used oil–water partition coefficients to correlate narcotic action of drugs. Later, Smith[6] discussed the possibility of such relationships between two solvent systems if the solute sets chosen were not too dissimilar. Collander[7] was the first to express the relationship clearly in formal terms. Collander showed that a good linear relation-

$$\log P_2 = a \log P_1 + b \qquad (1)$$

ship existed between partition coefficients in one system (P_1) and those in a second system (P_2) if the polar phase was water and the nonpolar phases contained the same functional group. In particular, he showed that eq 1 held between the systems isobutyl alcohol–water, isopentyl alcohol–water, octanol–water, and oleyl alcohol–water.

Hansch,[8] using Smith's data, later extended the comparison of relatively nonpolar systems using $CHCl_3$–water as P_1 and the following systems for P_2: CCl_4, xylene, benzene, and isoamyl acetate.

While eq 1 allows any partitioning system to be compared with any other, the most useful relationships for the study of solute–solvent interactions are obtained if each system is compared to a standard reference system; that is to say, a reference system should be chosen and made the independent variable P_1 in a set of equations of the form of eq 1.

Of course, objections can be raised to the choice of *any* of the systems for use as a reference standard. We have chosen the octanol–water system for a number of practical reasons: first, it is the system with the largest number of measured values, and it also contains the widest selection of solute functional groups; second, most of these values have been determined in a single laboratory and therefore they are more self-consistent than the values from any other system; and third, the usefulness of the octanol–water system as a model for describing the binding forces between small molecules and macromolecules has already been established.[2]

One might argue that the organic phase in the reference system should be as free of polar binding forces as possible. While in principle a hydrocarbon solvent such as cyclohexane or heptane might make a better reference system than octanol, there are several practical reasons why such a system cannot be constructed at the present time. Of the almost 500 values available in the cyclohexane–water system, a large fraction are for unusual molecules not reported in other systems. Only about 200 values are available in the heptane–water system and these are heavily weighted toward the nonpolar solutes. Furthermore, a basic disadvantage in using a hydrocarbon–water system is that in these solvents dimerization of the solute is maximized. While in principle this factor can be taken into account by measuring the variation of the apparent coefficient with concentration, many of the values reported in the early literature have not been corrected in this manner. Besides it being much more laborious to obtain true partition coefficients in hydrocarbons in which association occurs, the very limited solubility of many polar molecules in these solvents often sets an impossible requirement on the sensitivity of the analytical techniques available.

Another interesting feature of octanol which enhances its value as a partition reference solvent is that, while water is very soluble in it (see Table I), it is very insoluble in water (4.5 × 10⁻³ *M*). Thus, in comparison with many of the solvents in Tables I and II, it has relatively little effect on the aqueous phase.

(1) This work was supported by Grant CA-11110 from the National Institutes of Health.

(2) C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969).

(3) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963.

(4) H. Meyer, *Arch. Exp. Pathol. Pharmakol.*, **42**, 109 (1899).

(5) E. Overton, "Studien uber die Narkose," Fischer, Jena, Germany, 1901.

(6) H. Smith, *J. Phys. Chem.*, **25**, 204, 605 (1921).

(7) R. Collander, *Acta Chem. Scand.*, **5**, 774 (1951).

(8) C. Hansch, *Farmaco*, **23**, 294 (1968).

TABLE I

$$\text{Log } P_{solv} = a \text{ Log } P_{octanol} + b$$

Solvent (vs. H₂O)	Table of solutes[a]	(Mol of H₂O/l.) × 10³	Equation "A" a[b]	b[b]	n	r	s	Equation "B" a	b	n	r	s
Cyclohexane	III	2.5	0.675 (±0.24)	−1.842 (±0.48)	26	0.761	0.503	1.063 (±0.12)	−0.734 (±0.25)	30	0.957	0.360
Heptane	IV	3.3	1.056 (±0.73)	−2.851 (±1.46)	10	0.764	0.916	1.848 (±0.44)	−2.223 (±0.93)	11	0.954	0.534
CCl₄[c]	V	10.0	1.168 (±0.12)	−2.163 (±0.15)	24	0.974	0.282	1.207 (±0.27)	−0.219 (±0.37)	11	0.959	0.347
Xylene	VI	18.8	0.942 (±0.13)	−1.694 (±0.21)	19	0.963	0.225	1.027 (±0.08)	−0.595 (±0.16)	21	0.986	0.230
Toluene	VII	25.6	1.135 (±0.11)	−1.77 (±0.16)	22	0.980	0.194	1.398 (±0.22)	−0.922 (±0.37)	14	0.971	0.274
Benzene	VIII	26.0	1.015 (±0.11)	−1.402 (±0.14)	33	0.962	0.234	1.223 (±0.19)	−0.573 (±0.20)	19	0.958	0.291
CHCl₃[d]	IX	68.4	1.126 (±0.12)	−1.343 (±0.21)	28	0.937	0.308	1.276 (±0.14)	+0.171 (±0.17)	21	0.976	0.251
Oils	X	72.5	1.099 (±0.06)	−1.310 (±0.09)	65	0.931	0.271	1.119 (±0.11)	−0.325 (±0.19)	14	0.988	0.233
Nitrobenzene	XI	180	1.176 (±0.23)	−1.072 (±0.20)	9	0.977	0.217					
Isopentyl acetate	XII	456	1.027 (±0.08)	+0.072 (±0.13)	22	0.986	0.209					
Ether	XIII	690	1.130 (±0.04)	−0.170 (±0.05)	71	0.938	0.186	1.142 (±0.13)	−1.070 (±0.12)	32	0.957	0.326

"Sole" equation

Solvent (vs. H₂O)	Table of solutes[a]	(Mol of H₂O/l.) × 10³	a	b	n	r	s
Oleyl alcohol	XIV	712	0.999 (±0.06)	−0.575 (±0.11)	37	0.935	0.225
Methyl iso-butyl ketone	XV	950	1.094 (±0.07)	+0.050 (±0.11)	17	0.993	0.184
Ethyl acetate	XVI	1620	0.932 (±0.21)	+0.052 (±0.18)	9	0.969	0.202
Octanol	XVII	2300	0.0	+1.00			
Cyclohexanone	XVIII	4490	1.035 (±0.20)	+0.896 (±0.30)	10	0.972	0.340
Primary pentanols	XIX	5000	0.808 (±0.07)	+0.0271 (±0.09)	19	0.987	0.161
sec- and tert-pentanols	XX	5320	0.892 (±0.06)	+0.288 (±0.06)	11	0.996	0.091
2-Butanone	XXI	5460	0.493 (±0.07)	+0.315 (±0.07)	9	0.987	0.093
Cyclohexanol	XXII	6510	0.745 (±0.09)	+0.866 (±0.14)	12	0.985	0.100
Primary butanols	XXIII	9440	0.697 (±0.02)	+0.381 (±0.03)	57	0.993	0.123

[a] These tables are included in the microfilm edition of this paper.   [b] The values in parentheses are the 95% confidence intervals.
[c] The "N" equation is

$$\log P_{CCl_4} = 0.862 \log P_{octanol} - 0.626$$
$$(\pm 0.60) \qquad\qquad (\pm 0.70)$$

n	r	s
6	0.809	0.462

[d] The "N" equation is

$$\log P_{CHCl_3} = 1.10 \log P_{octanol} - 0.649$$
$$(\pm 0.12) \qquad\qquad (\pm 0.18)$$

23	0.971	0.292

It is clearly evident from Smith's data[6] that, when the nonpolar phases of the partitioning systems differ widely, and especially when the solute sets contain molecules which cannot hydrogen bond along with those which can, eq 1 does *not* give a good correlation. For example, in comparing benzene–water with octanol–water, one needs at least two equations to relate a wide variety of solute molecules with a correlation coefficient greater than 0.85. The simplest way to make such a separation is to take the values from a single equation and separate all the "minus deviants" into one category and the "plus deviants" into another. After one has done this for several solvent systems, one finds that the strong hydrogen-bond donors are the "minus devi-

ants" and the hydrogen-bond acceptors are the "plus deviants." The ether–water system is exceptional, for, while it also segregates the donors from acceptors, the deviations are reversed.

Since the importance of the role of hydrogen bonding in solvent–solute interactions has been appreciated for some time,[9–11] it seemed reasonable to try to assign a specific order to the H-bonding properties of both the solutes and the organic solvents used in the partitioning

(9) J. H. Hildebrand, "Solubility," 2nd ed, Reinhold, New York, N. Y., 1936, p 166.
(10) G. F. Zellhoeffer, M. J. Copley, and C. S. Marvel, *J. Amer. Chem. Soc.*, **60**, 1337 (1938).
(11) R. Ewell, J. Harrison, and L. Berg, *Ind. Eng. Chem.*, **36**, 871 (1944).

TABLE II

SOLUTES UNCLASSIFIED

Solvent	a	b	n	r	s
Cyclohexane	0.872	−1.241	56	0.649	1.015
	(±0.28)	(±0.55)			
Heptane	1.566	−2.661	21	0.731	1.354
	(±0.70)	(±1.45)			
CCl₄	1.307	−1.592	41	0.797	0.937
	(±0.32)	(±0.42)			
Xylene	1.033	−1.180	40	0.862	0.661
	(±0.20)	(±0.34)			
Toluene	1.328	−1.560	36	0.852	0.664
	(±0.28)	(±0.46)			
Benzene	0.979	−1.005	52	0.815	0.555
	(±0.20)	(±0.24)			
CHCl₃	1.012	−0.512	72	0.811	0.734
	(±0.17)	(±0.27)			
Oils	1.096	−1.147	79	0.945	0.470
	(±0.08)	(±0.15)			
Ether	1.184	−0.474	103	0.929	0.477
	(±0.09)	(±0.10)			

systems. However, at the present time there is not enough applicable data to carry out such a task. Higuchi, *et al.*,[12] have been able to assign a relative H-donor capacity to a series of substituted phenols, and Taft, *et al.*,[13] have measured the H-acceptor capacity of a series of 55 bases of widely different structures. However, from these data it is not possible to assign an H-bonding parameter to more than a small fraction of the solutes common to partitioning work. Furthermore, there appears to be little agreement on the relative H-bonding ability of each of the common functional groups, except the well-known rules based on the electronegativity and size of the two atoms bound by the hydrogen atom.[14] Undoubtedly the sizable variations within any such functional group category has tended to discourage such efforts.[15a] Nevertheless, with the deviations from the regression equations relating the partition coefficients as a guide, we ordered some common functional groups into general solute classes. These appear in Chart I. The numbers which appear on the left are primarily for the purpose of identifying each class in the tables which follow and are not necessarily the order of H-bonding ability *within* each of the three groups. This matter is covered in greater detail in the supplementary material for microfilm edition.[15b]

The classification scheme shown in Chart I has been followed as closely as possible in assigning every solute appearing in Tables III through XXIII[15b] to the proper equation group. We have labeled the equations which correlate acidic solutes (H donors) as "A," and those correlating the basic solutes (H acceptors) as "B." In the case of CHCl₃ and CCl₄ we felt that a third equa-

(12) T. Higuchi, J. Richards, S. Davis, A. Kamada, J. Hou, M. Nakano, N. Nakano, and I. Pitman, *J. Pharm. Sci.*, **58**, 661 (1969).

(13) R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, and J. W. Rakshys, *J. Amer. Chem. Soc.*, **91**, 4794, 4801 (1969).

(14) G. Pimentel and A. McClellan, "The Hydrogen Bond," Reinhold, New York, N. Y., 1960, p 229 ff.

(15) (a) For example, Taft's K_f values for substituted pyridine varies from 2.30 for 2,4,6-trimethylpyridine to 0.75 for 3,5-dichloropyridine, while the parent compound has a K_f of 1.88. (b) Tables containing the partition coefficient data for each of the solute molecules used to derive the 20 regression equations and further discussion of their application appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $9.00 for photocopy or $2.00 for microfilm.

CHART I

GENERAL SOLUTE CLASSES

Always "A" {
1. Acids
2. Phenols
}

Usually "A" Sometimes "N" {
3. Barbiturates
4. Alcohols
5. Amides (negatively substituted, but not di-N-substituted)
6. Sulfonamides
7. Nitriles
8. Imides
9.[a] Aromatic amines (not di-N-substituted)
}

10.[a] Amides

Always "B" {
11. Aliphatic amines and imines
12. Tertiary amines, including ring N compounds
13. Ketones
14. Ethers
15. Esters
16. Compounds with intramolecular H bonds (*e.g.*, *o*-nitrophenol)
17. Aromatic hydrocarbons
18. Miscellaneous acceptors
}

[a] Classes 9 and 10 must be reversed when considering the ether and oil solvent systems.

tion was needed to give a good correlation for solutes having both donor and acceptor ability; these equations are labeled "N."

It will be noted that a special H-acceptor classification (16) was assigned to groups which normally are H donors but which can satisfy this tendency by an intramolecular bond.

Whenever a solute molecule contained two or more noninteracting functional groups, each of which would require classification as "A" and "B," we have placed it in the class which gave the best fit with that particular equation. It was felt that the best fit of the data would serve to categorize the dominant solvation forces in such cases. For example, *p*-methoxybenzoic acid is both an acid (class 1) and an ether (class 14). Equation "A" is clearly the one of choice in the solvent systems: benzene, toluene, and xylene (see Tables VIII, VII, and VI).[15b] This suggests that the H-donor ability of the carboxyl group is dominating in placing *p*-methoxybenzoic acid in the most poorly accommodated category when these solvents are compared to octanol. In the CHCl₃–water system, however, *p*-methoxybenzoic acid is not so poorly accommodated (again in relation to the standard reference system), and actually the "N" equation fits it as well as the "A" (see Table IX).[15b] This suggests that the weak H-donor capability of the solvent, CHCl₃, increases the accommodation of this solute by interacting with the etherial oxygen.

There were not enough examples available to assign classes 7 and 8 with a satisfactory degree of confidence. The one value for acetonitrile in ether–water clearly places it in the "A" equation, but Taft's value for the formation constant of the complex with *p*-fluorophenol would indicate that it can act as an H acceptor to the same degree as does acetophenone. Of course, dipole forces *other* than hydrogen bonding may be involved in the partitioning process, and the —C≡N group may

retain its classification within the intermediate group as more partitioning values become available.

Phthalimide provides the only example of a true imide for which other solvent system values could be found (ether and $CHCl_3$). However, classification in this case is not so difficult because the imide group is known to be acidic. If saccharin is included under this heading, many other values also establish this classification.

In establishing a scale for *solvents*, and for purposes where hydrogen bonding is *not* a dominant factor, a scale based on either dipole moment, dielectric constant, or solubility parameter can be useful and informative. For comparing a wide variety of partitioning solvents, however, none of these parameters are suitable, even when corrected for the water content at saturation.[16,17]

A useful and certainly a simple scheme for classification of partitioning solvent systems is to arrange them according to the amount of water each contains in the saturated state. This quantity was measured in each of the solvents appearing in this study by the Karl Fischer titration procedure (see Experimental Section). The values appear in the second column of Table I in (moles of H_2O per liter of solvent) $\times 10^3$. Of course, using the solubility of water in the solvent to index solvent character is ambivalent. In one sense it is a measure of the affinity of the functional group in the solvent for water molecules; in another sense (for partitioning work) it is a measure of the character of the solvent phase itself.

The balance of Table I is comprised of the regression equation data for each solute group arranged in order of decreasing H-donor capability: "A," "N," "B." Table II contains the single regression equations prior to segregation of the solutes into classes.

The usefulness of the equations in Tables I and II lies in the fact that the parameters "*a*" (slope) and "*b*" (intercept) can be an indication of the solute–solvent interaction as compared to the standard solute–octanol interaction. Considering the *slope* value first, we can see that it is a measure of the solvent system's sensitivity to changes in lipophilicity of solutes. The solvent system with the lowest sensitivity is butanol–water, as expected. When this pair is saturated with one another, they are about as much alike as possible and still remain as separate phases. Since log P measures the difference in transfer energy between the two, changes in solute character will register as only small differences when compared to octanol.

As the hydrocarbon chain length in the solvent alcohol is increased, the alcohol–water phases become more and more unlike, and the sensitivity to solute changes increases. Apparently a maximum sensitivity is reached at octanol, for the slope in the oleyl alcohol equation is also 1.0.

It should be borne in mind that the kind of solute molecules comprising a set can have considerable influence on the slope and that for some of the sets a "normal" distribution of solutes is lacking. As expected, only the very lipophilic solvents such as CCl_4, benzene, toluene, and oils have slopes greater than 1.0. One might expect that xylene should be included in

this group and indeed, with a better selection of solutes, the slope might be appreciably greater.

There is some basis for the postulate that the partition process, outside of hydrogen bonding, is the same for solutes in each system, and therefore, if hydrogen bonding were accounted for separately, the slopes of all the equations in Tables I and II would be 1.0. Some of the results reported by Higuchi and his coworkers[12] can be interpreted in this manner. They have used the cyclohexane–water system, where the organic phase has a minimum of hydrogen-bonding ability, and to it have added a small amount of tributyl phosphate (TBP) or isopropoxymethyl phosphoryl fluoride (sarin) as H-bond acceptors. By partitioning a set of substituted phenols between the two phases, they have calculated an equilibrium constant for the solute–TBP complex. From their data and log $P_{octanol}$ values for the phenols, eq 2 and 3 have been formulated. The

$$\log P_{octanol} = 0.50 \log P_{cyclohexane} + 2.43 \quad \begin{array}{ccc} n & r & s \\ 9 & 0.791 & 0.391 \end{array} \quad (2)$$

$$\log P_{octanol} = 1.00 \log P_{cyclohexane} + \\ 1.20 \log K_{HB} + 2.35 \quad 9 \quad 0.979 \quad 0.140 \quad (3)$$

correlation between partition coefficients in octanol and cyclohexane is poor, as shown by eq 2. However, when correction is made for the hydrogen-bonding ability of the phenols by adding a term in log K_{HB}, a good correlation is obtained with eq 3. Moreover, the coefficient with log $P_{cyclohexane}$ is 1.00, indicating that in a rough sense the desolvation processes are the same for each system. As more hydrogen-bonding constants become available, it should be possible to construct a broadly based set of correlation equations relating free energies of transfer of solutes in many systems. If this objective can be realized, then the above procedure can be reversed and eq 3 can be used to calculate the relative hydrogen bonding constants.

The *intercept* value for each of the regression equations in Table I can be used as a measure of the lipophilicity of the solvent in a slightly different fashion. It is apparent that the intercept for a given solvent system is the log P for any solute which is distributed equally between water and octanol; *i.e.*, log $P_{octanol} = 0$. Thus a negative intercept for any equation indicates that the solvent is more lipophilic than octanol, and a positive intercept indicates that it is more hydrophilic. This is more readily apparent if one examines a homologous series of solutes, for example, the carboxylic acids. The octanol log P values begin at -0.54 for formic and rise to -0.17 for acetic and to $+0.33$ for propionic. Therefore, it takes between two and three lipophilic methylene groups to balance the hydrophilic carboxyl group and allow the octanol to share the solute equally with water.

In the oleyl alcohol–water system it takes one *additional* methylene group before a carboxylic acid becomes lipophilic enough to be equally shared; *i.e.*, log $P_{oleyl\ alc} = 0$ between propionic and butyric. Similarly, it is noted that in nitrobenzene–water it takes two *additional* methylenes, in benzene–water it takes three, and in CCl_4–water it takes about 4.5 additional groups

(16) H. Mottola and H. Freiser, *Talanta*, **13**, 55 (1966).
(17) M. Chertkoff and A. Martin, *J. Pharm. Sci.*, **49**, 444 (1960).

to bring the solute to an equal lipophilic level with the organic phase.[18]

Using the intercept values from either the "A" or "sole" equations as a measure of a solvent's lipophilicity, we see that there is a very good correlation between these values and the water content at saturation. The

$$\log [H_2O] = 1.077[\text{intercept}] + 0.249 \quad \frac{n}{17} \quad \frac{r}{0.979} \quad \frac{s}{0.217} \quad (4)$$

values for isopentyl acetate and cyclohexanone were not considered in deriving eq 4. This relationship is seen in graphic form in Figure 1.

Experimental Section

The water content at saturation in each of the partitioning solvents listed in Tables I and II was measured at 25.0° using Karl Fischer reagent and standard procedures.[19,20] A dual buret apparatus capable of measuring water contents over the range of 1 ppm to 100% water was used. The end point is indicated with this instrument by a conductance-type meter using platinum electrodes.

Each of the solvents was shaken vigorously for 1 min before being placed in a constant temperature bath at 25.0 ± 0.1° for 48 hr. Each container was shaken twice again for 30 sec during this period and then centrifuged at 10,000 RCF for 20 min. During centrifuging and prior to actual titration, the temperature was maintained at 25.0 ± 1°.

Anhydrous methanol was used as the titration solvent for the alcohols and esters. A 3:1 pyridine–methanol mixture was used for the ketones to reduce any tendency to form acetals or iodo compounds,[21] and a 1:1 mixture of methanol–dichloromethane was used for the hydrocarbons, chlorinated hydrocarbons, and olive oil. In this way a one-phase system was maintained throughout each titration, and the K–F end point, once attained for 30 sec, could always be regained with the addition of no more than 0.1 ml of reagent even after the equipment was left standing for 30 min.

Some differences in water content were observed when the saturation procedures were varied. For instance, when octanol was freshly shaken with water at 20° and allowed to separate by gravity for 30 min, a slight haziness was still apparent and the water content was measured as 2.36 mol. After centrifuging at 15,000 RCF for 10 min, it was water-clear and gave a value of 2.27 mol of water. After being allowed to stand over water in a 2-l. bottle for several weeks (with a temperature variation of ±3°), the water content was 2.02 mol, which perhaps indicates that it is not safe to assume that all water in excess of saturation can be removed by a large centrifugal force acting during a relatively short time.

Discussion

As pointed out earlier, a single equation is sufficient to give an excellent correlation ($r \geq 0.97$) with the octanol reference system even if the solute types vary widely, as long as the solvent in question has both H-donor and H-acceptor functional groups (see ref 24 in the microfilm edition of this paper). The R–OH group in the alcohol series provides both donor and acceptor capability, and, in the case of the low molecular weight esters and ketones, these solvents evidently dissolve sufficient water to also act effectively in both capacities. It appears quite likely that any organic solvent con-

(18) It should be remembered that this direct comparison can only be strictly applied over a wide range of solutes when the slope value for the equation is nearly unity; otherwise, it applies only in the range of solutes where log P = 0.

(19) J. Mitchell, Jr., and D. M. Smith, "Aquametry," Interscience, New York, N. Y., 1948.

(20) I. Kolthoff and P. Elvining, "Treatise on Analytical Chemistry," Part II, Vol. 1, Wiley, New York, N. Y., Section A, pp 69–165.

(21) J. Mitchell, Jr., *Anal. Chem.*, **23**, 1069 (1951).

Figure 1.

taining 1 mol of water at saturation can act both as an H donor and H acceptor in partitioning work if the solute concentration is 0.1 mol or less.

From Tables III, IV, Vc, VIb, VIIb, VIIIb, IXc, and XIIIb[15b] it is seen that solute classes 10 through 18 consistently fall into eq "B." It should be noted, however, that there is some ambivalence in the two functional groups, aromatic amines and amides. In the least polar solvents (cyclohexane, heptane, CCl₄, benzene, toluene, and xylene), the aromatic amines are better fitted if placed with the H acceptors and thus are assigned class 10. In the more polar solvents which still require two or more equations (ether and oils), the aromatic amines are better fitted in the H-donor category and are assigned class 9.

On the opposite end of the scale, acids and phenols are clearly to be placed in the category of the strongest H donors. The large negative intercepts for most of the equations of type "A" means that H-donor solutes are relatively less easily accommodated by all the solvents except ether (again when octanol is the reference for comparison).

In the case of chloroform, the need for a third equation to fill the gap between classes 2 and 10 seems real, and it appears safe to conclude that the H-donor capabilities of these groups are also intermediate. The exact order within the classes 3–8 and 11–18 cannot be determined from the present data, but, if a sufficient number of new solute values are measured, a further degree of order may be possible. For example, if it develops that most of the barbiturates in the CHCl₃ regression eq "N" show negative deviations from the calculated value while most imides show positive deviations, this would mean the barbiturates are more closely aligned with type "A" solutes while imides are more like type "B" solutes, and the difference in H-donor ability between classes 3 and 8 would be real.

Taft's system of measuring the formation constant in CCl₄ of the hydrogen-bonded complex between a set of acceptors and a standard fluorophenol donor[13] is well suited to establish the order within the group "B" of Table I. Based on his K_f values, ethers as a class should be the weakest acceptors (average of 5 K_f = 0.876), followed by pyrimidine (1.05), esters (ethyl acetate = 1.08), and ketones (average of 4 K_f = 1.12). Aliphatic amines are much stronger acceptors on this scale (average of 7 K_f = 1.63). Compounds with ni-

trogen in an aromatic ring are, as expected, greatly influenced by the polar nature of any substituents, but the K_f value for pyridine (1.88) places them, as a group, among the most capable H acceptors.

It is quite obvious that, in collecting data from hundreds of different laboratories where a variety of techniques were used over a span of 90 years, a sizable number of erroneous values are to be expected in Tables III–XXIII.[15b] However, these "random errors" are certainly as likely in the butanol–water system as in any other, and yet the correlation between it and octanol–water is remarkably good ($r = 0.993$). We must conclude, therefore, that the majority of the deviations noted, for example in the $CHCl_3$–water system, are real and are subject to interpretation on the basis of how the solvent–solute forces differ from the reference system.

Accumulation of partition coefficient data is continuing, and future compilations of more accurate values should place the structural interpretations on an even firmer basis.

Intermediates in Nucleophilic Aromatic Substitution. IX.[1,2] Kinetic and Proton Magnetic Resonance Investigations of the Interaction of Lyate Ions with N-*tert*-Butyl-2,4,6-trinitrobenzamide

E. J. FENDLER, DONALD M. CAMAIONI, AND J. H. FENDLER[*3]

Radiation Research Laboratories, Mellon Institute of Science, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213, and Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

The interaction of hydroxide and methoxide ions with *N-tert*-butyl-2,4,6-trinitrobenzamide (1) in water and in methanol, respectively, results in the equilibrium formation of the 1-OH- (or -OCH$_3$-) 1-CONHC(CH$_3$)$_3$-2,4,6-(NO$_2$)$_3$C$_6$H$_2$ Meisenheimer complex and the formation of nitrite ions. Rate constants for the formation, k_1, and decomposition, k_{-1}, of these complexes as well as those for nitrite ion production, k_2, have been determined. At 25.00° for hydroxide ion interaction with 1 in water, $k_1 = 17.6$ l. mol^{-1} sec^{-1}, $k_{-1} = 0.0156$ sec^{-1}, and $k_2 = 1.43 \times 10^{-5}$ sec^{-1}, and for the methoxide ion interaction with 1 in methanol, $k_1 = 1.13 \times 10^3$ l. mol$^-$ sec^{-1}, $k_{-1} = 0.46$ sec^{-1}, and $k_2 = 6.7 \times 10^{-5}$ sec^{-1}. Equilibrium constants ($K = k_1/k_{-1}$) have been determined from kinetic measurements of the attainment of equilibrium for complex formation, from those of nitrite ion elimination, and from linear Benesi–Hildebrand plots. Excellent agreement among the three independently determined K values has been found. Structures of the hydroxy, methoxy, and ethoxy Meisenheimer complexes of 1 have been substantiated by pmr measurements of the isolated and *in situ* generated complexes.

N-*tert*-Butyl-2,4,6-trinitrobenzamide (1) was reported to undergo nucleophilic substitution with "hydroxide ion" in aqueous methanol (50/50 v/v) producing nitrite ions.[4] The formation of a red color upon the addition of the base to 1 led to the postulation of the presence of a complex.[4] The nature of these experiments, however, precluded the quantitative assessment of all the kinetic steps involved. The replacement of a nitro group on the aromatic ring by lyate ions as well as the relative steric, inductive, and resonance effects of the *tert*-butylamido group on the equilibrium constant for complex formation render the detailed kinetic investigation of this system particularly important. We have obtained data for the attainment of the equilibrium for the formation of the hydroxy and methoxy adducts of 1, in pure water and in pure methanol, respectively, and for the formation of nitrite ions at different lyate ion concentrations. Using these data the rate constants k_1, k_{-1}, and k_2 in

2a, R = H
b, R = CH$_3$
c, R = CH$_2$CH$_3$

have been obtained. Additionally we have elucidated the structures of 2a, 2b, and 2c using proton magnetic resonance spectroscopy both for the isolated and the *in situ* generated complexes.
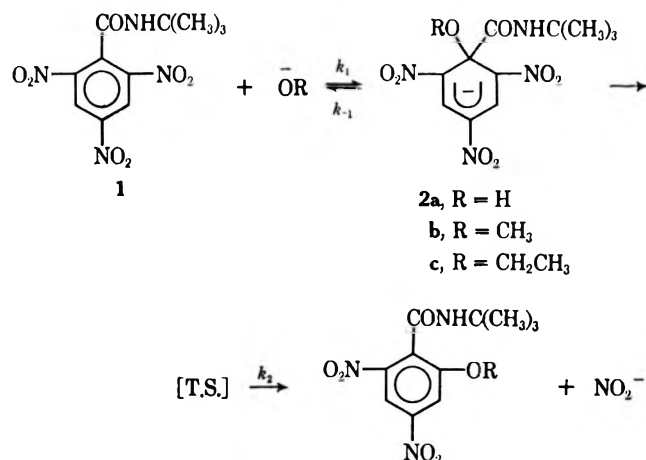
(1) Part VIII: J. H. Fendler and E. J. Fendler, *J. Org. Chem.*, **35**, 3378 (1970).

(2) For recent reviews on Meisenheimer complexes and their relevance in nucleophilic aromatic substitution, see (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); (b) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev. (London)*, **22**, 123 (1968); (c) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969); (d) J. Miller, "Aromatic Nucleophilic Substitutions," Elsevier, Amsterdam, 1968; (e) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969); (f) F. Pietra, *Quart. Rev. (London)*, **23**, 504 (1969).

(3) Address inquiries to Department of Chemistry, Texas A & M University, College Station, Texas 77843.

(4) P. J. Hutchinson and R. S. L. Martin, *Aust. J. Chem.*, **18**, 699 (1965).

Experimental Section

The solvents and reagents were prepared, purified, and standardized as previously described.[5] *N,N*-Dimethylacetamide (DMA, Baker analyzed reagent grade) was stored over Linde Type 5A Molecular Sieve and it spurity was verified by its pmr spectrum. The pH of the buffer solutions was measured at 25.00° either with an Orion-801 or a Radiometer PHM 26 pH meter.

2,4,6-Trinitrobenzoyl chloride was prepared, according to a slightly modified procedure of Hutchison and Martin,[4] by the portionwise addition of 10 g of 2,4,6-trinitrobenzoic acid to a refluxing solution of thionyl chloride (50 ml) and dry benzene (50 ml) over a period of 8 hr. The reaction mixture was refluxed for *ca.* 12 hr, cooled, and rotary evaporated *in vacuo* to dryness. Benzene (100 ml) was mixed with the product and then removed with a vacuum rotary evaporator. After recrystallization from benzene–petroleum ether (bp 40–60°), the product melted at 162–163° (lit.[4] 156–157°).

Compound 1 was prepared from 2,4,6-trinitrobenzoyl chloride and *tert*-butylamine in benzene according to the procedure of Hutchison and Martin.[4] After two elutions through a column of neutral alumina with benzene–methanol (9/1, v/v) followed by recrystallization from benzene–petroleum ether (bp 40–60°), the white crystals melted at 244–244.5° (lit.[4] mp 234–235°).

The hydroxy complex (2a) of *N-tert*-butyl-2,4,6-trinitrobenzamide was prepared by the addition of 0.25 ml (0.5 mmol) of 2.00 *M* aqueous potassium hydroxide (BDH) to a warm solution of 0.1495 g (0.5 mmol) of 1 in 0.90 ml of dioxane. The dark red crystals which appeared after *ca.* 2 min were removed by filtration under dry nitrogen and were washed with dry benzene and anhydrous ether. After drying *in vacuo* over phosphorus pentoxide, the crystalline product contained approximately 0.5 mol of dioxane of crystallization (by pmr integration of the dioxane singlet, τ 6.43).

Anal.[6] Calcd for $C_{11}H_{13}N_4O_8K \cdot 0.5C_4H_8O_2$: C, 37.9; H 4.16; N, 13.6; K, 9.50. Found: C, 37.24; H, 4.17; N, 13.01; K, 9.50.

The methoxy complex (2b) of *N-tert*-butyl-2,4,6-trinitrobenzamide was prepared analogously by the addition of 0.099 ml (0.5 mmol) of 5.05 *M* potassium methoxide in methanol to a warm solution of 0.1495 g (0.5 mmol) of 1 in 0.90 ml of dioxane under dry nitrogen. After filtration, washing, and drying, the fine red crystalline material was found to contain approximately 0.3 mol of dioxane of crystallization (pmr integration).

Anal.[6] Calcd for $C_{12}H_{15}N_4O_8K \cdot 0.3C_4H_8O_2$: C, 38.7; H, 4.28; N, 13.7; K, 9.55. Found: C, 35.26; H, 3.83; N, 13.22; K, 10.04.[7]

The same procedure was used to prepare the ethoxy complex (2c) of *N-tert*-butyl-2,4,6-trinitrobenzamide from 0.1495 g (0.5 mmol) of 1 in *ca.* 2.9 ml of dioxane and 0.207 ml (0.5 mmol) of 2.42 *M* potassium ethoxide in ethanol. The dark red product contained approximately 0.5 mol of dioxane of crystallization (pmr integration).

Anal.[6] Calcd for $C_{13}H_{17}N_4O_8 \cdot 0.5C_4H_8O_2$: C, 40.8; H, 4.82; N, 12.7; K, 8.90. Found: C, 38.14; H, 4.41; N, 12.71; K, 9.10.[7]

The attainment of the equilibria for the formation of 2a in water was followed at 430 nm in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. The temperature was measured inside the cells and was maintained within ±0.02°. The mixing techniques for fast reactions have been described previously.[10] Since the concentration of 1 was kept well below that of the hydroxide ion, good pseudo-first-order kinetics were observed for the attainment of the equilibrium for the formation of 2a. The decomposition of solid 2b was initiated by injecting a freshly prepared concentrated solution of 2b in dioxane–methanol (50/50 v/v) into a thermostated solution of methanol. In all cases the final concentration of dioxane was 1 vol %. An

increase in the dioxane concentration to 2 vol % had no observable effect on the rate constants.

Nitrite determinations were carried out on neutralized samples using the method of Rider and Mellon.[11] Good pseudo-first-order rate constants were obtained for the rate of nitrite appearance.

The 60-MHz pmr spectra were obtained with a Varian Associates A-60 spectrometer at ambient probe temperature, 31°. All spectra were determined on solutions in DMSO-d_6 or in DMA using tetramethylsilane (TMS) as an internal standard; chemical shifts are given on the τ scale in ppm relative to TMS (τ 10.00 ppm) and are accurate to ±0.03 ppm. Chemical shift data were taken from spectra determined at sweep widths of 500 Hz.

Results

In neutral aqueous buffered solution (pH 7.23), the absorption of *N-tert*-butyl-2,4,6-trinitrobenzamide (1) above 300 nm is negligible. At higher hydroxide ion concentrations (pH >9.0) a new absorption band, with a maximum at 430 nm, appears. This absorbance remains essentially constant over more than a decade of change in hydroxide ion concentration indicating the completion of the equilibrium (eq 1). In the concen-

$$1 + [\text{OH}^-] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2a \qquad (1)$$
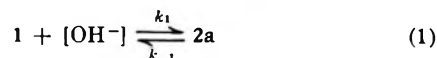
tration range of $(2.5-27.5)10^{-4}$ *M* hydroxide ion and 3×10^{-5} *M* 1, it was possible to follow the equilibrium attainment of 2a by measuring the increase in the absorbance at 430 nm [ϵ_{430} for 2a $(2.5 \pm 0.1)10^4$ cm^{-1} l. mol^{-1}] as a function of time. Under the experimental conditions, the observed first-order rate constant for the attainment of equilibrium, k_{obsd}, is given by

$$k_{obsd} = k_1[\text{OH}^-] + k_{-1} \qquad (2)$$

where k_1 is the second-order rate constant for the formation of 2a and k_{-1} is the first-order rate constant for its decomposition.[1,9,10] Table I contains the data for the

TABLE I

INTERACTION OF *N-tert*-BUTYL-2,4,6-TRINITROBENZAMIDE (1)
(*ca.* 3×10^{-5} *M*) WITH HYDROXIDE ION IN AQUEOUS SOLUTION

Temp, °C	$10^4[\text{OH}^-]$, M^a	$10^2 k_{obsd}$, sec^{-1}	k_1, M^{-1} sec$^{-1\,b}$	$10^2 k_{-1}$, sec$^{-1\,c}$
15.20	0.00		9.20	0.57
	2.50	0.75		
	4.30	0.85		
	4.90	0.94		
	10.50	1.25		
	17.30	1.75		
	20.20	2.00		
	26.90	2.40		
	35.40	3.01		
25.00	0.00		17.6	1.56
	4.30	2.37		
	6.30	2.65		
	8.40	3.05		
	14.90	4.25		
	17.70	4.70		
	27.50	6.35		

^{a} 1.0×10^{-2} *M* $Na_2B_4O_7$ or Na_2HPO_4 buffers. ^{b} Obtained from the slope of k_{obsd} *vs.* [OH$^-$], *M*. ^{c} Obtained from the intercept of the plot of k_{obsd} *vs.* [OH$^-$], *M*.

attainment of equilibrium for the formation of 2a at 15.20 and 25.00° at different hydroxide ion concentrations. Good linear plots of k_{obsd} *vs.* [OH$^-$] were obtained at both temperatures from which values for

(5) W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *J. Org. Chem.,* **32**, 2506 (1967).

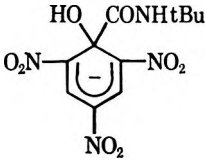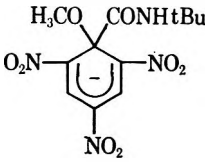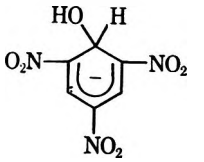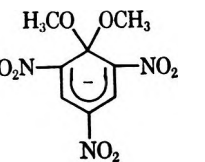(6) Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(7) As in the case of other crystalline Meisenheimer complexes,[1,8,9] the carbon and hydrogen analyses are low possibly due to the loss of methanol or ethanol during analysis or the presence of carbonate in the ash.

(8) E. Bergman, N. R. McFarlane, and J. J. K. Boulton, *Chem. Commun.,* 511 (1970).

(9) E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *J. Org. Chem.,* **35**, 287 (1970).

(10) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *ibid.,* **34**, 689 (1969).

(11) B. F. Rider and M. G. Mellon, *Anal. Chem.,* **18**, 96 (1946).

TABLE II

KINETIC AND THERMODYNAMIC PARAMETERS FOR MEISENHEIMER COMPLEXES AT 25.00°

	2a	**2b**	**3^a**	**4^b**
	in H$_2$O	in MeOH	in H$_2$O	in MeOH
k_1, l. mol^{-1} sec^{-1}	17.6	1.13 × 10^{3c}	37.5	17.3
k_{-1}, sec^{-1}	0.0156	0.46	9.8	1.0 × 10^{-3}
K, l. mol^{-1}	1130^d	548^e	3.7	17,000
	1240^e	520^f		
	1220^f			
$\Delta H_1{}^{\ddagger}$, kcal mol^{-1}	11.0 ± 1.0		15.6 ± 0.8	12.9 ± 1.0
$\Delta S_1{}^{\ddagger}$, eu	−15.6 ± 3.0		1.1 ± 2.7	−9.4 ± 3.4
$\Delta H_{-1}{}^{\ddagger}$, kcal mol^{-1}	19.4 ± 1.0		7.3 ± 0.8	18.4 ± 1.0
$\Delta S_{-1}{}^{\ddagger}$, eu	2.6 ± 3.0		−29.4 ± 2.7	−4.8 ± 3.4

^{a} Reference 17. ^{b} Reference 10. ^{c} Estimated value; see Results. ^{d} Obtained from eq 2. ^{e} Obtained from eq 8. ^{f} Obtained from eq 3.
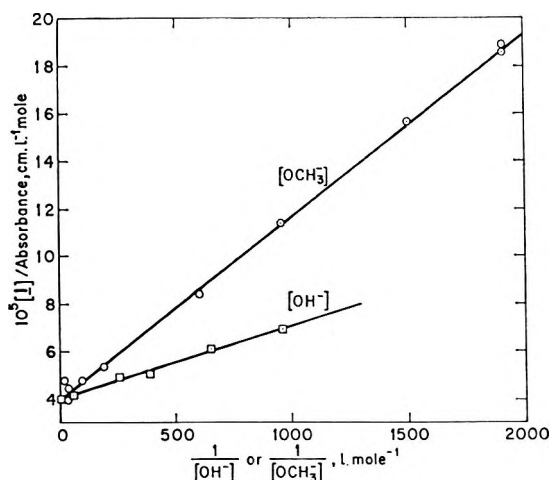
Figure 1.—Benesi–Hildebrand plots for the interaction of methoxide ion with 1 in methanol and for that of hydroxide ion with 1 in water at 25.00°.

k_1 and k_{-1} were calculated and are also given in Table I. Enthalpies and entropies of activation of these processes are given in Table II.

As the hydroxide ion concentration is increased above 10^{-1} M, the absorbance increases somewhat and the absorption band exhibits a bathochromic shift until it reaches 450 nm at 1.0 M NaOH.

The absorption spectra of 1 in methanol is similar to that in water, and in methanolic methoxide solutions it resembles that in aqueous solutions of sodium hydroxide with an absorption maximum at 430 nm.

Using the obtained absolute absorbances and the Benesi–Hildebrand equation[12]

$$\frac{[1]}{A} = \frac{1}{\epsilon} + \frac{1}{K\epsilon([OH^-] \text{ or } [OCH_3^-])} \tag{3}$$

where A is the absorbance in a 1.0-cm cell, ϵ is the molar extinction coefficient, and K is the equilibrium constant ($K = k_1/k_{-1}$), good linear relationships were obtained on plotting [1]/A against 1/[OH$^-$] or 1/[OCH$_3{}^-$] (Figure 1). The obtained equilibrium constants are given in Table II.

(12) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).

Attempts to follow the attainment of the equilibrium for the formation of 2b were unsuccessful. Even at the lowest methoxide ion concentration the reaction was found to be too rapid to measure by our techniques. The equilibrium constant could be obtained, however, by the use of eq 3 (Table II). The decomposition of isolated solid 2b in methanol at 25.00° gave k_{-1} = 0.46 sec^{-1} (mean of three determinations) which, with the value of $K_{OCH_3^-}$ = 520 l. mol^{-1} sec^{-1}, allows the estimation of k_1 to be 1.13 × 10^3 l. mol^{-1} sec^{-1}.

The observed first-order rate constants for the appearance of nitrite ion, $k_\psi{}^{NO_2^-}$, in methanol and in water are given in Table III. At infinity time the amount of nitrite ion formed ranged from 60 to 90% with respect to 1.

TABLE III

PSEUDO-FIRST-ORDER CONSTANTS FOR THE APPEARANCE OF NITRITE ION ($k_\psi{}^{NO_2^-}$) AT 25.00° ^{a}

In Methanol

10^4[NaOCH$_3$], M	10$^5 k_\psi{}^{NO_2^-}$, sec^{-1}
5.30	1.49
8.82	2.30
10.64	2.61
17.60	3.22
35.20	4.44
48.90	4.16
88.20	5.75

In Water

10^4[OH$^-$], M	10$^5 k_\psi{}^{NO_2^-}$, sec^{-1}
0.637^b	1.03
1.45^b	2.25
2.35^b	2.93
4.58^b	6.19
123.0^c	14.20

^{a} [1] ≃ 4 × 10^{-5} M. ^{b} 1.0 × 10^{-2} M Na$_2$B$_4$O$_7$ buffer. ^{c} 1.0 × 10^{-2} Na$_2$HPO$_4$ buffer.

The amide 1 has been shown to be stable to hydrolysis under the conditions used in these experiments and the product of the reaction of methoxide ions with 1 was previously established to be *N*-*tert*-butyl-2-methoxy-4,6-dinitrobenzamide.[4]

The pmr parameters for 1, 2a, 2b, and 2c are collected in Table IV.

TABLE IV

PMR SPECTRA OF N-*tert*-BUTYL-2,4,6-TRINITROBENZAMIDE AND ITS MEISENHEIMER COMPLEXES

	DMSO-d_8	DMA	DMSO-d_6	DMSO-d_6	DMA	DMSO-d_8
	1		**2a**	**2b**[a]		**2c**
$\tau_{C(CH_3)_3}$	8.65	8.59	8.71	8.72 (8.72)	(8.60)	8.71
τ_{NH}	1.28	1.19	2.82	3.10	(3.12)	3.06
$\tau_{H-3,H-}$	0.93	0.83	1.55	1.38 (1.36)	(1.28)	1.39
τ_{OCH_3}				7.13 (7.13)		
τ_{OH}			3.62			
$\tau_{OCH_2CH_3}$[b]						6.98
$\tau_{OCH_2CH_3}$[c]						8.98

[a] Values in parenthesis have been obtained in the *in situ* generation of **2b** by the dropwise addition of 5.05 M potassium methoxide in methanol to a solution of **1** in the indicated solvent.   [b] OCH_2CH_3.   [c] OCH_2CH_3.

Discussion

The interaction of hydroxide ion with N-*tert*-butyl-2,4,6-trinitrobenzamide (**1**) in aqueous solution results in the equilibrium formation of the hydroxyl adduct of **1** (**2a**). The structure of this adduct has been inferred from its absorption spectra and has been established unequivocally from the proton magnetic resonance spectra of the *in situ* generated and isolated complexes **2a** (*vide infra*) and elemental analysis of the isolated complex **2a**. It is of interest to consider the requirements for Meisenheimer complex formation in aqueous solutions. No detectable complex formation has been observed in the interaction of hydroxide ions with several picryl alkyl and aryl ethers,[13] picryl chloride,[13] and picryl fluoride[13] or with 1,2,4,5-tetranitrobenzene[14] in aqueous solutions. 1,3,5-Tri-[15] and 1,2,3,5-tetranitrobenzene[14] and 1-(β-hydroxyethoxy)-2,4,6-trinitrobenzene,[16] on the other hand, readily form cyclohexadienylide ions, Meisenheimer complexes, in aqueous solutions with equilibrium constants in the range of 3–10^5 1. mol^{-1}.[16] It appears, therefore, that steric factors in addition to inductive and resonance contributions affect the position of initial attack as well as the stability of the transient intermediate complex.

The observed pseudo-first-order rate constant for nitrite ion appearance is

$$k_\psi^{NO_2^-} = k_2[\textbf{2a}] \tag{4}$$

At time t the total amount of **1** is given by

$$[\textbf{1}]_{total} = [\textbf{1}]_{free} + [\textbf{2a}] \tag{5}$$

and the equilibrium constant for complex formation is expressed as

$$K = \frac{[\textbf{2a}]}{([\textbf{1}]_{total} - [\textbf{2a}])[OR^-]} \tag{6}$$

(13) J. Murto, *Acta Chem. Scand.*, **20**, 310 (1966).
(14) M. R. Crampton and M. El Ghariani, *J. Chem. Soc. B*, 391 (1970).
(15) V. Gold and C. Rochester, *J. Chem. Soc.*, 1710 (1964).
(16) J. Murto, *Suom. Kemistilehti B*, **38**, 255 (1965).
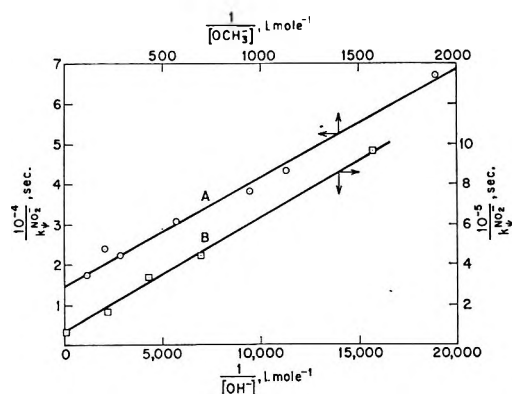
Figure 2.—(A) Plot of $10^{-4}/k_\psi^{NO_2^-}$ against $1/[NaOCH_3]$ in methanol at 25.00°.   (B) Plot of $10^{-5}/k_\psi^{NO_2^-}$ against $1/[OH^-]$ in water at 25.00°.

where R = H or CH_3. Since the nitrite ion appearance obeys pseudo-first-order kinetics, *i.e.*, $[\textbf{1}]_{total}$ < $[OR^-]$, combination of eq 4, 5, and 6 leads to

$$k_\psi^{NO_2^-} = \frac{k_2 K [OR^-]}{1 + K[OR^-]} \tag{7}$$

Inversion of eq 7 gives

$$\frac{1}{k_\psi^{NO_2^-}} = \frac{1}{k_2} + \frac{1}{k_2 K}\frac{1}{[OR^-]} \tag{8}$$

according to which a plot of $1/k_\psi^{NO_2^-}$ *vs.* $1/[OR^-]$ should give a straight line whose slope is $1/k_2 K$ and intercept is $1/k_2$. The observed linear relationships (Figure 2) support the postulated mechanism and indicate, not unexpectedly, that the liberated nitrite ions do not participate in the formation of complex **2a**. From the intercept of the plot for the hydroxide ion reaction (Figure 2), k_2 has been calculated to be 1.43 × 10^{-5} sec^{-1}. From this value and the slope of the plot (eq 8 and Figure 2), K has been calculated to be 1240 1. mol^{-1} (Table II). The excellent agreement among the three independently determined equilibrium constants is very gratifying.

Qualitatively, the reaction of methoxide ion with **1** is similar to that of hydroxide ion in that the equilibrium

formation of a complex is followed by nitrite ion elimination. Furthermore, eq 8 is obeyed quantitatively (Figure 2) and the equilibrium constant obtained from it agrees well with that determined by means of the Benesi–Hildebrand equation (Table II). Not unexpectedly, however, there are significant quantitative differences between the reactivities of the two lyate ions in water and in methanol. While the equilibrium constant for the formation of 2b is only a factor of 2 smaller than that for 2a, the rate constant for complex formation (k_1) is a factor of 100 greater for the former than for the latter.

It is instructive to compare the kinetic and thermodynamic parameters for 2a and 2b with those obtained for the hydroxy complex of 1,3,5-trinitrobenzene (3)[17] and for the methoxyl complex of 2,4,6-trinitroanisole (4)[10] (Table II). The 300-fold greater value for K_{2a} relative to K_3 is reflected mainly in the difference between their decomposition rates, k_{-1} for 2a/k_{-1} for 3 = 65 whereas k_1 for 2a/k_1 for 3 = 0.47, suggesting that the stability of 2a is primarily the consequence of the greater relief of steric strain by rehydridization of C-1 from sp² to sp³ in the case of 2a. The low enthalpy of activation required for the formation of 2a, $\Delta H_1^{\ddagger}$, is contrasted with the considerable energy required for its decomposition, $\Delta H_{-1}^{\ddagger}$ (Table II). Both steric and solvation effects must contribute to the extremely rapid formation and fast decomposition of 2b; however, the data does not allow a quantitative comparison of the activation parameters for 2b and 4 at the present time.

The production of nitrite ions from 1 and lyate ions most probably involves a species such as 5. Structures similar to 5 have been postulated in the interaction

5
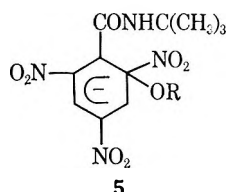
of lyate ions with 1,3,5-trinitrobenzene,[15] 3,5-dinitrobenzonitrile,[18] and 1,2,3,5- and 1,2,4,5-tetranitrobenzenes.[14] No nmr or spectrophotometric evidence has been obtained for the accumulation of 5. 5 is, therefore, unlikely to be an intermediate but rather a transition state through which the products are formed. The rate-determining step in the liberation of nitrite ion is the formation of complex 5, or a related structure, which rapidly loses nitrite ion. An analogous mechanism has been suggested for the reaction of hydroxide ion with 1,3,5-trinitrobenzene[15] and 1,2,3,5- and 1,2,4,5-tetranitrobenzene.[14] Lack of detection of 5 by usual kinetic and pmr spectroscopic techniques substantiates this postulation.

The rate constant for the formation of nitrite ions, k_2, has been calculated to be 1.43×10^{-5} sec^{-1} and 6.7×10^{-5} sec^{-1} for 2a and 2b, respectively. The rate

constant for product formation from 3[19] has been found to be some three orders of magnitude greater than those for 2a and 2b. These data, once again, reflect the differences in the equilibrium constants for the formation of 2a, 2b, and 3.

We continue to use proton magnetic spectroscopic techniques to confirm the postulated structure of complexes 2a, 2b, and 2c and to investigate the existence of other transient intermediates. No pmr data has previously been reported for Meisenheimer complexes of benzamides or other amido-substituted aromatic compounds.

The pmr parameters for the isolated complexes 2a, 2b, and 2c (Table IV) are completely consistent with the postulated structures, i.e., 1,1 complexes, and eliminate the possibility of alternative complexes such as those arising from attack at C-3, abstraction of the amido proton, or charge–transfer interactions. The pmr criteria for the structure of Meisenheimer complexes have been discussed previously[1,2,5,9,10,20] and therefore are not reiterated here in detail. Rehybridization of C-1 from sp² in 1 to sp³ in 2a, 2b, and 2c results in an upfield shift of the aromatic resonances ($\Delta\delta$ 0.62, 0.45, and 0.46 ppm, respectively) comparable to those found for 2,4,6-trinitroanisole[10] ($\Delta\delta$ 0.40), 4-cyano-2,6-dinitroanisole[10] ($\Delta\delta$ 0.65), 2,6-dicyano-4-nitroanisole[9] ($\Delta\delta$ 1.10), and diethyl 2,4,6-tricyanophenylphosphonate[21] ($\Delta\delta$ 0.38). The amido proton is also strongly shielded in complexes 2a, 2b, and 2c relative to the parent benzamide 1 ($\Delta\delta$ 1.54–1.82) primarily reflecting the increase in charge density in the π system.

In the case of several activated aromatic systems, initial attack of the nucleophile has been found to occur at C-3 forming a thermodynamically unstable 1,3 complex.[1,2,9,10,22] In order to investigate the existence of any fairly stable transients in the interaction of methoxide ions with 1, we examined the formation of 2b *in situ* in DMSO-d_6 and DMA. In both solvents[23] no additional resonances were observed and, therefore, on the time scale necessitated by pmr techniques,[1,9,10] the 1,3 complex of 1 or other transients are either not formed or are not detectable.

Registry No.—1, 3099-54-5; 2a, 28433-52-5; 2b, 28433-53-6; 2c, 28433-54-7.

(17) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 4682 (1970).

(18) C. E. Griffin, E. J. Fendler, N. L. Arthur, and J. H. Fendler, to be published.

(19) R. Gaboriaud, R. Schaal, and P. Letellier, *Bull. Soc. Chim. Fr.*, 2683 (1969).

(20) J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 977 (1968); E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *ibid.*, **33**, 4141 (1968).

(21) R. J. Minasz, E. J. Fendler, and C. E. Griffin, unpublished results.

(22) J. W. Larsen, J. H. Fendler, and E. J. Fendler, *J. Amer. Chem. Soc.*, **91**, 5903 (1969).

(23) DMA has been found to appreciably enhance the stabilities of 1,3-dimethoxycyclohexadienylide ions as compared to those in DMSO.[24]

(24) J. W. Larsen, E. J. Fendler, and J. H. Fendler, unpublished results

The Nature of the Carbonium Ion. VI. The anti-7-Norbornenyl and 7-Norbornadienyl Cations from Thiocyanate Isomerizations

Langley A. Spurlock[*1] and Yoshiko Mikuriya[2]

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 18122

Received August 5, 1970

The thermal isomerizations of anti-7-norbornenyl (7) and 7-norbornadienyl (11) thiocyanates were investigated in various polar aprotic solvents. Both compounds gave isothiocyanates of retained structure only (8 and 12, respectively), despite special attention to the isolation of tricyclic products. Rates of isomerization were measured and activation parameters calculated. The reactions used in preparation of 7 and 11 and the effects of potassium thiocyanate, lithium perchlorate, and tetramethylammonium azide on the isomerizations were utilized to explain the unexpected inability of the thiocyanate ion to give tricyclic products from the cationic intermediates.

In this paper, we describe the results from studies of ionization at the C_7 positions of norbornyl and norbornadienyl skeleta[3] utilizing the thiocyanate–isothiocyanate isomerization technique[4] for the examination of ion pairs. In other papers of this series[5] we have shown that only those primary and secondary sites which receive appreciable intramolecular assistance from an internal nucleophile (including resonance stabilization) are capable of supporting the isomerization of alkyl thiocyanates. As the anti C_7-substituted norbornenyl and the C_7-substituted norbornadienyl derivatives seemed quite qualified to meet this criterion,[6] they were logical choices for further study of ion-pair behavior and the influences of structure on thiocyanate reactivity.

It was assumed that the very stable "bishomocyclopropenyl" cations, 2 and 5, which contribute to solvolytic reactivities of 1 OTs[7] and 4 Cl,[8] respectively, would contribute similarly to isomerization. These compounds were interesting also because of more work by Winstein[9a] and by Tufariello[9b] which showed that upon neutral hydrolyses of anti-7-norbornenyl p-toluenesulfonate or benzoates 1 (X = OTs, OPNB, OPMB) there is quantitative conversion via ion 2 to alcohol of retained structure with no indication of endo-tricyclo[3.2.0.0²,⁷]heptan-6-ol (3 OH) found. This occurred despite the stability of the latter to
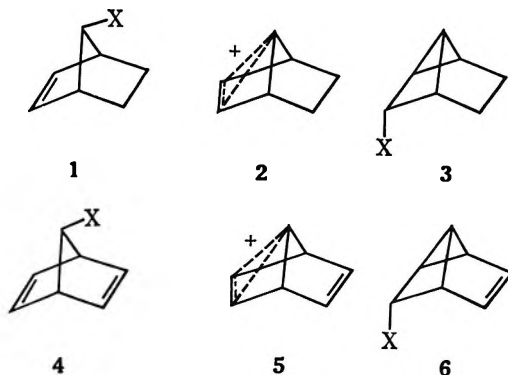
reaction conditions; thus it was concluded that 1 OH must be the product of kinetic control. Since the corresponding thiocyanate isomerization must proceed through ion pairs with cations resembling 2, it was of interest to determine if the ions of isomerization showed similar behavior with regard to structural preference. Whether stable tricyclic products could be obtained by this method was not clear; however, it did seem possible on the bases of the high nucleophilicity of thiocyanate ion and reports[9,10] which indicated that with sufficiently strong nucleophiles cation 2 could be attacked appreciably at the endo C_2–C_3 face as well as at C_7.

Most of these same questions were also pertinent to the 7-norbornadienyl analog since cation 5 had been shown[10] to undergo similar behavior in the presence of very good nucleophiles. We therefore synthesized 7-norbornadienyl thiocyanate (11) and isothiocyanate (12), as well anti-7-norbornenyl thiocyanate (7) and isothiocyanate (8), in order to explore these problems.

Results

anti-7-Norbornenyl thiocyanate (7) and isothiocyanate (8) were prepared from the known[7] anti-7-norbornenyl p-toluenesulfonate (1 OTs). Treatment of the sulfonate ester with potassium thiocyanate in dimethylformamide or sulfolane gave a mixture consisting of 7 and 8 in a 75:25 ratio[11] (Scheme I). The separation of this mixture by chromatography on silica

(1) Department of Chemistry, Brown University, Providence, R. I. 02912.

(2) From the thesis submitted by Y. Mikuriya in fulfillment of the requirements for the M.S. Degree, Temple University, 1969.

(3) For a review of the pertinent ionic reactions of these skeleta, see J. A. Berson in "Molecular Rearrangements," part 1, P. de Mayo, Ed., Interscience, New York, N. Y., Chapter 3.

(4) For recent reviews, see L. A. Spurlock and T. E. Parks in "Mechanisms of Reactions of Sulfur Compounds," Vol. 3, N. Kharasch, Ed., Intra-Science Research Foundation, Santa Monica, Calif.; A. Fava in "Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Oxford, England, p 73.

(5) (a) L. A. Spurlock and W. G. Cox, J. Amer. Chem. Soc., 91, 2961 (1969); (b) L. A. Spurlock and T. E. Parks, ibid., 92, 1279 (1970); (c) L. A. Spurlock and R. J. Schultz, ibid., 92, 6302 (1970); (d) L. A. Spurlock and W. G. Cox, ibid., 93, 146 (1971).

(6) The syn-7-norbornenyl position was briefly considered for this study. It was observed, however, that the corresponding p-toluenesulfonate solvolyzed 54,000 times slower than cyclohexyl p-toluenesulfonate. Since cyclohexyl thiocyanate could not be made to isomerize, presumably due to insufficient stability of the cation, there was negligible likelihood that syn-7-norbornenyl thiocyanate would behave differently. Isomerization of this compound was therefore not attempted.

(7) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, J. Amer. Chem. Soc., 77, 4183 (1955); S. Winstein and M. Shatavsky, ibid., 78, 592 (1956).

(8) S. Winstein and C. Ordronneau, ibid., 82, 2084 (1960).

(9) (a) A. Diaz, M. Brookhart, and S. Winstein, ibid., 88, 3133 (1966); (b) J. J. Tufariello, T. F. Mich, and R. J. Lorence, Chem. Commun., 1202 (1967); (c) J. Lhomme, A. Diaz, and S. Winstein, J. Amer. Chem. Soc., 91, 1548 (1969); (d) J. J. Tufariello and R. J. Lorence, ibid., 91, 1546 (1969).

(10) S. Winstein, A. Lewin, and K. Pande, ibid., 85, 2324 (1963); H. C. Brown and H. M. Bell, ibid., 85, 2324 (1963); H. Tanida, T. Tsuji, and T. Irie, ibid., 88, 864 (1966); H. Tanida and T. Hata, J. Org. Chem., 30, 977 (1965).

(11) The fact that this mixture was obtained constitutes a support of structural assignment in itself since a displacement reaction, giving syn product, would be expected to produce almost exclusively thiocyanate product. See A. Fava, A. Iliceto, A. Ceccon, and P. Koch, J. Amer. Chem. Soc., 87, 1045 (1965).

SCHEME I
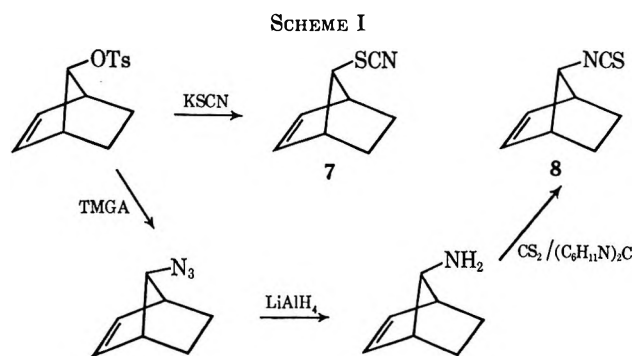
gel gave pure **7**, whose infrared spectrum showed a sharp absorption at 2150 cm^{-1} characteristic of the alkyl thiocyanate group, and pure **8**, which showed the broad intense absorption between 2160 and 2070 cm^{-1} typical of isothiocyanates. Addition of *n*-butylamine to the crude mixture of **7** and **8** also gave pure thiocyanate after distillation, while **8** reacted to give the crystalline 1-*n*-butyl-3-(*anti*-7-norbornenyl)thiourea. Analyses by nmr and gc of the crude mixture, purified **7** and **8**, and the thiourea indicated that neither tricyclic compound **9** or **10** had been formed. For further confirmation of structure, 1 OTs was allowed to react with tetramethylguanidinium azide.[12] The resultant *anti*-7-norbornenyl azide was then reduced to the corresponding amine which was subjected to a conven-

tional[5a] preparation of isothiocyanates (Scheme I). The product obtained and its *n*-butylthiourea derivative were identical with the minor component and its derivative from the treatment of 1 OTs with thiocyanate ion. Interestingly, despite attempts to provide as low temperatures as were feasible for the preparative reactions, and the employing of various excesses (tenfold maximum) of the nucleophiles, SCN$^-$ and N$_3^-$, no appearances of tricyclic products were detectable. The compositions of **7** and **8** were further authenticated by elemental analyses.

A mixture of 7-norbornadienyl thiocyanate (**11**) and isothiocyanate (**12**) was obtained by the reaction of potassium thiocyanate with 7-norbornadienyl chloride[8]
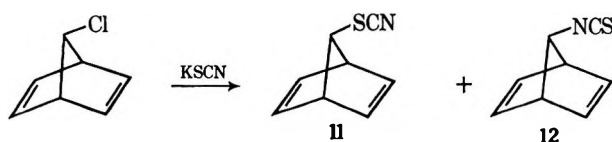
in acetone. Gc and nmr analyses revealed a 95:5 ratio of thiocyanate to isothiocyanate. These rather unstable compounds (a sample of the crude mixture turned to a semisolid white polymer after 1 week at −20°) could be separated only by the aforementioned amine treatment. Pure thiocyanate **11** was obtained in this fashion along with crystalline 1-*tert*-butyl-3-(7-norbornadienyl)thiourea (from *tert*-butylamine). Due to the instability of 7-norbornadienyl azide, an

authentic sample of isothiocyanate **12**, free of **11**, was obtainable only by heating **11** at 80° for several hours in acetonitrile. This material and its *tert*-butylthiourea derivative were identical by infrared, nmr, and gc analyses to the product from 7-norbornadienyl chloride and its thiourea derivative, respectively. The proper elemental analyses were also obtained for these compounds. As before, no tricyclic compounds (such as **13** or **14**) were to be found.
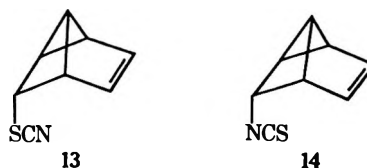
The isomerizations of **7** were carried out in sulfolane dimethylformamide, acetonitrile, and tetramethylurea. Effects of salts on isomerization were studied by the addition of potassium thiocyanate or lithium perchlorate to solutions of **7**, in sulfolane only, since it was apparent that this was the most efficient solvent for isomerization and gave the cleanest results. Material recovery from all solvents was never less than 95%. Identification of isomerization products and measurements of remaining thiocyanate **7** at various time intervals were carried out by nmr and by gc. The identity of the single isomerization product with **8** was confirmed by a comparison of nmr spectra and gc retention times on three columns of different liquid phases.

Isomerizations of 7-norbornadienyl thiocyanate (**11**) could be reliably effected only in acetonitrile and at lower temperatures than used for **7** due to the extreme reactivity and limited stability of the diene–thiocyanate. Potassium thiocyanate was the only salt utilized for study of the effects of added ionic substances. Even at the lowest temperature reasonable for the isomerization, the only identifiable product was the isothiocyanate of retained structure **12**. The methods of analysis were analogous to those employed for isomerizations of **7**.

Since for both **7** and **11** no tricyclic products were detected, the possibility of an equilibration process was suspected. This had precedent as it had been observed[13] that an equilibrium exists between furfuryl thiocyanate and isothiocyanate in these same solvents. Because the efficiency of this equilibration was apparently related to the extreme stability of the furfuryl cation, it seemed possible that the stabilities of the cations from **7** and **11** might also lead to this result. The isomerization of **7** was therefore carefully followed at 80 and 110° by nmr analyses of aliquots taken at short intervals. Ultimately the spectra showed the complete disappearance of **7** and only the appearance of **8** in every case. Gc examinations confirmed this result to the limits of detectability (<0.1%). Similar experiments beginning with pure isothiocyanate **8** showed neither the additional presence of **7** nor any other species after 2 days. While this does not rule out the ionization of **8**, it does confirm the fact that like most isomerizing alkyl systems[2] the equilibrium position lies far to the side of the isothiocyanate. A further examination of the isothiocyanate ionization

(12) A. J. Papa, *J. Org. Chem.*, **31**, 1426 (1966).

(13) L. A. Spurlock and R. G. Fayter, *ibid.*, **34**, 4035 (1969).

question was effected by adding five- and tenfold molar excesses of tetraethylammonium azide, first to sulfolane solutions of **7** (and **11**) and then to solutions of **8**. After heating at 80 or 110°, much tar was formed in the thiocyanate solutions but nearly none in the isothiocyanate solutions. Gc analysis of the products from the thiocyanates revealed only the presence of the corresponding azides, while **8** was solely detectable in the isothiocyanate samples. An attempt to improve the quantitative aspects of this observation by utilization of tetraethylammonium bromide failed due to the inability of bromide ion to compete successfully with thiocyanate ion for the intermediate cations. On the basis of the azide results, we therefore concluded that ionization of **8** probably does not occur to any appreciable extent and is therefore unimportant to the overall reaction.

The first-order rate constants for isomerizations of **7** and **11**, followed by gc, were determined graphically from plots of log [relative mole fraction RSCN] *vs.* time. Activation parameters were calculated where appropriate. The results, which are the averages of at least two runs, are tabulated in Table I. The reactions

TABLE I
RATE DATA FOR ISOMERIZATIONS OF 7 AND 11

Solvent	Salt, M	T, °C	$10^5 k$, sec^{-1}	$\Delta H^{\ddagger}$, kcal/ mol	$\Delta S^{\ddagger}$, eu
		7			
Sulfolane		81.0	0.44 ± 0.01		
		111.0	8.45 ± 0.25	26	−8
	KSCN (0.2)	110.0	9.68 ± 0.36		
	LiClO₄ (0.1)	110.0	13.2 ± 0.05		
CH₃CN		111.0	2.32 ± 0.02	26	−13
		130.5	13.0 ± 0.2		
DMF[a]		110.0	3.94 ± 0.20		
TMU[a]		110.0	0.24 ± 0.02		
		11			
CH₃CN		59.2	1.16 ± 0.02		
		81.5	12.5 ± 0.2		
		110.0	185[b]	25	−5[b]
	KSCN (0.5)	79.0	16.7 ± 0.2		

[a] DMF = dimethylformamide; TMU = tetramethylurea.
[b] Extrapolated from data at other temperatures.

were followed to 50–70% completion depending on the rates of decomposition by starting material and product in the particular solvent.

Discussion

The very facile isomerizations of **7** and **11**, and the strong solvent dependence of the rates, bore out our original hopes that these compounds would isomerize *via* the ionic routes typical[4,5] of many other nonallylic alkyl thiocyanates. These are in fact the most rapidly isomerizing alkyl thiocyanates which we have encountered and, excepting some substituted benzhydryl[14] isomerizations, are the most reactive ionic thiocyanate conversions yet measured. This strongly implies that the ion pairs formed from **7** and **11** may resemble at least **15a** and **16a**, respectively (Schemes II and III), if

(14) The rate of isomerization of **11** at 81.5° is about four times greater than that reported for benzhydryl thiocyanate at 70° in the same solvent: A. Iliceto, A. Fava, U. Mazzucato, and O. Rosetto, *J. Amer. Chem. Soc.*, **83**, 2729 (1961).

SCHEME II

SCHEME III
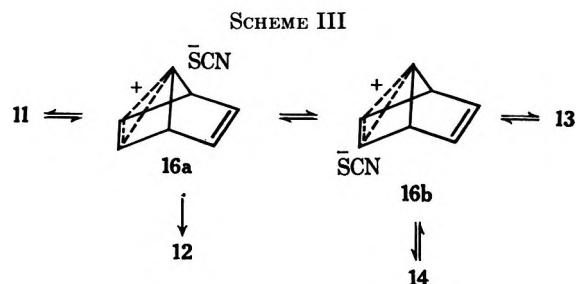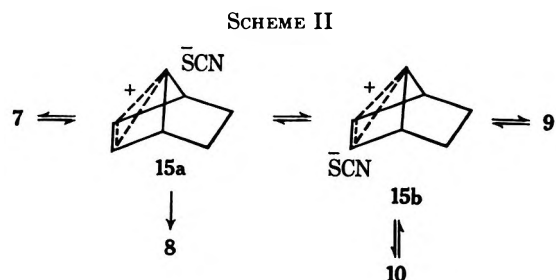
the analogies to solvolytic intermediates and to the norbornyl isomerizations[5a,b] hold. Even the initially surprising compression of the rates of these thiocyanates (k_7/k_{11} = 80), when compared with solvolytic results from the chlorides (k_{1Cl}/k_{4Cl} = 1000), becomes understandable if one considers that the transition state for isomerization probably involves tighter bonding between carbonium ion and leaving group.[4] The one plausible alternate pathway to isomerization, direct displacement by thiocyanate ion, can be eliminated by failure, even in large excesses of the ion, to find any syn-7-norbornenyl products of back-side attack on **7**. Two problems therefore present themselves: (1) to what degree of dissociation the ions proceed, and (2) the reasons for the absence of tricyclic products.

The formation of anti-7-norbornenyl azide and 7-norbornadienyl azide from treatment of isomerizing solutions of **7** and **11** with large azide ion excesses showed some indication that dissociation past the intimate pair must take place.[15] It was unfortunate that the stabilities of the azides, and the insufficient nucleophilicity of bromide ion, did not allow quantitative estimates of this effect. Since these same problems were encountered in our studies of exo-2-norbornyl thiocyanate (**17**) and ultimately resolved by use of rather involved isotopic labeling experiments,[5b] we preferred to draw conclusions by analogies to this isomerizing system and the similarly studied[16] 4,4'-dimethylbenzhydryl thiocyanate (**18**). In the case of **7** the rate of isomerization at
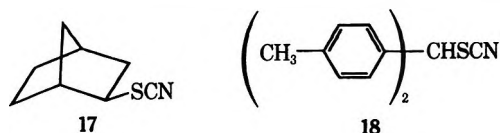
81.0° in sulfolane (Table I) is identical with that of **17** in the same solvent at 130.0° (k_1 = 0.43 × 10^{-5} sec^{-1}). Estimations, based on the amount of incorporation of ³⁵S-labeled thiocyanate ion into the product and starting

(15) Ionic strengths of these solutions were admittedly greater than those of the uncatalyzed isomerizations but were at least equivalent to those reactions where potassium thiocyanate demonstrated only minor effects on the isomerization.

(16) A. Fava, A. Iliceto, A. Ceccon, and P. Koch, *J. Amer. Chem. Soc.*, **87**, 1045 (1965).

material at this temperature and a RSCN/RNCS ratio of 2 for attack by the two ends of thiocyanate on the carbonium ion, lead to the conclusion that approximately 88% of the intermediates from **17** dissociate no further than the intimate pairs.[5b] Lacking the exchange data for **7**, but utilizing the known RSCN/RNCS = 3 value and the isomerization rate, we have assumed[17a] the rate of ionization to be about one-third higher than that for **17** and calculate[17b] that a *minimum* of 16% of the intimate ion pairs from **7** dissociate further in sulfolane at 81°. A similar treatment of **11** gives an estimate of 37% dissociation past the intimate stage during isomerization at 81.5°. These observations lend support to the notion that the failure to observe tricyclic products may be at least partially the result of thermodynamic favoring of the 7-norbornenyl and 7-norbornadienyl skeleta rather than solely the failure of ions like **15a** and **16a** to change the relative positions of nucleophile and carbonium ions to those indicated in **15b** and **16b**.

The most conclusive evidence in this behalf is the inability to observe tricyclic products from the preparative reactions with thiocyanate ion and **1** OTs or **4** Cl. As great care was taken to preserve the structural integrity of the products, and conditions were utilized where a lesser nucleophile (CN⁻) does lead to tricyclic materials,[10] it seems safe to conclude that these must revert to norbornenyl and norbornadienyl compounds very rapidly.[18] Support for this comes from recent reports[9c,d] that the tricyclic-substituted benzoate esters **3** OPNB and **3** OPMB solvolyze 10^{10}–10^{12} times faster than their *anti*-7-norbornenyl counterparts. The lack of tricyclic products in the isomerization mixtures may then be the result of conditions too drastic to isolate them.

The nature of cationic mobility relative to the thiocyanate ion remains only partly defined by these observations due to the extreme instabilities of the tricyclic skeleta relative to the bicyclic ones. As a consequence, in the succeeding paper[5d] of this series we turned to the 5-norbornenyl cations where the situation is clarified by the thermodynamic favoring of the nortricyclyl skeleton over its bicyclic counterpart.

Experimental Section[19]

anti-7-Norbornenyl *p*-Toluenesulfonate (**1** OTs).—To a solution of 1.10 g (0.01 mol) of *anti*-7-norborneol[20] (**1** OH) in 2.5 ml

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(17) (a) The relationship[5b] used to estimate the ionization rate (k_i) was $k_i = (k_S + k_N/k_N)k_t$. (b) Assuming also that the ionization rate and exchange rate are related similarly ($k_i \approx k_{ex}$) for **7** and **17** (as they are for **17** and **18**) the following equation, employing the isomerization rate (k_t) and RSCN–RNCS ratio (k_S/k_N), was used for calculation: $k_{ex}k_N/k_t (k_S + k_N)$ = fraction of dissociated ion pairs.

(18) The isomerization rates of the isothiocyanates, **10** and **14**, must indeed be spectacular since they clearly would exceed by many powers of ten that of furfuryl isothiocyanate, the only other ionically isomerizing isothiocyanate on which has been observed any measurable rate.[13]

(19) Melting points and boiling points were uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137B using sodium chloride optics. Nmr determinations were carried out on a Varian Associates A-60A spectrometer. An F & M gas chromatograph (Model 700) was employed for analyses and kinetics using 2 ft × 0.25 in. columns. Packing materials were 15% diethylene glycol succinate on 70–80 mesh Chromosorb W (LAC 728) and 20% fluorosilicone (FS-1265) on 70–80 mesh Chromosorb W (QF-1). Organic solvents were of ACS reagent grade unless otherwise stated. Sulfolane was treated with potassium permanganate and distilled under vacuum. Dimethylformamide was distilled from calcium hydride and acetone from potassium permanganate. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

(20) B. Franzus and E. I. Snyder, *J. Amer. Chem. Soc.*, **87**, 3423 (1965).

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of pyridine being stirred at 5° was added dropwise a solution of 2.80 g (0.015 mol) of *p*-toluenesulfonyl chloride in 3 ml of pyridine. During addition, the temperature of the mixture was kept between 5 and 10°. The mixture was stirred for 2 hr at 10° and then kept in the refrigerator overnight. It was poured into 30 ml of ice water and extracted with a 50% ether–pentane solution. The combined extracts were washed first with iced 10% hydrochloric acid, then saturated sodium carbonate solution, and dried over magnesium sulfate. The solvent was evaporated affording 2.51 g (95%) of pinkish white crystalline **1** OTs. The crude product was used immediately since it decomposed within a few hours at room temperature; ir (Nujol mull) 2900, 1370, 1180, 1190, 950, and 870 cm⁻¹ was obtained.

anti-7-Norbornenyl Thio- (**7**) and Isothiocyanate (**8**).—To a solution of 8.0 g (0.03 mol) of crude **1** OTs in 400 ml of distilled dimethylformamide was added 32.0 g (0.3 mol) of potassium thiocyanate. The mixture was stirred at room temperature for 65 hr. It was poured into 400 ml of water and extracted with pentane. The combined extracts were washed with water and dried over magnesium sulfate. The solvent was evaporated and the distillation of the crude product gave 3.3 g (73%) of a mixture of **7** and **8**: bp 54–60° (0.08 mm); ir (film) 3000, 2220, 2180, 2100, 1560, 1320, 750, and 710 cm⁻¹; nmr (CCl₄) τ 8.8 (multiplet), 8.1 (multiplet), 7.1 (multiplet), 4.05 (triplet). The gc analysis (LAC-728) showed a 75:25 ratio of **7** to **8**.

anti-7-Norbornenyl Thiocyanate (**7**).—The following methods were employed for the isolation of **7** from the mixture.

Method A.—To a solution of 1.85 g (0.025 mol) of *n*-butylamine dissolved in 55 ml of purified dry dioxane was added 3.31 g of the mixture of **7** and **8**. The solution was stirred at room temperature for 7 hr. It was then poured into ice water and extracted with pentane. During the extraction, *anti*-7-norbornenyl-*n*-butylthiourea precipitated out necessitating filtration before separating the layers. The combined extracts were washed with ice-cold 10% hydrochloric acid, then saturated sodium bicarbonate, and dried over magnesium sulfate. The solvent was evaporated and distillation of the crude product afforded 1.70 g of **7**: bp 28–30° (0.07 mm); ir (film) 2950, 2180, 1275, 815, and 800 cm⁻¹; nmr (CDCl₃) τ 8.8 (multiplet), 8.05 (multiplet), 7.0 (quartet), 6.6 (triplet), 3.8 (triplet).

Anal. Calcd for C₈H₉NS: C, 63.59; H, 5.96; N, 9.27. Found: C, 63.41; H, 6.23; N, 9.23.

1-(*anti*-7-Norbornenyl)-3-*n*-butylthiourea, obtained as a byproduct above, was recrystallized from ether–pentane, mp 84.0–85.0°.

Anal. Calcd for C₁₂H₂₀N₂S: C, 64.22; H, 8.98; N, 12.49. Found: C, 64.21; H, 8.82; N, 12.55.

Method B.—A 7.46-g (0.049 mol) portion of the mixture of **7** and **8** was chromatographed on 400 g of silica gel. **8** (1.47 g) was eluted with pentane and distilled: bp 75.0° (3 mm); ir (film) 2930, 2200, 2100, 790, and 775 cm⁻¹. Continued elution with ether gave 5.81 g of **7**: bp 60.0–65.0° (1.0 mm); ir (film) 2950, 2150, 1280, 815, and 805 cm⁻¹.

Tetramethylguanidinium azide was prepared by the procedure described by Papa.[12] The hygroscopic product was kept in a vacuum desiccator.

anti-7-Norbornenyl Azide.—To 15.0 g (95 mmol) of tetramethylguanidinium azide dissolved in 200 ml of chloroform was added a solution of 2.50 g (9.5 mmol) of **1** OTs in 8 ml of chloroform. Addition took place over a period of 10 min. The mixture was then stirred at room temperature for 15 min and allowed to stand for 20 hr. The solution was concentrated and 200 ml of ether was added. A precipitate formed and was removed by filtration and washed with ether. Evaporation of the filtrate yielded 1.47 g (100%) of the crude azide: ir (film) 2950, 2100, 1370, 1330, 1180 and 1190 cm⁻¹.

anti-7-Norbornenyl Amine.—To a solution of 0.84 g (0.022 mol) of lithium aluminum hydride in 40 ml of ether being stirred at room temperature was added a solution of 1.46 g (0.011 mol) of the crude azide in 20 ml of ether over a period of 30 min. The mixture was stirred at room temperature for 66 hr and then were added 0.84 ml of water followed by 2.5 ml of 15% potassium hydroxide and finally 0.84 ml of water. The precipitate was removed by filtration and washed with ether, and the combined filtrate and washings were dried over magnesium sulfate. Evaporation of the solvent afforded 0.88 g (75%) of the crude amine. A further purification was not attempted; ir (film) 3300, 2900, 1630, 1120, and 1050 cm⁻¹ was obtained.

anti-7-Norbornenyl Isothiocyanate (**8**).—To a solution of 1.68 g (8.1 mmol) of *N,N'*-dicyclohexylcarbodiimide and 3.2 ml of

carbon disulfide in 17 ml of ether was added 0.88 g (8.1 mmol) of crude amine dropwise at −10°. The mixture was stirred and the temperature was allowed to rise to 20° over a period of 3 hr. The stirring was continued for 18 hr. The mixture was then filtered and the residue was washed with ether. Evaporation of the solvent followed by distillation of the residue gave 0.31 g of **8** which was slightly contaminated with *N,N′*-dicyclohexylcarbodiimide, bp 37–80° (0.5–0.1 mm). The product was purified by gc collection (2 ft × 0.25 in. LAC 728) and further by distillation: bp 34.0° (0.08–0.06 mm); ir (film) 2900, 2160, 2070, and 775 cm⁻¹; nmr (CCl₄) τ 8.3 (multiplet), 6.9 (quartet), 6.45 (singlet), 3.6 (triplet).

Anal. Calcd for C₈H₉NS: C, 63.59; H, 5.96; N, 9.27. Found: C, 63.30; H, 6.03; N, 9.58.

7-Norbornadienyl Thio- (11) and Isothiocyanate (12).—To a solution of 10.6 g (0.084 mol) of 7-norbornadienyl chloride[8] (4 Cl) in 500 ml of dry acetone was added 86.0 g (0.88 mol) of potassium thiocyanate. The mixture was stirred at room temperature for 17 hr, then poured into ice water, and extracted with pentane. The combined extracts were washed with water and dried over magnesium sulfate; the pentane was evaporated. Distillation of the residue yielded 8.3 g (67%) of a mixture of 11 and 12, bp 58–60° (0.08 mm). Gc analysis indicated a 95:5 ratio of 11 to 12.

7-Norbornadienyl Thiocyanate (11).—Since the isolation of thiocyanate 11 from the mixture by column chromatography was not successful due to decomposition of both 11 and 12 on silica gel, the following procedure was used.

To a solution of 0.15 g (2.1 mmol) of *tert*-butylamine in 5 ml of purified dioxane was added 2.0 g (0.013 mol) of mixture. The solution was stirred at room temperature for 4 hr and work-up was similar to that employed for the isolation of *anti*-7-norbornenyl thiocyanate (7). The crude product was distilled affording 1.35 g of 11: bp 53.5–55.0° (0.07 mm); ir (film) 2950, 2140, 1300, 1240, and 800 cm⁻¹; nmr (CDCl₃) τ 6.1 (sextet), 3.25 (triplet), 3.15 (triplet).

Anal. Calcd for C₈H₇NS: C, 64.39; H, 4.73; N, 9.39. Found: C, 64.55; H, 4.67; N, 9.24.

The crude 1-(7-norbornadienyl)-3-*tert*-butylthiourea, obtained as a by-product above, was recrystallized from ether–pentane after use of decolorizing carbon giving white crystals: mp 179.5–180.0°; ir (Nujol mull) 3200, 2900, 1520, 1450, 1190, and 730 cm⁻¹.

Anal. Calcd for C₁₂H₁₈N₂S: C, 64.82; H, 8.12; N, 12.60. Found: C, 64.62; H, 8.01; N, 12.40.

7-Norbornadienyl Isothiocyanate (12).—A solution of 0.688 g (4.6 mmol) of 11 in 60 ml of acetonitrile was sealed into a Pyrex tube and heated at 80° for 7.5 hr. The tube was opened and the contents were poured into 200 ml of water. The product was extracted with pentane and the combined extracts were washed with water and dried over magnesium sulfate. The pentane was evaporated and the distillation of the crude product gave 0.375 g (55%) of 12: bp 42–44° (0.08 mm); ir (film) 2926, 2200, 2100, 1330, 1310, 1230, 1190, 1110, and 815 cm⁻¹; nmr (CDCl₃) τ 6.25 (sextet), 3.25 (triplet).

Anal. Calcd for C₈H₇NS: C, 64.82; H, 8.12; N, 12.60. Found: C, 64.91; H, 8.11; N, 12.53.

Product Studies.—Approximately 0.05 M solutions of 7 or 11 in purified sulfolane, acetonitrile, dimethylformamide, or tetramethylurea were sealed in glass ampoules under a nitrogen atmosphere and heated at constant temperatures ranging from 40 to 130° for various times. After quenching by cooling, the material was reisolated by subjecting these solutions to water and extraction with pentane, followed by drying and concentration of the extracts. Material recovery was always in excess of 95% (crude); thus the material was analyzed directly by nmr infrared, tlc (silica gel support with cyclohexane as liquid phase), and gc (see kinetic studies section for conditions and retention times). Both starting material, thiocyanate, and product, isothiocyanate, were always homogeneous to those methods of analysis.

Isomerizations in the Presence of Salts.—Product studies were carried out as previously described except the 0.05 M solutions of 7, 8, or 11 were also 0.1–0.5 M in potassium thiocyanate, lithium perchlorate, or tetraethylammonium azide. Material recovery was the same as before with the exception of the azide solutions of 7 and 11 where a pentane-insoluble, ether-soluble brown tar was also isolated. The pentane extracts in these cases (10–15% of the original mixture) consisted only of the corresponding alkyl azide by gc analysis.

Kinetic Studies.—The following methods were employed for analysis.

Method A.—Solutions approximately 0.04 M in pure 7 were prepared using sulfolane as a solvent. Aliquots (5 ml) were sealed in glass tubes and heated at the appropriate temperature in a constant temperature bath. The tubes were removed at various time intervals and quenched by immersion in cold water, and the contents were poured into 20.0 ml of 0.019 N n-butylamine in dioxane. These mixtures were allowed to stand overnight protected from moisture and titrated with 0.01 N hydrochloric acid to the methyl red end point.

Method B.—Solutions about 0.04 M in pure 7 were made using dimethylformamide, tetramethylurea, acetonitrile, and sulfolane. The solutions were placed in 50-ml flasks fitted with septum caps and heated at 110.0 ± 0.5, 80 ± 0.1, or 130.0 ± 0.1°. Aliquots (3 ml) were drawn from the flasks by a syringe at various time intervals and quenched with cold water. The aliquots were poured into 30 ml of water and extracted with pentane, and the combined extracts were washed with water and dried over magnesium sulfate. Evaporation of the pentane gave residues which were analyzed by gc using a 2 ft × 0.25 in. LAC-728 column (temperature 115.0°, carrier flow 85 ml/min; R_t (min) **8**, 4.4; **7**, 10.1).

Method C.—Aliquots (3 ml) of acetonitrile solutions approximately 0.04 M in 11 were sealed in glass tubes and heated at 80.0 ± 0.5 and 59.0 ± 0.5°. Tubes were removed at various time intervals, quenched by immersion in cold water, and stored at −20° until used. The work-up was similar to method B. Gc analyses were carried out by using a 2 ft × 0.25 in. QF-1 column (temperature 95°, carrier flow 260 ml/min; R_t (min) 12, 3.6; 11, 9.6).
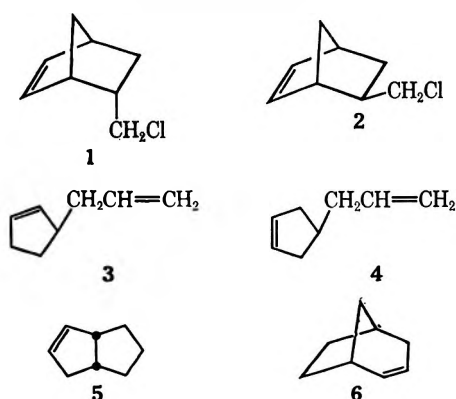
5-Norbornenyl- and 2-Norbornylcarbene Intermediates

PETER K. FREEMAN*[1] AND KANTILAL B. DESAI

Department of Chemistry, University of Idaho, Moscow, Idaho 83843

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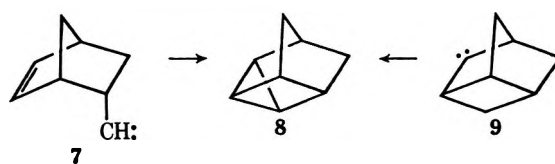Carbenoid decomposition of *endo*-5-norbornenecarboxaldehyde tosylhydrazone produces a mixture of 5-methylenenorbornene and *endo*-tricyclo[3.2.1.0²,⁴]octene-6 in a ratio of 57:42. Decomposition of epimeric *exo*-5-norbornenecarboxaldehyde tosylhydrazone gives 5-methylenenorbornene and *exo*-tricyclo[3.2.1.0²,⁴]octene-6 in a ratio of 23:76. In contrast, the reaction of *endo*-2-norbornylmethyl chloride with sodium in *n*-decane produces a mixture of *endo*-2-methylnorbornane, bicyclo[3.2.1]octene-2, and *endo*-tricyclo[3.2.1.0²,⁴]octane in the ratio of 65:24:11. The exo epimer, *exo*-2-norbornylmethyl chloride, reacts with sodium under identical conditions to generate a hydrocarbon mixture of *exo*-2-methylnorbornane and *exo*-tricyclo[3.2.1.0²,⁴]octane in a 68:32 ratio. Carbenoid decomposition of *endo*-2-norbornanecarboxaldehyde tosylhydrazone yields a hydrocarbon mixture of 2-methylenenorbornane, bicyclo[3.2.1]octene-2, and *endo*-tricyclo[3.2.1.0²,⁴]octane in a ratio of 41:4:55. The epimeric *exo*-2-norbornanecarboxaldehyde tosylhydrazone decomposes under the same conditions to generate a mixture of methylenenorbornane and *exo*-tricyclo[3.2.1.0²,⁴]octane in a ratio of 11:89. The mechanistic implications of these results are discussed.

The present study of 5-norbornenyl- and 2-norbornylcarbenes and carbenoids was initiated for several reasons. Previously we have reported that treatment of either *exo*- or *endo*-5-norbornenylmethyl chloride (1 or 2) with sodium in *n*-decane at 85–90° leads to a mixture of C_8H_{12} hydrocarbons composed of allylcyclopentenes (3 and 4) and bicyclooctenes (5 and 6).[2] Thus the formation of products appears to be most reasonably explained on the basis of cleavage of the initially formed alkylsodium intermediates. The major products (3, 4, and 5) are formed by cleavage to a resonance-stabilized allylcyclopentenyl carbanion, which may generate either 3 or 4, or undergo ring reclosure, which leads to *cis*-bicyclo[3.3.0]octene-2. The formation of bicyclo[3.2.1]octene-2 may be rationalized by suggesting that an intramolecular addition of *endo*-5-norbornenylmethylsodium generates 2-tricyclo[3.2.-1.0³,⁶]octylsodium, which produces 6 by a ring cleavage route. Thus, all volatile hydrocarbon products are formed directly from alkylsodium intermediates; no carbenoid products (C_8H_{10}) were detected in the volatile hydrocarbon fraction investigated.

Therefore, we were interested in the reaction routes which would be utilized by both *endo*- and *exo*-5-norbornenylcarbene intermediates. The *endo*-5-norbornenylcarbene intermediate appears to be especially interesting, since intramolecular interaction with the double bond seems to be a likely possibility and should provide some distortion (geometry intermediate between 7 and 8) and stabilization. Such intramolecular

interaction should lead to intramolecular addition generating symmetrical (C_s) tetracyclooctane (8), previously synthesized *via* a carbene insertion path of 2-carbenatricyclo[3.2.1.0³,⁶]octane,[3] or, if the increase in strain energy for intramolecular reaction is prohibitive, intramolecular addition may be prevented, but the interaction with the double bond may confer nonclassical character upon the carbene intermediate (a "foiled reaction" methylene).[4]

Results

The tosylhydrazone of *endo*-5-norbornenecarboxaldehyde was prepared and then converted to the sodium salt using excess sodium methoxide (3.26 equiv) in bis(2-ethoxyethyl) ether. Decomposition of the sodium salt of 10 was effected by heating the bis(2-ethoxyethyl) ether solution at 180°; a 13% yield of volatile hydrocarbons was isolated, which consisted of 57% 5-methylenenorbornene (11) and 42% *endo*-tricyclo[3.2.1.0²,⁴]octene-6 (12), which were readily identified by spectral comparison with spectra of authentic standards, and a 1% component, which was not identified, but was determined not to be bicyclo[3.2.1]octa-2,6-
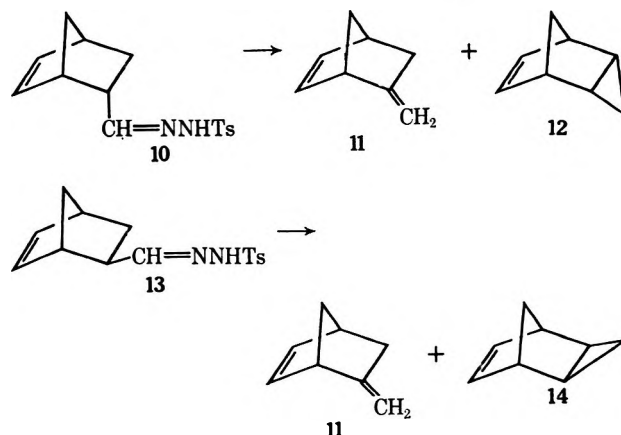
(1) Address all correspondence to this author at the Department of Chemistry, Oregon State University, Corvallis, Oreg. 97331.
(2) P. K. Freeman, V. N. M. Rao, D. E. George, and G. L. Fenwick, *J. Org. Chem.*, **32**, 3958 (1967).

(3) P. K. Freeman, V. N. M. Rao, and G. E. Bigam, *Chem. Commun.*, 511 (1965).
(4) R. Gleiter and R. Hoffman, *J. Amer. Chem. Soc.*, **90**, 5457 (1968).

diene. The epimeric tosylhydrazone (13) was prepared and decomposed in an identical manner yielding a 9% yield of hydrocarbons, which consisted of 23% 5-methylenenorbornene (11) and 76% exo-tricyclo-[3.2.1.0^{2,4}]octene-6 (14), which was identified by infrared and nmr spectral comparison with the spectra of an authentic sample of 14.

Thus the exo- and endo-5-norbornenylcarbene intermediates generate different ratios of hydrogen shift and C–H insertion products. In order to focus attention on the role of the double bond, we chose to investigate the related exo- and endo-2-norbornylcarbene intermediates. Treatment of endo-2-norbornylmethyl chloride with sodium in n-decane, under the same conditions used in the investigation of the cleavage reactions of exo and endo-5-norbornenylmethyl chloride with sodium, resulted in a 28% yield of a volatile hydrocarbon fraction which was composed of 65% endo-2-methylnorbornane (16), 24% bicyclo[3.2.1]octene-2 (17), and 11% endo-tricyclo[3.2.1.0^{2,4}]octane (18). The analogous reaction of exo-2-norbornylmethyl chloride with sodium in n-decane at 85–90° produced a 47% yield of hydrocarbons, which consisted of 68% exo-2-methylnorbornane (20) and 32% exo-tricyclo[3.2.1.0^{2,4}]octane (21). Tricyclo[3.2.1]octene-2, formed in the reaction of 15, was identified by spectral comparison with the corresponding data of an authentic sample, while 18, formed from 15, and 21, from 19, were identified by comparison of infrared and nmr data with those of standards prepared by reduction of olefins 12 and 14.
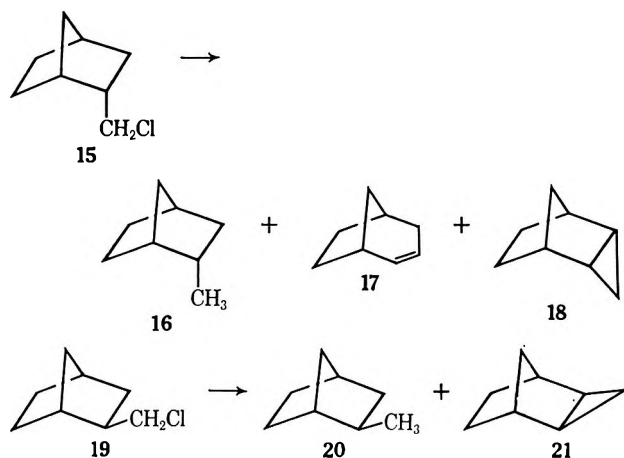
Since the reaction of primary chlorides 15 and 19 with sodium should generate carbenoids, rather than carbenes, additional reaction pathways, as illustrated by the formation of ring expansion product 17, might be the result of the complexed nature of the bivalent intermediate. We chose, therefore, to consider the exo- and endo-2-norbornylcarbene intermediates generated by decomposition of the corresponding tosylhydrazone precursors in excess sodium methoxide in bis(2-ethoxyethyl) ether. Decomposition of tosylhydrazone 22 under conditions similar to those used for decomposition of 10 and 13 resulted in a 43% yield of a hydrocarbon fraction which was composed of 41% 2-methylenenorbornane, 4% bicyclic 17, and 55% insertion product 18. In contrast, decomposition of tosylhydrazone 24, under identical conditions, generated a mixture of volatile hydrocarbons in 14% yield, which was composed of 11% 23 and 89% 21.
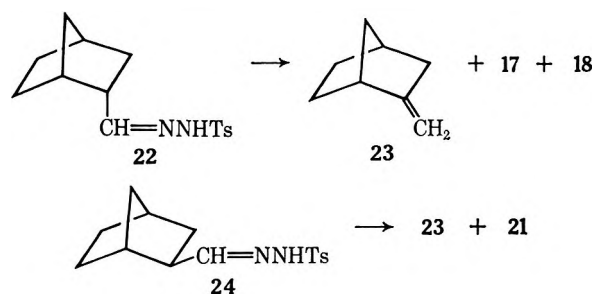
Discussion

Since in the thermal decomposition of the sodium salt of tosylhydrazone 10 no tetracyclic 8 was detected, and since the reaction conditions used were similar to those employed for the generation of 8 via 2-carbenatricyclo[3.2.1.0^{3,6}]octane (9), it seems reasonably certain that if tetracyclic 8 were formed in the carbenoid decomposition of tosylhydrazone 10 it would have survived. Thus the alternatives available for intermediate 7 are that it might exhibit characteristics of a foiled carbene addition process or that the interaction might be chemically insignificant. If one assumes that the bivalent intermediates formed in the base-induced decompositions of hydrazones 10 and 13 are singlet-state intermediates, interaction of the empty p orbital on the carbene carbon (C_α) with the π cloud of the double bond might effect the relative rates of insertion and hydrogen migration. Thus in the intermediate formed from decomposition of 10, overlap of the p orbital with the π bond should bend the carbene carbon toward the double bond and reduce the eclipsing interaction between C_α and the endo C-6 hydrogen. Since the favored transition state geometry is believed to be syn periplanar,[5] the insertion rate should be retarded relative to that for the exo epimer. On the other hand, inspection of models indicates that overlap of the p orbital with the π system should align the p orbital in a syn periplanar fashion with the exo C-5 hydrogen and thus facilitate hydrogen migration. Since Kirmse found that base-induced decomposition of cyclopentanecarboxaldehyde tosylhydrazone produces methylenecyclopentane and bicyclo[3.1.0]hexane in a 27.5:72.5 ratio,[5a] the ratio of 23:76 for hydrogen migration/insertion in the case of exo-5-norbornenylcarbene appears normal and the corresponding ratio of 57:42 for endo-5-norbornylcarbene appears to be altered as anticipated for a delocalized carbene intermediate.

However, if the double bond and its geometric relationship to the carbenoid carbon were the most important factors, one would expect this to be reflected in the product ratios produced in the decompositions of 10 and 13 as contrasted with those of tosylhydrazones 22 and 24. Since, instead, we find that the ratios of hydrogen migration to insertion are quite similar for norbornenyl- and norbornylcarbene intermediates of similar geometry, a rationalization of the dependence of product composition upon the exo or endo positioning of the carbene carbon (C_α) must lie with other steric factors. Although torsional steric effects tend to cancel in the formation or destruction of exocyclic double bonds at C-2 on the norbornane skeleton,[6] if there is

(5) (a) W. Kirmse and G. Wächtershäuser, *Tetrahedron*, 22, 63 (1966); (b) W. Kirmse and G. Münscher, *Justus Liebigs Ann. Chem.*, 726, 42 (1969).

(6) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, 89, 701 (1967).

more single- than double-bond character in C-2–C$_\alpha$ in the transition state for hydrogen migration, one would expect the eclipsing of C-1–H and C-2–C$_\alpha$ in the case of the exo carbene intermediates to inhibit formation of 2-methylenenorbornane or 5-methylenenorbornene.

The product compositions formed as a result of generation of *exo*- and *endo*-2-norbornyl carbenoids by α elimination on primary chlorides 15 and 19 are more difficult to place in perspective. An overall similarity to the reactions of the carbenes generated in the decompositions of 22 and 24 is evident, and it is of interest to note that a ring expansion occurs for both *endo*-2-norbornylcarbene and for the analogous carbenoid. The fact that *endo*-2-norbornylcarbene undergoes ring expansion, while *endo*-5-norbornenylcarbene does not, is perhaps a hint that intermediate 7 does possess some nonclassical carbene character. Inspection of models reveals that alignment of the p orbital in intermediate 7 for maximum overlap with the π bond system provides an alignment which should inhibit ring expansion. Thus, while evidence supporting a foiled carbene addition reaction for intermediate 7 is not revealed by the ratio of hydrogen migration to insertion, the ring expansion reaction found for 22 suggests that nonclassical interaction may be of some importance in the *endo*-5-norbornenylcarbene system, and that 7 may be similar in this respect to the 9-carbenabicyclo[3.3.1]non-2-ene intermediate studied by Fisch.[7] We have underway at the present time additional experimentation directed toward revealing intramolecular interactions in similar carbene and carbenoid intermediates.

Experimental Section[8]

Separation of *exo*- and *endo*-Bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde.—A 183-g mixture of *exo*- and *endo*-bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde[9] was distilled in an 18-in. semimicrospinning-band column at a reflux ratio of 15:1. Three fractions were collected. The first 50 g distilled at 62–63° (17 mm). This fraction, on a 20-ft DC-200 column, was found to be enriched in exo isomer. The second fraction (62.3 g) distilled at 63–65° (17 mm). This was found to be a mixture of both the isomers on the same column. The last fraction (70.7 g) distilled at 65–66° (17 mm) and gave 52.5 g of 99% pure endo isomer. The first fraction on careful redistillation gave 26.2 g of 99% pure exo isomer. Infrared spectra of both the isomers indicated ν_{max} at 3010 (HC=C), 1700 (C=O), 720 (cis olefinic hydrogens), and 1570 cm^{-1} (norbornene C=C). The endo isomer showed a characteristic band at 930 cm^{-1}, while the exo isomer had a characteristic band at 880 cm^{-1}. The structure of exo isomer was further confirmed by elemental analysis.

Anal. Calcd for C$_8$H$_{10}$O: C, 78.68; H, 8.19. Found: C, 78.56; H, 8.19.

endo-Bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde *p*-Toluenesulfonylhydrazone (10).—In a three-necked round-bottom flask equipped with a mechanical stirrer, 37.2 g (0.200 mol) of *p*-toluenesulfonylhydrazine was dissolved in 200 ml of 60% aqueous methanol by warming to about 60°. To this warm solution was added a solution of 24.4 g (0.200 mol) of *endo*-bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde in 60 ml of methanol, with stirring. Stirring was continued while allowing the mixture to cool to room temperature. The white, solid product was filtered, washed with ether, and recrystallized from methanol. White crystalline tosylhydrazone, 47.4 g (82%), mp 133–134°, was obtained.

Anal. Calcd for C$_{15}$H$_{18}$N$_2$O$_2$S: C, 62.07; H, 6.21. Found: C, 62.24; H, 6.37.

Decomposition of *endo*-Bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde *p*-Toluenesulfonylhydrazone (10).—The procedure was based on that reported by Friedman and Shechter.[10] A three-necked round-bottom flask was fitted with a nitrogen inlet, dropping funnel, stirrer, and a 12-cm Vigreux column heated to 70° with heating tape. The Vigreux column was connected to two receiving traps arranged in series and cooled with a Dry Ice–isopropyl alcohol bath. Dry reagent grade sodium methoxide (8.77 g, 0.163 mol) was added to the nitrogen-purged flask along with 300 ml of bis(2-ethoxyethyl) ether, which previously had been distilled from lithium aluminum hydride. The stirred suspension was raised to 180° in an oil bath. A slurry of *p*-toluenesulfonylhydrazone 10 (14.5 g, 0.050 mol) in 150 ml of bis(2-ethoxyethyl) ether was then added during 2 hr, under the nitrogen flow in order to sweep out volatile products as they formed. The reaction was continued at this temperature for an additional hour, sweeping the system with nitrogen. The material in the cold traps was diluted 5:1 with water and extracted with pentane. The pentane solution was dried and the solvent removed by careful distillation, which gave 0.695 g (13.1%) of C$_8$ hydrocarbons consisting of 57% of 5-methylenebicyclo[2.2.1]hept-2-ene, 42% of *endo*-tricyclo[3.2.1.0^{2,4}]oct-6-ene, and 1% of a component which was not characterized. The products were isolated by vapor phase chromatography using a 25-ft DC-200 column at 130°. The structure of 5-methylenebicyclo[2.2.1]hept-2-ene was confirmed by comparing its infrared and nuclear magnetic resonance spectra with those of an authentic sample (Dow Chemical Co.), while *endo*-tricyclo[3.2.1.0^{2,4}]oct-6-ene was confirmed by carbon and hydrogen analyses and by comparison of infrared and nuclear magnetic resonance spectra with published data.[11]

Anal. Calcd for C$_8$H$_{10}$: C, 90.56; H, 9.43. Found: C, 90.41; H, 9.55.

exo-Bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde *p*-Toluenesulfonylhydrazone (13).—A solution of *exo*-bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde (12.2 g, 0.100 mol) in 30 ml of methanol was added to 18.6 g (0.10 mol) of *p*-toluenesulfonylhydrazine in 100 ml of 60% aqueous methanol at 60°, with stirring. The reaction mixture was allowed to cool; the solid was filtered, washed with pentane, and crystallized from methanol, giving 19.7 g (68%) of crystalline tosylhydrazone, mp 118–119°.

Anal. Calcd for C$_{15}$H$_{18}$N$_2$O$_2$S: C, 62.07; H, 6.21. Found: C, 62.22; H, 6.39.

Decomposition of *exo*-Bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde *p*-Toluenesulfonylhydrazone (13).—As described in the case of endo isomer, the slurry of tosylhydrazone of *exo*-bicyclo[2.2.1]-hept-2-ene-5-carboxaldehyde (10.73 g, 0.0370 mol) in 100 ml of bis(2-ethoxyethyl) ether was decomposed at 180° in the presence of sodium methoxide (6.5 g, 0.12 mol) and bis(2-ethoxyethyl) ether (150 ml) under a nitrogen atmosphere. The material in the cold traps was worked up as above, which gave 0.35 g (9.0%) of C$_8$ hydrocarbons. The product mixture was separated by vapor phase chromatography on a 25-ft DC-200 column and consisted of 23.0% 5-methylenebicyclo[2.2.1]hept-2-ene, 76.0% *ero*-tricyclo[3.2.1.0^{2,4}]oct-6-ene, and 1% of an unidentified product. The isomers were characterized by their infrared and nuclear magnetic resonance spectra. Each structure was ultimately confirmed by direct comparison of its infrared and nuclear magnetic resonance spectra with an authentic sample.

exo-2-Hydroxymethylbicyclo[2.2.1]heptane.—The procedure of Berson and his coworkers[12] was adapted to fit the requirements of this laboratory. A solution of 50 g (0.4 mol) of 5-*exo*-hydroxymethylbicyclo[2.2.1]hept-2-ene in 200 ml of methanol was hydrogenated over 1 g of a 10% palladium-on-charcoal catalyst in a Parr apparatus. The theoretical quantity of hydrogen was absorbed within 0.5 hr. The reaction was continued for an additional 2 hr. After removal of the catalyst by filtration and the solvent by distillation, 48 g (92%) of *exo*-5-hydroxymethylbicyclo[2.2.1]heptane, bp 98–99° (15 mm), was collected by distillation through an 18-in. semimicrospinning-band column. The infrared spectrum of the product indicated complete disappearance of the bands due to double bond in the starting olefin.

endo-2-Hydroxymethylbicyclo[2.2.1]heptane.—Application of the procedure described above for the reduction of 5-*exo*-hydroxymethylbicyclo[2.2.1]hept-2-ene to reduction of 45 g (0.36 mol) of

(7) M. H. Fisch and H. D. Pierce, Jr., *Chem. Commun.*, 503 (1970).

(8) Elemental analyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach über Engelskirchen, West Germany.

(9) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928).

(10) L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **81**, 5512 (1959).

(11) K. B. Wiberg and W. J. Bartley, *ibid.*, **82**, 6375 (1960).

(12) J. A. Berson, J. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *ibid.*, **83**, 3986 (1961).

the endo epimer gave 40 g (88%) of 5-*endo*-hydroxymethylbicyclo[2.2.1]heptane, bp 94–96° (15 mm).

exo-5-Chloromethylbicyclo[2.2.1]heptane (19).—*exo*-5-Hydroxymethylbicyclo[2.2.1]heptane, 44.1 g (0.350 mol), together with a few drops of piperidine, was placed in a three-necked flask equipped with a condenser, stirrer, dropping funnel, and nitrogen inlet. The flask was heated to 85–90° (oil bath) and 62.5 g (0.525 mol) of thionyl chloride was added during a 1-hr period under a nitrogen atmosphere. The reaction mixture was heated at reflux at the same temperature for an additional 2 hr. Excess thionyl chloride was removed by distillation using a rotary evaporator. Distillation of the residue through a spinning-band column yielded 43 g (85%) of *exo*-5-chloromethylbicyclo[2.2.1]heptane, bp 64–65° (13 mm). The infrared spectrum of the product indicated complete disappearance of OH frequency and showed a characteristic frequency at 715 cm^{-1} due to the CCl linkage.

This compound was also prepared by reducing catalytically *exo*-5-chloromethylbicyclo[2.2.1]hept-2-ene,[2] using 10% palladium-on-carbon as a catalyst. The infrared spectra of the two samples were identical and vpc analysis on a 25-ft DC-200 column and a 25-ft Carbowax 20M column showed only one peak in each case.

Anal. Calcd for C$_8$H$_{13}$Cl: C, 66.43; H, 8.99. Found: C, 66.31; H, 9.09.

endo-2-Chloromethylbicyclo[2.2.1]heptane (15).—Similarly, as in the case of *exo*-5-chloromethylbicyclo[2.2.1]heptane, the reaction of 37.8 g (0.300 mol) of *endo*-5-hydroxymethylbicyclo[2.2.1]heptane with 53.5 g (0.45 mol) of thionyl chloride gave 34 g (80%) of *endo*-5-chloromethylbicyclo[2.2.1]heptane. *endo*-5-Chloromethylbicyclo[2.2.1]hept-2-ene was reduced, with 10% palladium on carbon, to the saturated compound. The infrared spectra of samples prepared by these two different routes were identical. Vpc analysis of these samples provided evidence for identity by demonstrating identical retention times on a 25-ft DC-200 and a 25-ft Carbowax 20M column. The retention time on each column differed from that exhibited by the exo epimer.

Anal. Calcd for C$_8$H$_{13}$Cl: C, 66.43; H, 8.99. Found: C, 66.30; H, 9.02.

Reaction of *exo*-2-Chloromethylbicyclo[2.2.1]heptane with Sodium (19).—A 100-ml three-necked flask was fitted with a pressure-equalized dropping funnel, condenser, and ground-glass stirrer shaft and bearing. The dropping funnel was fitted with a nitrogen inlet tube; the condenser was connected to a calcium chloride drying tube; and the stirrer shaft was fitted with a Teflon stirrer blade. Under 15 ml of redistilled *n*-decane (bp 168–169°), 2.3 g (0.10 g-atom) of freshly pulled sodium ribbon was weighed out and cut into very small pieces. The sodium and decane were transferred to the reaction flask, the system was flushed out with nitrogen, and the flask was heated to 85–90° in an oil bath. A solution of 7.23 g (0.050 mol) of *exo*-5-chloromethylbicyclo[2.2.1]heptane in 10 ml of redistilled decane was added dropwise during 0.5 hr with mechanical stirring. The resulting reaction mixture was stirred for an additional 1.5 hr at the same temperature to complete the reaction.

When the reaction flask had cooled to room temperature, a vacuum pump was attached through a Dry Ice trap and a distillation head to the top of the condenser. The reaction mixture was subjected to a pressure of 20 mm; the reaction flask was heated until decane (bp 70°, 20 mm) reached the thermometer in the distillation head. The C$_8$ products collected in the Dry Ice trap.

Methanol was added to the remaining decane mixture to destroy the alkylsodium and unreacted sodium. The mixture was then washed with water. Upon standing, a solid precipitated from the decane solution. This material was probably the C$_{16}$ (Wurtz) hydrocarbons, but was not investigated further. The Dry Ice trap contained 2.57 g (46.8%) of C$_8$ hydrocarbons which by vapor phase chromatographic analysis on a 30-ft 25% Carbowax 1500 on Chromosorb column consisted of 68% 5-*exo*-methylbicyclo[2.2.1]heptane and 32.0% *exo*-tricyclo[3.2.1.0^{2,4}]octane. The products were identified by comparing infrared and nuclear magnetic resonance spectra with authentic samples synthesized as described below.

Similarly, the reaction of 3.610 g (0.025 mol) of 5-*exo*-chloromethylbicyclo[2.2.1]heptane with 0.575 g (0.025 g-atom) of sodium gave 0.59 g (31.1%) of C$_8$ hydrocarbons consisting of 68% 5-*exo*-methylbicyclo[2.2.1]heptane and 32% *exo*-tricyclo[3.2.1.0^{2,4}]octane.

Reaction of *endo*-2-Chloromethylbicyclo[2.2.1]heptane (15) with Sodium.—The reaction of 7.23 g (0.050 mol) of *endo*-

5-chloromethylbicyclo[2.2.1]heptane with 2.3 g (0.10 g-atom) of freshly pulled, finely cut sodium ribbon, was carried out in the same manner as described for the exo isomer.

The Dry Ice trap contained 1.53 g (28.4%) of C$_8$ hydrocarbons, which by vapor phase chromatography on a 30-ft 25% Carbowax 1500 on Chromosorb column consisted of 65% *endo*-5-methylbicyclo[2.2.1]heptane, 24% bicyclo[3.2.1]oct-2-ene, and 11% *endo*-tricyclo[3.2.1.0^{2,4}]octane. The products were characterized by comparison of their infrared and nuclear magnetic resonance spectra with those of authentic samples.

Similarly, the reaction of 3.620 g (0.025 mol) of 5-*endo*-chloromethylbicyclo[2.2.1]heptane with 0.575 g (0.025 g-atom) of sodium gave 0.64 g (23.7%) of C$_8$ hydrocarbons consisting of 72% 5-*endo*-methylbicyclo[2.2.1]heptane, 21% bicyclo[3.2.1]oct-2-ene, and 7.0% *endo*-tricyclo[3.2.1.0^{2,4}]octane.

exo-2-Methylbicyclo[2.2.1]heptane (20).—In a three-necked flask equipped with a dropping funnel, stirrer, and condenser attached with a calcium chloride tube, a solution of 1.0 g (0.026 mol) of lithium aluminum hydride in 15 ml of diglyme (previously distilled over sodium) was placed. The flask was heated to 125° and to it a solution of 3.62 g (0.025 mol) of *exo*-5-chloromethylbicyclo[2.2.1]heptane in 10 ml of diglyme was added. The reaction mixture was stirred and kept at 125° for 48 hr, after which it was cooled and treated successively with water and 20% hydrochloric acid. It was then extracted with pentane, washed with water, and dried over anhydrous sodium sulfate. Evaporation and distillation gave 1.32 g (48%) of 5-*exo*-methylbicyclo[2.2.1]-heptane, bp 66–67° (115 mm).

Anal. Calcd for C$_8$H$_{14}$: C, 87.27; H, 12.73. Found: C, 87.17; H, 12.83.

endo-2-Methylbicyclo[2.2.1]heptane (16).—Similarly, as described above in the case of the exo isomer, the reaction of 3.62 g (0.025 mol) of *endo*-5-chloromethylbicyclo[2.2.1]heptane with 1.0 g (0.026 mol) of lithium aluminum hydride in diglyme at 125° for 48 hr, gave 1.37 g (50%) of 5-*endo*-methylbicyclo[2.2.1]-heptane, bp 67–68° (115 mm).

Anal. Calcd for C$_8$H$_{14}$: C, 87.27; H, 12.73. Found: C, 87.11; H, 12.62.

exo-Tricyclo[3.2.1.0^{2,4}]octane (21).—A solution of 1.06 g (0.01 mol) of *exo*-tricyclo[3.2.1.0^{2,4}]oct-6-ene[13] in 10 ml of methanol was hydrogenated over 0.05 g of a 10% palladium-on-charcoal catalyst in a low-pressure hydrogenation apparatus. The hydrogenation was stopped when the uptake of hydrogen ceased. The catalyst was removed by filtration and the methanol by careful distillation. The product fraction was collected by vapor phase chromatography on 10-ft 25% Carbowax 1500 on Chromosorb column. *exo*-Tricyclo[3.2.1.0^{2,4}]octane, 0.54 g (50%), was obtained. The absorption at 1560 cm^{-1} in the infrared spectrum of the unsaturated compound was no longer present in the spectrum of the product.

endo-Tricyclo[3.2.1.0^{2,4}]octane (18).—In a fashion similar to that described above for the case of the exo isomer, 0.10 g (0.001 mol) of *endo*-tricyclo[3.2.1.0^{2,4}]oct-6-ene (obtained from decomposition of the *p*-tosylhydrazone of *endo*-bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde) was hydrogenated in 2.0 ml of methanol over 10% palladium-on-charcoal catalyst. The product, *endo*-tricyclo[3.2.1.0^{2,4}]octane, 0.065 g (70%), was collected by vapor phase chromatography using a 10-ft 25% Carbowax 1500 on Chromosorb column.

Anal. Calcd for C$_8$H$_{12}$: C, 88.88; H, 11.12. Found: C, 88.75; H, 11.31.

endo-Bicyclo[2.2.1]heptane-2-carboxaldehyde.—A solution of 18.3 g (0.15 mol) of *endo*-bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde in 200 ml of methanol with 1 g of a 10% palladium-on-charcoal catalyst was hydrogenated in a Parr apparatus. The theoretical quantity of hydrogen was absorbed within 1 hr. The catalyst was removed by filtration, and then on distillation through the spinning-band column, after removal of solvent, 15 g (80%) of *endo*-bicyclo[2.2.1]heptane-2-carboxaldehyde, bp 62–64° (12 mm), was obtained.

endo-Bicyclo[2.2.1]heptane-2-carboxaldehyde *p*-Toluenesulfonylhydrazone (22).—*p*-Toluenesulfonylhydrazine (18.6 g, 0.10 mol) was dissolved in 100 ml of 60% aqueous methanol by warming to about 60°. To this warm solution was added a solution of 12.2 g (0.1 mol) of *endo*-bicyclo[2.2.1]heptane-2-carboxaldehyde in 30 ml of methanol, while stirring. The reaction mixture was allowed to cool to room temperature slowly, and the white solid product obtained was filtered, washed with ether, and re-

(13) H. E. Simons and R. D. Smith, *J. Amer. Chem. Soc*, **81**, 4256 (1959).

crystallized from methanol. White crystalline tosylhydrazone, 21.2 g (72.4%), mp 114–115°, was obtained.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.64; H, 6.84. Found: C, 61.81; H, 6.96.

Decomposition of *endo*-Bicyclo[2.2.1]heptane-2-carboxaldehyde *p*-Toluenesulfonylhydrazone (22).—As described earlier in this section, dry reagent grade sodium methoxide (7.16 g, 0.133 mol) was added to the nitrogen-purged flask along with 200 ml of bis(2-ethoxyethyl) ether (previously distilled over lithium aluminum hydride). The stirred suspension was raised to a temperature of 180° in an oil bath. The slurry of the tosylhydrazone of *endo*-bicyclo[2.2.1]heptane-2-carboxaldehyde (11.1 g, 0.0375 mol) in 100 ml of bis(2-ethoxyethyl) ether was then added during 1.5 hr, under nitrogen flow to sweep away the volatile products formed. The reaction was continued at this temperature for an additional hour, sweeping the system with nitrogen to remove all the products formed. The material in the cold traps was worked up as usual, giving 1.45 g (43.2%) of C_8 hydrocarbons. The products were separated by vapor phase chromatography on a 25-ft DC-200 column and consisted of 41% 5-methylenebicyclo-[2.2.1]heptane, 4% bicyclo[3.2.1]oct-2-ene, and 55% *endo*-tricyclo[3.2.1.0²,⁴]octane. 5-Methylenebicyclo[2.2.1]heptane was characterized by infrared and nuclear magnetic resonance data and confirmed by comparing its infrared data with a published infrared spectrum.[14] Bicyclo[3.2.1]oct-2-ene and *endo*-tricyclo-[3.2.1.0²,⁴]octane were identified by infrared and nmr spectral comparisons with the corresponding data of authentic samples.

exo-Bicyclo[2.2.1]heptane-2-carboxaldehyde.—In a manner similar to that described above for the endo epimer, 12.2 g (0.10 mol) of *exo*-bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde, on hydrogenation in methyl alcohol over 10% palladium-on-charcoal catalyst gave 9.3 g (75%) of *exo*-bicyclo[2.2.1]heptane-2-carboxaldehyde, bp 66–68° (12 mm).

exo-Bicyclo[2.2.1]heptane-2-carboxaldehyde *p*-Toluenesulfonylhydrazone (24).—*p*-Toluenesulfonylhydrazine (14.0 g, 0.075 mol) was dissolved in 75 ml of 60% aqueous methanol at 60°. To this 9.3 g (0.075 mol) of *exo*-bicyclo[2.2.1]heptane-2-carbox-

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(14) R. R. Sauers, *J. Amer. Chem. Soc.*, **81**, 4873 (1959).

aldehyde in 23 ml of methanol was added. The reaction mixture was allowed to cool slowly to room temperature and the product was filtered, washed with pentane, and recrystallized from methanol. White tosylhydrazone (14.3 g, 65%), mp 94–95°, was obtained.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.64; H, 6.84. Found: C, 61.83; H, 6.89.

Decomposition of *exo*-Bicyclo[2.2.1]heptane-2-carboxaldehyde *p*-Toluenesulfonylhydrazone (24).—Tosylhydrazone 24 was decomposed in a manner similar to that employed for the endo epimer 22. A mixture of dry reagent grade sodium methoxide (6.05 g, 0.112 mol) and 150 ml of bis(2-ethoxyethyl) ether (previously dried by distillation over lithium aluminum hydride) was placed in a nitrogen-purged flask. This mixture was heated to 180° in an oil bath, and a suspension of the *p*-toluenesulfonylhydrazone of *exo*-bicyclo[2.2.1]heptane-2-carboxaldehyde (10.2 g, 0.350 mol) in 100 ml of bis(2-ethoxyethyl) ether was added during 1 hr, under the nitrogen flow. The reaction was continued for an additional 2 hr at this temperature, sweeping the system with nitrogen to remove all the products formed. The material in the cold traps was worked up as described above for the endo isomer, which gave 0.83 g (13.7%) of C_8 hydrocarbons, consisting of 11% 5-methylenebicyclo[2.2.1]heptane and 83% *exo*-tricyclo-[3.2.1.0²,⁴]octane. These products were isolated by vapor phase chromatography using a 25-ft DC-200 column. Comparison of infrared and nuclear magnetic resonance spectra of the *exo*-tricyclo[3.2.1.0² ⁴]octane component with corresponding data of an authentic sample established its identity.

Registry No.—10, 28455-84-7; 13, 28455-85-8; 16, 765-90-2; 18, 22389-16-8; 19, 6518-44-1; 20, 872-78-6; 22, 28455-92-7; 24, 28455-93-8; *exo*-bicyclo-[2.2.1]hept-2-ene-5-carboxaldehyde, 19926-88-6; *endo*-bicyclo[2.2.1]hept-2-ene-5-carboxaldehyde, 19926-90-0; *exo*-5-hydroxymethylbicyclo[2.2.1]heptane, 13118-79-1; 5-*endo*-hydroxymethylbicyclo[2.2.1]heptane, 13137-31-0; *exo*-bicyclo[2.2.1]heptane-2-carboxaldehyde, 3574-55-8.

Electron Spin Resonance Observations of Semidiones from Alkali Metal Reduction of 7-Norbornenone and 9-Benzonorbornenone[1]

John P. Dirlam[*2] and S. Winstein[3]

*Department of Chemistry,
University of California, Los Angeles, California 90024*

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As part of our continued effort to study potentially nonclassical and homoaromatic species by esr,[4] attempts were made to prepare the ketyls[5] of 7-norbornenone (1) and 9-benzonorbornenone (2) by alkali metal reduction in 1,2-dimethoxyethane (DME) or tetrahydrofuran (THF).[7] Although radical anions are obtained, it appears that semidiones 3 and 4, respectively, are formed. The ketyls 5 and 6 could not be detected. This result, to our knowledge, constitutes the first example of carbonyl insertion in the formation of semidiones from monoketones in this reduction medium.[8]

7-Norbornenone (1) in DME was treated with potassium, and the esr spectrum was resolved into a 1:2:1 triplet, $a_H = 2.69$ G (2 H). Each peak was further split into a 1:4:6:4:1 quintet, $a_H = 0.44$ G (4 H). The esr spectrum from potassium reduction of 9-benzonorbornenone (2) in DME consisted of a 1:2:1 triplet, $a_H = 2.35$ G (2 H), with additional small hyperfine splitting. The hyperfine-splitting constants obtained from the reduction products of 1 and 2 were found to be strikingly similar to those for the corresponding semidiones 3 and 4, respectively, which were previously

1 2 3

4 5 6

prepared by Russell, Holland, and Chang[9] from the diketones 7 and 8. When 7 and 8 were reduced to semidiones 3 and 4, respectively, under the same conditions used for reduction of 1 and 2, identical hyperfine-

7 8

splitting constants were indeed obtained.[10] The study of deuterio derivatives 9, 10, and 11 allows the assignment of values as in Table I.

9 10 11

Taken alone, the hyperfine-splitting patterns do not permit differentiation between a semidione and its decarbonylated analog, a ketyl (*e.g.*, 3 and 5).[9] However, the following data are consistent with semidione formation. Russell and coworkers[9] have measured hyperfine-splitting by ^{13}C in natural abundance for the semidione 12. For 12 in DME at 25° they found $a_C =$

12

6.15 G (attributed to the carbonyl carbon).[11] For the semidione 3, prepared from 7, we observed $a_C = 6.12$ G from ^{13}C in natural abundance. As Russell has

(1) This research was supported by a grant from the National Science Foundation.

(2) (a) Taken in part from the Ph.D. thesis of J. P. D., UCLA, 1969; National Science Foundation Trainee, 1965–1969. (b) Author to whom inquiries should be addressed at the Department of Chemistry, Yale University, New Haven, Conn. 06520.

(3) Deceased Nov 23, 1969.

(4) (a) R. Rieke, M. Ogliaruso, R. McClung, and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 4729 (1966); (b) G. Moshuk, G. Petrowski, and S. Winstein, *ibid.*, **90**, 2179 (1968).

(5) In this paper the term ketyl is restricted to one-electron reduction products of monoketones, whereas one-electron reduction products of conjugated diketones will be referred to as semidiones.[6]

(6) G. A. Russell, "Radical Ions," E. T. Kaiser and L. Kevan, Ed., Wiley, New York, N. Y., 1968, pp 87–150.

(7) During the course of this investigation the nature of the 7-norbornenyl and 9-benzonorbornenyl radicals were reported: (a) J. Warketin and E. Sanford, *J. Amer. Chem. Soc.*, **90**, 1667 (1968); (b) G. A. Russell and G. W. Holland, *ibid.*, **91**, 3968 (1969); and (c) S. J. Cristol and A. L. Noreen, *ibid.*, **91**, 3969 (1969).

(8) (a) For an excellent review of a wide variety of semidione preparations see ref 6. Russell[6] has suggested that a carbonyl insertion reaction occurs in the electrolytic reduction of acetophenone at high electrode potentials in dimethylformamide (DMF), forming the 1-phenylpropane-1,2-semidione. Russell[6] has speculated that the additional carbonyl group comes from the DMF. A similar example of carbonyl insertion has recently been reported in the electrolysis of 3,4,5-trimethoxybenzaldehyde in DMF: C. Corvaja, P. L. Nordio, and G. Giacometti, *J. Amer. Chem. Soc.*, **89**, 1751 (1967). (b) We have just learned from Professor G. A. Russell that he and his coworkers have recently observed results similar to those reported here. For example, they have found that the ketyl of 2,2,4,4-tetramethylcyclobutanone, obtained by potassium reduction in THF, undergoes carbonyl insertion at −50° forming the 3,3,5,5-tetramethylcyclopentan-1,2-semidione.

(9) G. A. Russell, G. W. Holland, and K.-Y. Chang, *J. Amer. Chem. Soc.*, **89**, 6629 (1967).

(10) Reduction of 2 and 8 in DME with sodium gave rise to identical 1:1:1:1 quartet splitting due to one sodium atom as well, $a_{Na} \approx 0.7$ G.

(11) E. T. Strom and G. A. Russell, *J. Chem. Phys.*, **41**, 1514 (1964).

### TABLE I
OBSERVED HYPERFINE SPLITTING CONSTANTS[a]

Structure	Precursor	Reagent	Solvent	H_e	H_n	H_v
	1	Potassium	DME	0.44	2.69	0.44
	1	Potassium	THF	0.41	2.59	0.41
	7	Potassium	DME	0.46	2.68	0.46
	7[b]	Enolate anion of propiophenone	DMSO	0.41	2.60	0.41

Structure	Precursor	Reagent	Solvent	H_e	H_n	H_a
	2	Potassium	DME	c	2.35[d]	c
	8	Potassium	DME	c	2.35	c
	8	Sodium[e]	DME	0.18	2.35	0.09
	8[b]	Enolate anion of propiophenone	DMSO	0.20	2.35	0.09

[a] All values are in gauss. The bridgehead hydrogens (in the nodal plane of the pz orbital) give rise to no detectable splitting.[9] [b] These values are taken from the work of Russell, Holland, and Chang.[9] [c] Small hyperfine splitting was observed, but the multiplicity could not be determined (0.09-G peak separation). [d] This value was assigned to the endo proton by analogy with the corresponding radical anion from the diketone.[9] [e] The value for a_{Na} is 0.73 G at $-20°$.

pointed out,[9] these values appear to exclude ketyl structures, where a value of a_C^{CO} approaching 50 G would be expected.[12] Unfortunately, it was not possible to obtain a_C values for the reduction products prepared from the monoketones, because the signal intensities were not high enough to observe hyperfine splitting by ^{13}C in natural abundance.

Two additional, although less conclusive, arguments can be presented in support of semidione formation from reduction of the monoketones 1 and 2. The signal amplitude necessary to observe the radical anions was a factor of 100 or greater in the case of those generated from the monoketones, compared with those generated from the diketones. This is consistent with a secondary reduction product being formed from the monoketones in low yield. Secondly, the radical anions generated in this study were stable for hours at room temperature. In fact, the reduction product from 1 showed a 1:2:1 triplet even after 6 days at 8°. To our knowledge ketyls do not possess such stability.[13]

Attempts were made to obtain the radical anions of several compounds that are related to 7-norbornenone. However, no esr signal was detected when either 13, 14, or 15 in DME was treated with potassium.
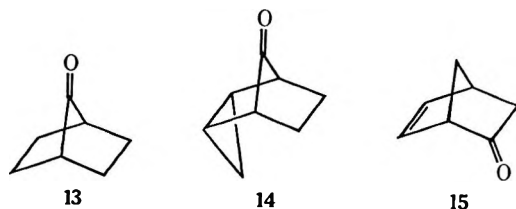
The present study affords no evidence concerning the detailed mechanism of this unusual conversion (*i.e.*, 1 to 3). One possible means of forming the semidione 3 from the monoketone 1, which can be visualized, involves rearrangement of the dimer 16 to give 3 and cyclohexadiene. Some support for this scheme comes from a set of known equilibria involving aliphatic ketyls and the corresponding dimers.[13] However, no esr

(12) N. Hirota and S. I. Weissman, *J. Amer. Chem. Soc.*, **82**, 4424 (1960).

(13) N. Hirota, "Radical Ions," E. T. Kaiser and L. Kevan, Ed., Wiley, New York, N. Y., 1968, pp 35–85.
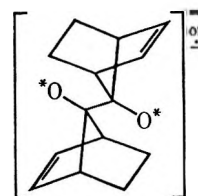
16
(asterisks equal
– or ·)

signal was detected for any known by-products of this rearrangement.[14,15]

Experimental Section

General.—Nmr spectra were obtained in carbon tetrachloride using a Varian Associates Model A-60 spectrometer with tetramethylsilane (τ 10.0) as the internal standard unless otherwise specified. Gas–liquid chromatography (glpc) was performed on a Varian-Aerograph A-90-P instrument, employing the following column: 6.0 ft $\times$ 0.25 in. 20% XF 1150 on Chromosorb W, nonacid washed 60–80 mesh. Ir spectra were recorded in carbon tetrachloride on a Perkin-Elmer 421 instrument.

7-Norbornenone (1). A.—This compound was prepared according to the procedure of Gassman and Pape[16] and was purified by preparative glpc: ir 1770 cm^{-1} (C=O); nmr τ 3.50 (t, 2 H, olefinic protons), 7.23 (m, 2 H, bridgehead protons), 8.09 (m, 2 H, exo C-5 and C-6 protons), and 8.87 (m, 2 H, endo C-5 and C-6 protons). *Anal.* Calcd for C$_7$H$_8$O: C, 77.75; H, 7.46. Found: C, 77.80; H, 7.57.

B.—Ketone 1 was also prepared by Oppenauer oxidation[17] of 2-norbornen-7-(*anti*)-ol.[18]

exo,exo-5,6-Dideuterio-2-norbornen-7-one (9) was prepared by Oppenauer oxidation[17] of *exo,exo*-5,6-dideuterio-2-norbornen-7-(*anti*)-ol.[19] The product was purified by preparative glpc: ir 1770 cm^{-1} (C=O); nmr τ 3.47 (t, 2 H, olefinic protons), 7.25 (t, 2 H, bridgehead protons), and 8.82 (broad singlet, 2 H, endo C-5 and C-6 protons). This spectrum indicated that exo C-5 and C-6 positions contained $\geq95\%$ D.

1,2,3,4-Tetradeuterio-2-norbornen-7-one (10) was prepared using the Gassman and Pape[16] procedure for 1 with the exception

(14) A 1:1 doublet (a = 15.2 G) was detected upon potassium reduction of 1 in DME or THF that was symmetrically disposed about the 1:2:1 triplet. At 25° this doublet disappeared within *ca.* 2 hr, whereas the triplet remained unchanged. The species giving rise to this doublet is unknown. Such a doublet was not observed in the reduction of 2.

(15) The possibility that the CO moiety arises from solvent, though remote, cannot be excluded.

(16) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964).

(17) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **82**, 1240 (1960).

(18) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

(19) B. Franzus and E. I. Snyder, *J. Amer. Chem. Soc.*, **87**, 3423 (1965).

that *tert*-BuOD was used instead of *tert*-BuOH in the dechlorination of 7,7-dimethoxy-1,2,3,4-tetrachloro-2-norbornene. The ketone was purified by preparative glpc: ir 1770 cm^{-1} (C=O); nmr τ 8.05 (m, 2 H, exo C-5 and C-6 protons) and 8.83 (m, 2 H, endo C-5 and C-6 protons). This spectrum indicated $\geq 95\%$ D at all C-1, C-2, C-3, and C-4 positions.

2,3-Dideuterio-2-norbornen-7-one (11).—The vinyl protons of 7,7-dimethoxynorbornene[16] were exchanged with lithium cyclohexylamide-*N*-D and cyclohexylamine-*N*-D$_2$[20] at 25°. The ketal was purified by preparative glpc. The nmr spectrum indicated *ca.* 1.4 atom D per molecule in the olefinic region (τ 4.00), and only the vinyl protons were exchanged under these conditions. Mass spectral analysis (AEI Model MS 9) indicated that the total atom D per molecule was 1.38. The deuterio ketal was converted to 11 in the normal manner[16] and purified by preparative glpc: ir 1770 cm^{-1} (C=O); nmr indicated *ca.* 1.4 atom D per molecule in the olefinic region (τ 3.48).

7-Norbornanone (13).—Hydrogenation of 1 according to the procedure of Gassman and Pape[16] gave 13: mp 77–79° (lit.[16] mp 79.5–80.5°); ir 1785 cm^{-1} (C=O); nmr (CS$_2$, external TMS) showed a multiplet at τ 7.80–8.60.

endo-**Tricyclo[3.2.1.0^{2,4}]octan-8-one (14)** was obtained from M. A. Battiste[21] and was purified by preparative glpc: mp 62–69° (lit. mp 58–61°[21] and 71–72°[22]); ir 1760 cm^{-1} (C=O); nmr (external TMS) τ 7.78 (m, 2 H) and 8.0–9.3 (m, 8 H).

2-Norbornenone (15) was obtained from R. K. Lustgarten and was purified by preparative glpc: nmr τ 3.48 (m, 1 H, olefinic proton), 3.90 (m, 1 H, olefinic proton), 6.85 (m, 1 H, bridgehead proton), 7.10 (m, 1 H, bridgehead proton), and 7.68–8.37 (m, 4 H).

9-Benzonorbornenone (2).—Oxidation of *anti*-9-benzonorbornenol[17] in the same manner as that described by Bartlett and Giddings[17] led to the desired product, which was purified by preparative glpc: ir 1770 cm^{-1} (C=O); nmr τ 2.82 (broad peak, 4 H, aromatic protons), 6.78 (m, 2 H, bridgehead protons), 7.92 (m, 2 H, exo C-2 and C-3 protons), and 8.76 (m, 2 H, endo C-2 and C-3 protons). *Anal.* Calcd for C$_{11}$H$_{10}$O: C, 83.51; H, 6.37. Found: C, 83.49; H, 6.27.

Esr Spectra.—The radical anions were prepared under vacuum (*ca.* 0.1 μ) by the reduction of ketones and diketones with alkali metals using standard procedures described elsewhere.[2a] All reactions were carried out in a sealed-off glass apparatus that included a cell for esr measurement. Esr spectra were obtained with a Varian 4502 spectrometer with a "field dial" using 100-kc field modulation. Low-temperature experiments were made using a Varian variable-temperature control unit. The temperature reading was found to be accurate within ±3°. Hyperfine frequencies were calibrated using a Harvey-Wells proton gaussmeter and a Beckman frequency counter.

A. Reduction of 7-Norbornenone (1).—The ketone (10 mg) in DME (*ca.* 2.5 ml) was treated with potassium at −78°. The solution became yellow-orange at 25° and the esr spectrum was resolved into a 1:2:1 triplet, $a_H = 2.69$ G (2 H). Each peak was further split into a 1:4:6:4:1 quintet, $a_H = 0.44$ G (4 H). A 1:1 doublet ($a = 15.2$ G) was detected that was symmetrically disposed about the center peak and slightly less intense.[14] The use of THF instead of DME as solvent gave similar results at 25°, $a_H = 2.59$ G (2 H) and $a_H = 0.41$ G (4 H). A 1:1 doublet, $a = 15.2$ G, was also observed. When the ketone (10 mg) in DME (*ca.* 2 ml) was treated with sodium at 25°, only a single peak (width *ca.* 13 G) was detected. All attempts to obtain a resolved spectrum at temperatures ranging from −80 to 50° failed.

B. Reduction of 9, 10, and 11.—The ketones in DME were treated with potassium at −78°. The following values were obtained at 25°: from 9, $a_H = 2.69$ G (2 H) and $a_H = 0.44$ G (2 H); from 10, $a_H = 2.65$ G (2 H) and $a_H = 0.46$ G (2 H); and from 11, $a_H = 2.68$ G (2 H) and $a_H = 0.4$ G (2 H).

C. Attempted Reduction of 13, 14, and 15.—The ketones in DME were treated with potassium at −78°. No esr signals were observed at temperatures ranging from −78 to 25°. The results were the same when the solutions were maintained at 25° for several hours.

D. Reduction of Bicyclo[2.2.2]oct-5-ene-2,3-dione (7).—The diketone[9] (1 mg) in DME (*ca.* 1.5 ml) was treated with potassium at 25°. The spectrum was well simulated using values of $a_H = 2.68$ G (2 H) and $a_H = 0.46$ G (4 H). Additional hyperfine splitting of $a = 0.1$ G was also observed, but it was not possible to determine the multiplicity. This hyperfine splitting is most likely due to the potassium cation. When the signal level was increased by a factor of 100, the hyperfine splitting by ^{13}C in natural abundance was easily observed. The value obtained, $a_C = 6.12$ G, is attributed to the carbonyl carbon.[11]

E. Reduction of 9-Benzonorbornenone (2).—The ketone (25 mg) in DME (*ca.* 3.5 ml) was treated with potassium at −78°. The best resolved spectra were recorded at −40°, where a 1:2:1 triplet, $a_H = 2.35$ G (2 H), was observed. Each peak was split into 11 additional peaks and possibly more, with a separation of 0.09 G. Some of this additional hyperfine splitting is most likely due to the potassium cation. In another experiment, the ketone (10 mg) in DME (*ca.* 2 ml) was treated with sodium at 25°. At −40° the relative intensities of the various lines were in accord with a triplet splitting of $a_H = 2.35$ G (2 H) and a 1:1:1:1 quartet splitting of $a_{Na} = 0.7$ G (1 Na).

F. Reduction of Benzobicyclo[2.2.2]oct-5-ene-2,3-dione (8).—The diketone[9] (2 mg) in DME (*ca.* 2 ml) was treated with potassium at 25°, and a triplet, $a_H = 2.35$ G (2 H), was observed. Additional splitting, as found in the reduction of 2, was detected. In another experiment, the diketone (2 mg) in DME (*ca.* 3 ml) was treated with sodium at 25°. The best resolved spectra were recorded at −20°, where the following values were obtained: $a_H = 2.35$ G (2 H), $a_{Na} = 0.73$ G (1 Na, 1:1:1:1 quartet splitting), $a_H = 0.18$ G (2 H), and $a_H = 0.09$ G (4 H).

Reactions of Some Methylene Ketones with Dimethyl Phthalate. A New Route to 2-Substituted 1,3-Indandiones

WILLIAM A. MOSHER* AND ROBERT W. SOEDER

Department of Chemistry, University of Delaware, Newark, Delaware 19711

The reactions of methyl ketones with dialkyl phthalates to yield 2-acyl-1,3-indandiones have been the object of several investigations.[1-3] The present note describes the reactions of ketones containing one or two methylene groups adjacent to the carbonyl, hereafter called methylene ketones, with dimethyl phthalate (1). Symmetric and unsymmetric methylene ketones have been condensed with 1 in the presence of sodium methoxide or sodium hydride. 3-Pentanone and 4-heptanone gave respectively 2-methyl- and 2-ethyl-1,3-indandione. The mechanism shown in Scheme I is

(20) A. Streitwieser, Jr., D. E. Van Sickle, and W. C. Langworthy, *ibid.*, **84**, 244 (1962).

(21) M. A. Battiste, C. L. Deyrup, R. E. Pincock, and J. Haywood-Farmer, *ibid.*, **89**, 1954 (1967).
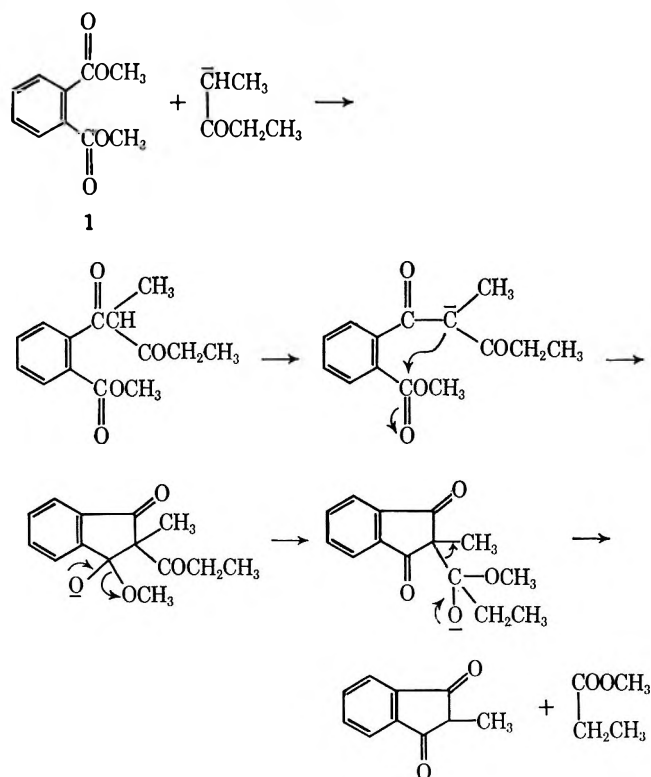
(22) H. Tanida, T. Tsuji, and T. Irie, *ibid.*, **89**, 1953 (1967).

(1) E. Schwerin, *Chem. Ber.*, **27**, 104 (1894).

(2) L. B. Kilgore, J. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

(3) S. Shapiro, K. Geiger, and L. Freedman, *J. Org. Chem.*, **25**, 1860 (1960).

SCHEME I

1

suggested for the reaction of 3-pentanone with phthalate 1. The identification of methyl propionate as one of the products of this reaction supports the above mechanism.

In the reaction of the unsymmetric methylene ketones with phthalate 1, a combination of steric and electronic factors are involved, since there is the possibility of the formation of two different anions.
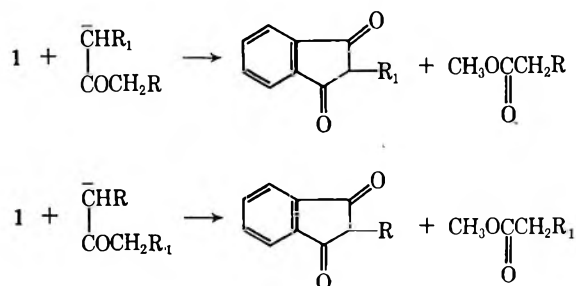
The reaction of 3-hexanone with 1 gave a mixture of 2-methyl- and 2-ethyl-1,3-indandiones in a ratio of 3.3:1. 1-Phenyl-2-butanone yielded 2-phenyl- and 2-methyl-1,3-indandiones in the ratio of 1.55:1. Reaction of 1 with methylene pyridyl ketones, such as 1-(2-pyridyl)- and 1-(4-pyridyl)-2-butanones and 1-phenyl-3-(2-pyridyl)- and 1-phenyl-3-(4-pyridyl)-2-propanones, gave 2-(2-pyridyl)- and 2-(4-pyridyl)-1,3-indandiones (2 and 3), respectively, indicating that the activating effect of the pyridine ring dictates which anion is formed.

Propiophenone, a methylene ketone containing one methylene group instead of two as the ketones above mentioned, reacted with 1 to give 2-methyl-1,3-indandione.

Experimental Section[4]

Reaction of 3-Pentanone with Phthalate 1.—To a dispersion of sodium hydride (50% in mineral oil, 24 g) in anhydrous benzene (500 ml) was added slowly a mixture of 3-pentanone (41 g) and phthalate 1 (100 g), and the mixture was refluxed for 15 hr. The deep red solid formed on cooling was collected by filtration, dried *in vacuo*, and dissolved in water (750 ml), and the solution was acidified with concentrated HCl to give a 68% yield of 2-methyl-1,3-indandione, mp 83–84°, identical (mixture melting point and ir) with an authentic sample.[5]

In a second preparation, using freshly distilled solvent and reactants, the reaction mixture, after the 15-hr refluxing period, was distilled almost to dryness. Four cuts were taken. The first three cuts contained benzene and a little methanol. The fourth cut contained methyl propionate, identified by comparison (vpc and ir) with an authentic sample.

Reaction of 4-Heptanone with Phthalate 1.—The crude product obtained by condensing 4-heptanone with phthalate 1 as in the procedure described above was chromatographed on alumina (elution with chloroform) to give a 54% yield of a pale yellow compound of mp 51–51.5°, identical (mixture melting point and ir) with an authentic sample of 2-ethyl-1,3-indandione.[5]

Reaction of 3-Hexanone with Phthalate 1.—A mixture of 3-hexanone (1 g), dimethyl phthalate 1 (1.94 g), benzene (1.5 ml), and sodium methoxide (0.54 g) was heated in a sealed tube at 100° for 48 hr. The cooled tube was opened, the charge filtered into a Dry Ice trap, the filtrate flash distilled into another Dry Ice trap, and the liquid analyzed by vapor phase chromatography. 2-Methyl- and 2-ethyl-1,3-indandione in molar ratio 3.3:1 were obtained.

Reaction of 1-Phenyl-2-butanone with Phthalate 1.—A mixture of 1-phenyl-2-butanone (19.8 g) and 1 (19.4 g) was added slowly to sodium methoxide (5.4 g) in anhydrous benzene (175 ml) and heated to reflux. After 48 hr, the red reaction mixture was cooled and the solid washed with ether, dried *in vacuo*, dissolved in water, and acidified with concentrated HCl. The resultant red oil was extracted with benzene and the benzene layer, after drying over sodium sulfate, was chromatographed on an alumina column made up with benzene. The first band gave 2-methyl-1,3-indandione (1 g), mp 80° [mmp (with an authentic sample) 79–80°] and the second band yielded 2-phenyl-1,3-indandione (2.15 g) as orange plates, mp 144–146° (ethanol) (lit.[6] 145°). The molar ratio of 2-phenyl- to 2-methyl-1,3-indandione was 1.55:1.

The dioxime of 2-phenyl-1,3-indandione melted at 197–199° (lit.[7] 193–196°).

2-(2-Pyridyl)-1,3-indandione (2). Method A.—A solution of 1-(2-pyridyl)-2-butanone[8] (14.9 g) and phthalate 1 (19.4 g) in anhydrous benzene (50 ml) was added to sodium methoxide (5.4 g) in anhydrous benzene (150 ml). The mixture was refluxed for 48 hr, then cooled, and filtered. The precipitate was dissolved in water. Neutralization of the aqueous solution with concentrated HCl gave 2 as a yellow solid, mp 278–281 (ethanol). An additional amount of 2 was obtained by extracting the mother liquor with water and neutralizing the aqueous solution with concentrated HCl. A total yield of 3.2 g was obtained. Compound 2 was identified by mixture melting point determination with an authentic sample prepared from phthalic anhydride and 2-picoline.[9]

Method B.—A solution of 1-phenyl-3(2-pyridyl)-2-propanone (14.5 g) (prepared by the procedure of Uhlemann,[10] with the exception that phenylacetyl chloride was used in place of ethyl phenylacetate) and compound 1 (13.3 g) in anhydrous benzene (100 ml) was added to sodium methoxide (4.0 g) in anhydrous benzene (125 ml) under nitrogen. The reaction mixture was refluxed for 88 hr, allowed to cool, and poured into water, and

(4) Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. For high melting point compounds a sealed capillary tube was used. The infrared spectra were determined in potassium bromide pellets with a Baird Model B recording spectrophotometer. Elemental analyses were performed by Dr. A. Bernhardt, Microanalytisches Laboratorium Max Planck Institute für Kohlenforschung, Mulheim (Ruhr), West Germany.

(5) C. F. Koelsch and D. J. Byers, *J. Amer. Chem. Soc.*, **62**, 560 (1940).

(6) F. Nathanson, *Chem. Ber.*, **26**, 2576 (1893).

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(9) K. Zalukaev and E. Vanag, *J. Gen. Chem. USSR*, **27**, 3314 (1957).

(10) I. E. Uhlemann, *J. Prakt. Chem.*, **14**, 281 (1961).

the benzene layer was extracted twice with water. The combined water layers were extracted with chloroform, treated with concentrated HCl to pH 7, and again extracted with chloroform. The chloroform layer was dried and chromatographed on an alumina column made up with benzene (elution with chloroform) to give, upon distillation of the solvent and recrystallization of the residue from ethanol–chloroform, 0.4 g of 2, mp 278–280°, identical with an authentic sample (mmp 277–279°).

2-(4-Pyridyl)-1,3-indandione (3). Method A.—1-(4-Pyridyl)-2-butanone[11] was condensed with compound 1 following the procedure above described for compound 2 (method A). Recrystallization from ethanol gave 3 as yellow crystals, mp 309–312°. The identity of 3 was established by mixture melting point determination with an authentic sample prepared from phthalide and picolinaldehyde (see method C).

Method B.—1-Phenyl-3(4-pyridyl)-2-propanone, prepared by the procedure above reported for 1-phenyl-3(2-pyridyl)-2-propanone, was condensed with compound 1 under the conditions above described for compound 2 (method B). Chromatography and recrystallization from ethanol gave 3 as yellow crystals, mp 313–316°, identical (mixture melting point) with an authentic sample.

Method C.—This method is similar to that used by Horton and Murdock for preparing 2-aryl-1,3-indandiones.[12] Sodium methoxide (14 g) was added slowly to a solution of phthalide (33.5 g) and picolinaldehyde (27 g) in ethanol (100 ml) under nitrogen, and the mixture was heated at reflux for 3 hr. The red precipitate formed on cooling was collected by filtration and dissolved in hot water (750 ml), and the solution was made slightly acid with concentrated HCl. The precipitate crystallized from ethanol gave a 40% yield of 3 as yellow crystals, mp 312–314°.

Anal. Calcd for $C_{14}H_9NO_2$: N, 6.28. Found: N, 5.91.

Reaction of Propiophenone with Phthalate 1.—A mixture of propiophenone (33.5 g) and compound 1 (48.5 g) was added to a dispersion of sodium hydride (50% in mineral oil, 12 g) in anhydrous benzene (500 ml). The reaction mixture was refluxed for 22 hr, cooled, and filtered. The red solid was washed with ether, dried *in vacuo*, and dissolved in water, (800 ml), and the solution was acidified with concentrated HCl. Chromatography of the resultant yellow oil on an alumina column made up with benzene–hexane (elution with chloroform) gave 11 g (27.5%) of 2-methyl-1,3-indandione as yellow solid, mp 78–80°.

(11) C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 939 (1957).
(12) R. L. Horton and K. C. Murdock, *ibid.*, **25**, 938 (1960).

Heterocyclic Analogs of Fulvene and Fulvalene. III. Δ³,³'-Bi-3H-indazole

JOHN H. M. HILL, D. M. BERKOWITZ, AND K. J. FREESE

Department of Chemistry, Hobart and William Smith Colleges, Geneva, New York 14456

In an earlier part of this series we described the synthesis of Δ²,²'-bi-2H-benzimidazole (I).[1] Here we report the synthesis and properties of the remaining dibenzotetraazafulvalene, Δ³,³'-bi-3H-indazole (II). A common intermediate in all routes to this compound was 3,3'-bi-1H-indazole (III); the routes differed only in the method of synthesis of III and its subsequent oxidation.

(1) J. H. M. Hill, *J. Org. Chem.*, **28**, 1931 (1963).

The most satisfactory of the several pathways to III investigated involved the direct synthesis of the biindazole from a suitably substituted bibenzyl derivative. 2,2'-Dinitrobibenzyl (IV) was simultaneously reduced and acetylated by catalytic hydrogenation in acetic anhydride, and the resulting 2,2'-diacetamidobibenzyl (V) was nitrosated with nitrosyl chloride. Nitrogen trioxide or nitrogen tetroxide was found to be less satisfactory in this particular case.[2] The resulting N,N'-dinitroso-2,2'-diacetamidobibenzyl (VI) was isomerized to bibenzyl-2,2'-diazoacetate (VII) by gentle warming in solution.[3] Cyclization of VII to III occurred when the temperature was raised to reflux.[4]

In this sequence all steps except the final ring closure proceeded with good yield. This last step gave erratic results and the reaction product was contaminated with appreciable amounts of tar, which was difficult to remove. Carrying out the rearrangement and cyclization in a variety of other solvents did not improve the yield or produce a cleaner product. The following yields are typical of those obtained in other solvents: C_6H_6, 29%; $CHCl_3$, 11%; CCl_4, 14%; *tert*-BuOH, 23%; C_6H_{12}, 14%.
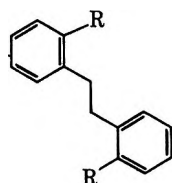
IV, R = NO₂
V, R = NHCOCH₃
VI, R = N(NO)COCH₃
VII, R = N₂OCOCH₃
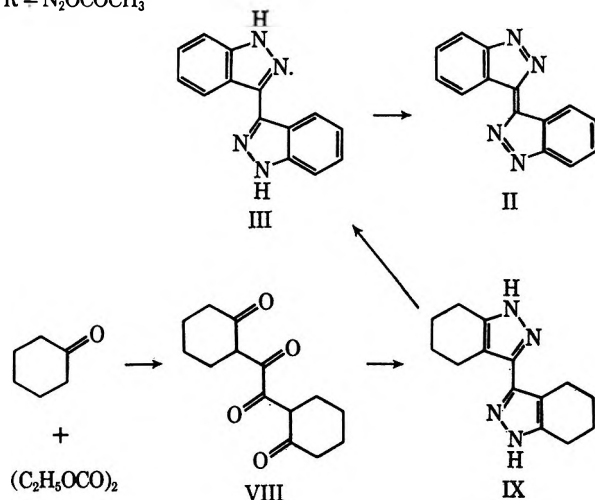
A second successful stepwise route to III was developed: cyclohexanone condensed with ethyl oxalate to yield the tetraketone VIII. Examination of the –OH and –C=O absorbances in the infrared spectrum of VIII indicated that it was almost totally enolized. Treatment of VIII with hydrazine cyclized it to the bipyrazole (IX) which was aromatized to III by prolonged heating with palladium catalyst. Overall, this

(2) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008 (1955).
(3) The loss of the nitroso function was monitored by infrared; this was complete in about 5 hr.
(4) R. Huisgen and H. Nakaten, *Justus Liebigs Ann. Chem.*, **586**, 84 (1954).

route was less satisfactory than the former, as the initial condensation to produce VIII often gave a product contaminated with appreciable amounts of ethyl cyclohexanone-2-glyoxalate, which was difficult to remove.

Interestingly, it had earlier been claimed that IX was the product of the reaction of 2-cyanocyclohexanone semicarbazone with acid.[5] We repeated this reaction and found that the reaction product was, in fact, 1,2,-3,4-tetrahydroindazolo[3,2,-*b*]-1,2,3,4-tetrahydroquinazol-7-imine. Authentic material was made from the reaction of 2-cyclocyclohexanone azine with acid.[6,7]

Oddo and Raffa claimed that oxidative dimerization of indole to 3,3'-biindole occurred when indole was heated with sulfur.[8] A similar experiment with indazole yielded a tarry product from which most of the indazole could be isolated unchanged. There was no evidence for the formation of III. The Ullmann reaction of 3-iodoindazole with copper in dimethylformamide also failed to yield any III; only the copper salt of 3-iodoindazole was isolated.

While the oxidation of 2,2'-bibenzimidazole to I was easily effected by lead peroxide in chloroform,[1] III was destroyed under these conditions, and from the reaction mixtures the only recognizable product isolated was a small amount of phenanthraquinone. We found, however, that lead tetraacetate in anhydrous acetonitrile,[9] containing sufficient magnesium oxide to ensure that the acetic acid liberated during the reaction would be removed rapidly, converted III into II which could be isolated as a deep red solid by low-temperature evaporation of the resulting crimson solution. A more satisfactory indirect oxidation involved treatment of III with *N*-bromosuccinimide, isolation of the relatively stable 1,1'-dibromo-3,3'-bi-1*H*-indazole (X), and its subsequent debromination with silver powder. In this way reasonably stable solutions of II were easily prepared in a variety of solvents and a crystalline product could be isolated by evaporation of the solvent *in vacuo* at low temperature. The intense color of X is surprising, as *N*-bromo compounds are usually colorless. An alternative formulation for X, which is consistent with the analytical and spectroscopic data, is that of a charge-transfer complex between molecular bromine and II. The fact that treatment of II with an equivalent amount of bromine results in the regeneration of X supports this suggestion.

The identity of products from both synthetic routes does not rule out completely the possibility that the cyclization steps in each case gave rise to the isomeric structure with fused six-membered rings. This being the case, II would be cinnolino[4,3-*c*]cinnoline (XI) and III would be the corresponding 6,12-dihydro derivative. In the absence of an available synthesis of XI or the unsubstituted dihydro derivative for comparison, the evidence appears to support the original formulation. Several substituted 6,12-dihydrocinnolino[4,3-*c*]cinnolines have been described in patent literature as highly colored compounds;[10] III is colorless and has an ultraviolet spectrum similar in both wavelength and absorbance to indazole. In the infrared III shows a peak at 6.18 μ which is also observed in indazole and several substituted indazoles. The observed photochemical and thermal lability of II and its facile, reversible conversion into III is inconsistent with an aromatic structure such as XI. Furthermore, it seems unlikely that the aromatization of VIII to III would stop at the dihydro stage and not continue to the fully aromatic structure XI. In fact, the ready conversion of II to III affords an efficient titrametric assay for II in solution. II reacts rapidly and quantitatively with hydroquinone to give *p*-benzoquinone and III.[11] End points are easily observed using the color of II.

At the inception of this work it was hoped that II would demonstrate some interesting photochemical and thermal properties, *e.g.*, benzocyclopropene formation.[12] This expectation has not been realized. Although II was rapidly photolyzed in a variety of solvents and at several wavelengths and temperatures, mainly polymeric products were formed. For example, photolysis in methanol under nitrogen yielded very small amounts of phenanthrene, and in air, in benzene, phenanthraquinone was the only isolable product. In both cases polymer constituted the bulk of the product. Photolysis at low temperature (~−60°) under the same conditions also yielded polymeric material. Heating II in solution or in the solid phase also produced a yellow polymer from which small amounts of phenanthraquinone and occasionally benzil could be obtained.

The polymer from II contained a negligible amount of nitrogen. Consequently, a process must operate by which nitrogen is lost sequentially or simultaneously from the indazole rings. An analogous compound, spiro[fluorene-9,3'-indazole] (XII), loses nitrogen, thermally or photochemically, *via* intermediate XIII, which is either a singlet or triplet diradical.[13,14] Similarly II could produce an intermediate XIV which, *via* an appropriate rotamer, could cyclize and rearrange and then yield the observed products phenanthrene, phenanthraquinone, or benzil by abstraction of hydrogen from solvent or reaction with molecular oxygen. Attempts to trap XIV by low-temperature photolysis in

XII · XIII · XIV
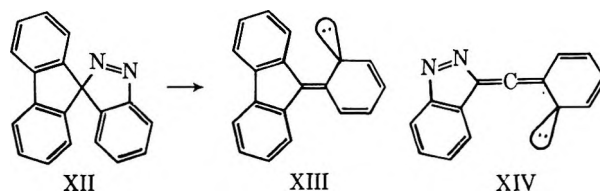
the presence of *N*-phenylmaleimide or cyclohexene yielded only a polymer whose infrared spectrum showed incorporation of the alicyclic group. No nonpolymeric material could be isolated.

Further attempts to characterize II showed that it was unreactive to dienes[9] and stable to bases. It re-

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(13) G. Baum, R. Bernard, and H. Shechter, *ibid.*, 89, 5307 (1967).

(14) Attempts to prepare the more directly analogous system, spiro[indazole-3,3'-indazole] by addition of benzyne to 3-diazoindazole have, to date, been unsuccessful.

acts rapidly with acids to regenerate moderate amounts of III.

Experimental Section

Infrared spectra were determined on a Beckman IR-8 spectrophotometer. Electronic spectra were obtained on a Beckman DB spectrophotometer. Nmr spectra were determined on a Varian T-60 spectrometer. Melting points were uncorrected and determined in sealed capillaries.

2,2′-Diacetamidobibenzyl (V).—A solution of 2,2′-dinitrobibenzyl (27.1 g, 0.1 mol) in a mixture of acetic anhydride (120 ml) and acetic acid (70 ml) containing 10% palladium-on-carbon catalyst (0.2 g) was hydrogenated at an initial pressure of 4 atm at room temperature. The exothermic reaction was complete in 40 min; hydrogen uptake ceased abruptly. The solution was filtered hot, concentrated *in vacuo* to 100 ml, and cooled to 0°. The crude product was recrystallized from glacial acetic acid to give V as white crystals (16.8 g, 57%): mp 268–269° (lit.[15] 249–250°); ir (Nujol) 6.12 μ (C=O); nmr (TFA) δ 7.2 (m, 8, aromatic), 3.05 (s, 4, –CH₂CH₂–), 2.31 (s, 6, CH₃CO) ppm.

N,N′-Dinitroso-2,2′-diacetamidobibenzyl (VI).—A solution of V (38 g, 0.128 mol) in acetic acid (200 ml) containing acetic anhydride (70 ml) and sodium acetate (28 g) was stirred for 1 hr at room temperature and cooled to 0°; nitrosyl chloride was bubbled in for 4 hr, maintaining the temperature between 0 and 4°. The resulting dark red solution was stored at 0° for 10 hr and then added slowly to 1 l. of water and 500 g of crushed ice with stirring. The yellow oil which separated crystallized. This was dissolved in the minimum amount of hexane and stored at −20° overnight. VI separated as pale yellow crystals (21.4 g, 47%): mp 75° dec; ir (CCl₄) 5.81 (C=O), 6.62 μ (N=O); nmr (CDCl₃) δ 7.28 (m, 8, aromatic), 3.18 (s, 4, –CH₂CH₂–), 2.28 (s, 6, CH₃CO) ppm.

Anal. Calcd for C₁₈H₁₈N₄O₄: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.86; H, 4.81; N, 16.04.

3,3′-Bi-1H-indazole (III).—A solution of VI (15.4 g, 0.044 mol) in benzene (800 ml) was maintained at 35° for 1 hr and at 45° for 7 hr. The solution went from pale yellow to light brown. After 10 hr at room temperature it was refluxed for 10 hr. The solvent was distilled *in vacuo* and the black residue was recrystallized three times from aqueous acetic acid using charcoal. III was obtained as tan crystals (3.1 g, 29%): mp 328–330°; uv (EtOH) 314 nm (log ε 4.27); ir (Nujol) 3.13 (N–H), 6.18, 7.46, 7.95 (aromatic C=C, C=N), 9.21, 9.96, 10.22, 11.21, 13.08, 13.68 μ; nmr (DMSO-d₆) δ 6.6–7.8 (m, aromatic) ppm.

An analytical sample was prepared by sublimation (120°, 0.1 mm).

Anal. Calcd for C₁₄H₁₀N₄: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.58; H, 4.33; N, 24.08.

Bis(2-oxocyclohexylidene)glyoxal (VIII).—To a slurry of sodium methoxide (35 g, 0.65 mol) in anhydrous ether (300 ml) was added, with vigorous stirring at 0°, a mixture of cyclohexanone (49 g, 0.5 mol) and ethyl oxalate (36.5 g, 0.25 mol). When addition was complete (1 hr) the mixture was stirred at room temperature for 2 days. The sodium methoxide dissolved initially to form an orange solution from which precipitated a solid. The solid was filtered, washed with ether, and dissolved in water (250 ml). The solution was extracted once with ether (100 ml), acidified to pH 3 with acetic acid, and extracted in a continuous extractor with ether. Washing of the ether (saturated aqueous NaCl), drying (MgSO₄), and evaporation yielded a yellow gum which could not be induced to crystallize. Some purification was effected by solution in aqueous base, extraction with ether, acidification, and reextraction. IX was obtained as a yellow gum (32.7 g, 52%): uv (EtOH) 288 nm (log ε 3.35), 236 nm (log ε 4.31); ir (film) 3.1 (enolic OH), 3.42 (C–H), 5.85 μ (C=O); nmr (CDCl₄) δ 1.72 (s, 12, –CH₂–), 2.42 (m, 4, –CH₂–), 9.4 (broad s, 2, enolic OH) ppm.

An analytical sample of IX was prepared by thick layer chromatography (SiO₂ with 1:1 methanol:methylene chloride elution).

Anal. Calcd for C₁₄H₁₈O₄: C, 67.18; H, 7.25. Found: C, 66.88; H, 7.39.

3,3′-Bi-4,4′,5,5′,6,6′,7,7′-tetrahydro-1H-indazole (IX).—A solution of IX (2.48 g, 0.01 mol) in ethanol (25 ml) was treated with hydrazine hydrate (1.0 g, 0.02 mol). After the exothermic reaction had ceased the solution was refluxed for 2 hr and then

poured into water (200 ml); the gummy product was separated and triturated with benzene. The resulting white solid was sublimed (120°, 0.01 mm) to yield X (0.84 g, 33%): mp 320–322° dec; ir (Nujol) 3.08 (N–H), 6.33 (C=C or C=N), 7.72, 7.91, 8.08, 9.02, 10.15 μ; nmr (DMSO-d₆) δ 1.73 (broad s, 8, –CH₂–), 2.62 (broad s, 8, –CH₂–) ppm; nmr (TFA) 2.00 (broad s, 8, –CH₂–), 2.83 (d, 8, J = 14 Hz, –CH₂–) ppm.

Anal. Calcd for C₁₄H₁₈N₄: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.08; H, 7.33; N, 22.87.

3,3′-Bi-1H-indazole (III).—A mixture of X (0.5 g, 0.002 mol) in decalin (10 ml) containing 10% palladium on carbon (0.5 g) was refluxed for 24 hr and filtered while hot. The filtrate was diluted with hexane (20 ml) and cooled to 0° for 12 hr. The precipitate (0.08 g) was purified by sublimation (140°, 0.1 mm) to yield III (0.04 g, 8%), mp 328–330°, identical in all respects with the material from the other synthetic route.

Δ³,³′-Bi-3H-indazole (II). Method A.—A solution of III (0.5 g, 0.002 mol) in anhydrous acetonitrile (50 ml) containing magnesium oxide (5 g) was treated at 0° under nitrogen with lead tetraacetate (2.0 g, 0.0045 mol) in small portions. The resulting deep red solution was stirred for 3 hr and poured into an ice-cold two-phase mixture of chloroform (50 ml) and 5% aqueous sodium bicarbonate (200 ml). The chloroform was separated, the aqueous phase was extracted with chloroform (two 50-ml portions), and the combined chloroform extracts were thoroughly washed with ice-cold 5% aqueous sodium bicarbonate, dried (MgSO₄), and evaporated *in vacuo* at 0° to yield II as an unstable deep red solid (0.17 g, 34%), which decomposed to a yellow polymer on warming: uv (CHCl₃) 442 nm (log ε 3.37); ir (CHCl₃) 3.30 (=CH), 6.28, 6.84, 7.05, 7.51, 7.82 μ (C=C or N=N); nmr (CDCl₃) δ 7.2–7.6 (m, aromatic) ppm.

Anal. Calcd for C₁₄H₈N₄: C, 72.40; H, 3.47; N, 24.12. Found: C, 72.06; H, 3.30; N, 23.80. (Nitrogen analysis was determined on separately prepared sample.)

Method B.—A suspension of III (0.234 g, 0.001 mol) in carbon tetrachloride (50 ml) containing magnesium oxide (2 g) was treated at room temperature with N-bromosuccinimide (0.356 g, 0.002 mol), added in small portions. The solution became deep red. After 2 hr the solution was filtered and cooled to −20°. Precipitation of X as brown crystals was complete in 3 hr. X was stable at −20° for several days without change. It was recrystallized by solution in carbon tetrachloride at 30° followed by cooling to −20° and was obtained as dark brown needles (0.18 g, 46%), no definite melting point: uv (EtOH) 457 nm (log ε 4.04); ir (CHCl₃) 6.25, 7.56 μ (C=C or C=N).

Anal. Calcd for C₁₄H₈N₄Br₂: C, 42.88; H, 2.05; N, 14.29. Found: C, 43.05; H, 2.28; N, 14.08.

XI (0.1 g, 0.00025 mol) was dissolved in distilled chloroform (25 ml), and silver powder (0.5 g) was added. The mixture was stirred at 0° for 2 hr, filtered, and evaporated *in vacuo* at 0° to yield II (0.053 g, 90%). The spectroscopic properties of this material were identical with the product from method A.

Photolysis of II.—The following is representative of several runs. A solution of II (0.464 g, 0.002 mol), in benzene, prepared by method B was photolyzed at 0° in a Rayonet photochemical reactor (360-nm lamps). The color faded in several minutes and a yellow solid precipitated. The solvent was evaporated and the residue sublimed (100°, 0.01 mm) to yield pale yellow crystals of phenanthraquinone (0.033 g, 8%), mp 207–208° (lit.[16] 208.5–210°), identical in all respects with authentic material. The nonsublimable material was insoluble in all common solvents. It showed ir (Nujol) 5.92 μ (C=O).

Thermolysis of II.—Solid II (0.100 g, 0.0004 mol) was placed in a sublimation apparatus and immersed in an oil bath at 100°. The color rapidly faded and a yellow solid remained. Vacuum was applied (0.01 mm) and a yellow solid sublimed. This was analyzed by tlc (silica gel G with benzene elution). Exposure of the plate to iodine vapor showed several spots; the major ones had R_f values identical with those of phenanthraquinone and benzil. Thick layer chromatography of the sublimate (0.009 g) with benzene elution afforded two main fractions which were phenanthraquinone (0.008 g, 6%) and benzil (0.001 g, 1%) identified by mixture melting points and ir comparison.

Registry No.—II, 28228-82-2; III, 28228-83-3; V, 28228-84-4; VI, 28228-85-5; VIII, 28228-86-6; IX, 28228-87-7; X, 28312-63-2.

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(16) J. Kenner and J. Wilson, *J. Chem. Soc.*, **130**, 1111 (1927).

Reactions of Tetramethyl-2-tetrazene with Diphenylketene and Isocyanates
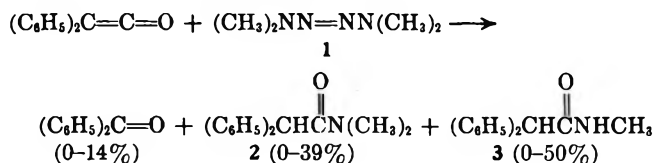
ROBERT C. KERBER* AND THOMAS J. RYAN

*Department of Chemistry, State University of
New York at Stony Brook, Stony Brook, New York   11790*

Although the reactions of 2-tetrazenes with acids were first reported in 1878 and have received considerable attention since then,[1] reactions with other electrophiles, especially alkylating[2] and acylating[3] agents, have only recently begun to receive attention. Reaction in all of these cases is initiated by coordination of a terminal nitrogen of the tetrazene with the electrophilic reagent, followed by breaking of the N–N single bonds, with formation of molecular nitrogen and radical and/or ionic species. We here report the analogous reactions of tetramethyl-2-tetrazene (1) with diphenylketene and with phenyl and p-toluenesulfonyl isocyanates.

Diphenylketene and tetramethyl-2-tetrazene (1) react in carbon tetrachloride to afford variable yields of benzophenone, N,N-dimethyl-2,2-diphenylacetamide (2), and N-methyl-2,2-diphenylacetamide (3). The yields of the individual products varied widely in the several runs carried out, as did the time required to consume all the diphenylketene.

$$(C_6H_5)_2C=C=O + (CH_3)_2NN=NN(CH_3)_2 \longrightarrow$$

1

$$(C_6H_5)_2C=O + (C_6H_5)_2CHC\overset{O}{\overset{\|}{C}}N(CH_3)_2 + (C_6H_5)_2CHC\overset{O}{\overset{\|}{C}}NHCH_3$$

(0–14%)   2 (0–39%)   3 (0–50%)

Phenyl isocyanate (4) reacts with the tetrazene 1 to yield 1-phenyl-3,3-dimethylurea (6) (94–100%), molecular nitrogen, and a small amount of another product which was assigned the structure 8 (Scheme I) on the basis of its spectra. The infrared spectrum of 8 had bands at 3.04 (NH), 6.00 (urea carbonyl), and 13.14 and 14.33 μ (monosubstituted phenyl). The nmr (CDCl₃) had peaks at δ 2.53 (s, 6 H), 2.92 (s, 3 H), and 6.92–7.62 (m, *ca.* 5 H). The ultraviolet spectrum had λ_{max} (EtOH) at 275 nm (ε 1200) and 240 (26,000). A model compound, 1-formyl-1,4,4-trimethyl-2-tetrazene, has λ_{max} (EtOH) at 275 nm (ε 18,800) and nmr peaks at 3.03 (s, 6 H) and 3.16 (s, 3 H).[4]

When the reaction of phenyl isocyanate and 1 was carried out in a flask with a low actinic coating (spectral transmission varies between 0 at 300 nm and 4% at 500 nm), the yield of 6 was sharply reduced (to 60%). This reaction also afforded a small amount of an oil whose nmr spectrum indicated that it contained 1,3,5-trimethylhexahydro-1,3,5-triazine, presumably formed from N-methylmethylenimine.[5]

(1) (a) E. Fischer, *Justus Liebigs Ann. Chem.*, **190**, 67 (1878); (b) H. Weiland, *Ber.*, **41**, 3498 (1908); *Justus Liebigs Ann. Chem.*, **392**, 133 (1912); (c) W. R. McBride and W. E. Thun, *Inorg. Chem.*, **5**, 1846 (1966); (d) C. G. Overberger and B. S. Marks, *J. Amer. Chem. Soc.*, **77**, 4097 (1955).

(2) (a) W. H. Bruning, C. J. Michejda, and D. Romans, *Chem. Commun.*, 11 (1967); (b) C. J. Michejda and D. Romans, *Tetrahedron Lett.*, 4213 (1969).

(3) (a) S. F. Nelsen, *J. Amer. Chem. Soc.*, **88**, 5666 (1966); (b) S. F. Nelsen, R. B. Metzler, and M. Iwamura, *ibid.*, **91**, 5103 (1969).

(4) W. E. Thun and W. R. McBride, *J. Org. Chem.*, **34**, 2997 (1969).

(5) E. A. Werner, *J. Chem. Soc.*, 844 (1917).

SCHEME I

$$RN=C=O + (CH_3)_2NN=NN(CH_3)_2 \longrightarrow$$

4, R = C₆H₅
5, R = Ts   1

11

$$RNHC\overset{O}{\overset{\|}{N}}N=NN(CH_3)_2 \overset{?}{\longrightarrow} RNHC\overset{O}{\overset{\|}{N}}NHCH_3 + CH_2=NCH_3 + N_2$$

|
CH₃

8, R = C₆H₅   9, R = Ts
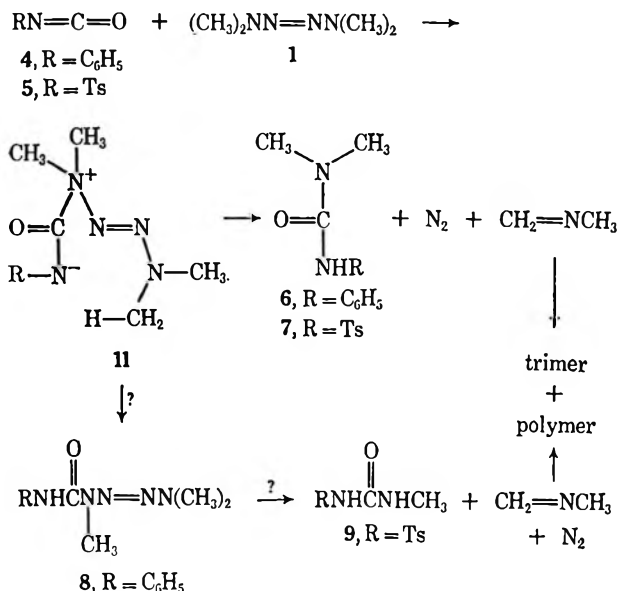
p-Toluenesulfonyl isocyanate (5) reacts rapidly with 1 in carbon tetrachloride to yield 62% of 3,3-dimethyl-1-p-toluenesulfonylurea (7). This compound was identified by comparison of its infrared and nmr spectra with those of an authentic sample synthesized from 5 and dimethylamine. In addition to 7, a small amount of a material similarly identified as 3-methyl-1-p-toluenesulfonylurea (9) was obtained in one run.

Phenyl isocyanate and tetrabenzyl-2-tetrazene afforded after 11 days 3,3-dibenzyl-1-phenylurea (8%), unreacted tetrabenzyl-2-tetrazene (23%), and 6% of a white solid which was assigned the structure 10, analogous to the previously obtained 8. The infrared

$$C_6H_5NHC\overset{O}{\overset{\|}{N}}N=NN(CH_2C_6H_5)_2$$

|
CH₂C₆H₅

10
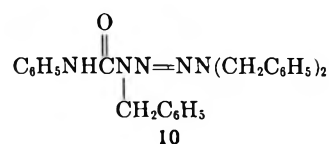
spectrum had bands at 2.99 (NH), 5.99 (urea carbonyl), and 13.32 and 14.45 μ (monosubstituted phenyl). The nmr spectrum (CDCl₃) had peaks at δ 4.50 (s, 4 H), 5.18 (s, 2 H), and 6.93–7.58 (m, *ca.* 20 H). The elemental analysis and a molecular weight determination were consistent with the proposed structure. The mother liquor from the recrystallization of 10 yielded on evaporation an oil which, when treated with 2,4-dinitrophenylhydrazine in strongly acidic ethanol, yielded the 2,4-dinitrophenylhydrazone of benzaldehyde (5%). This is presumed to have been produced from N-benzylbenzylidenimine.

The apparently general reaction which gives rise to 2 from diphenylketene and 1, and to 7 from p-toluenesulfonyl isocyanate and 1, appears to be almost the exclusive path in the phenyl isocyanate–tetramethyltetrazene system. Therefore, our discussion will center on the latter reaction, assuming that the analogous products in the other cases arise by analogous routes. Since the reactions were carried out in carbon tetrachloride, the hydrogen bonded to the 1 nitrogen in the urea product must arise from one of the methyl groups of 1.

Also, since loss of molecular nitrogen occurs, initial attack by the 2 nitrogen of the tetrazene is unlikely. We have not undertaken any mechanistic study as such, but examination of the reaction products suggests a possible mechanism (Scheme I). Initial nucleophilic attack by one of the terminal nitrogens of 1 on the carbonyl of the isocyanate is followed by loss of nitrogen from the resulting species 11, with proton transfer from a methyl group on the other terminal nitrogen to the urea anion. Isolation, in small amounts, of the two compounds 8 and 10, in which the starting tetrazene structure has been maintained, indicates that a species like 11 is a likely intermediate in these reactions. These products (8 and 10) presumably arise from displacement of a methyl (or benzyl) group, presumably as a radical, from 11, followed by hydrogen abstraction from another molecule of tetrazene.

Since the yield of 3,3-dimethyl-1-phenylurea (6) was sharply reduced when light was excluded by carrying out the reactions in coated flasks, one or more reactions leading to this product must be light-induced. Indeed, this effect of light and the variability of the rates and products suggest the involvement of free radicals in the reaction. Perhaps breakup of 11 produces chain-initiating free radicals in addition to the paths sketched in Scheme I. The benzophenone produced from diphenylketene and tetramethyltetrazene might have been formed as a consequence of cycloaddition, the process which we sought (Scheme II). However, no evidence

SCHEME II

$$Ph_2C{=}C{=}O \ + \ (CH_3)_2NN{=}NN(CH_3)_2 \ \longrightarrow$$

$$(CH_3)_2NN{=}C{=}O$$
$$+$$
$$Ph_2C{=}NN(CH_3)_2$$
$$\xrightarrow{+H_2O} \ Ph_2C{=}O$$
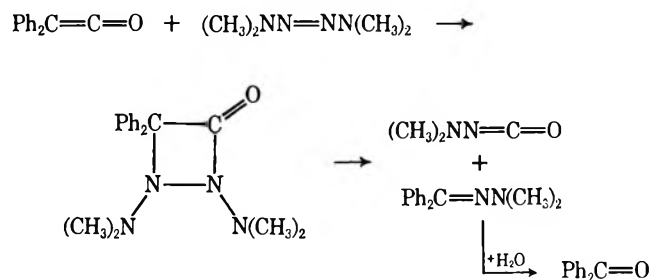
of the dimethylamino isocyanate fragment[6] was obtained. An alternative route to benzophenone would involve reaction of the ketene with oxygen; however, the presence of tetrazene appears to be necessary in order for benzophenone to be obtained in more than trace amounts.

The products 6, 7, and 9 could also have arisen by reaction of dimethylamine or methylamine, formed by acid-catalyzed decomposition of the tetrazene 1,[1] with the appropriate isocyanate. However, the tetrazene was stable in CCl₄ in the absence of isocyanate or ketene. Hydrolysis of the ketene by adventitious water would produce diphenylacetic acid, but the isocyanates, which reacted more rapidly, would not produce acids by this method; we therefore regard the acid-catalyzed route as improbable.

Experimental Section

All melting points and boiling points are uncorrected. The nuclear magnetic resonance spectra were measured with a Varian

A-60 spectrometer. Infrared spectra were determined on a Perkin-Elmer Infracord Model 137. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Tetramethyl-2-tetrazene was prepared by oxidizing 1,1-dimethylhydrazine with mercuric oxide, according to a literature procedure.[7] Tetrabenzyl-2-tetrazene was prepared by oxidizing 1,1-dibenzylhydrazine with quinone.[8] Diphenylketene was prepared from diphenylacetic acid by conversion to the acid chloride, followed by dehydrohalogenation with triethylamine.[9] The phenyl isocyanate was Eastman White Label or redistilled practical grade. p-Toluenesulfonyl isocyanate was used as obtained from the Upjohn Co., Carwin Organic Chemicals, North Haven, Conn.

Reaction of Diphenylketene with Tetramethyl-2-tetrazene.—Diphenylketene (4.04 g, 21 mmol) and tetramethyl-2-tetrazene (3.01 g, 26 mmol) were stirred together in 75 ml of carbon tetrachloride for 3.5 days, after which time no band for diphenylketene (4.79 μ) remained in the infrared spectrum of the reaction mixture.

After the solvent had been stripped off at reduced pressure, the residue was chromatographed on a column of Florisil to afford (a) benzophenone (0.45 g, 12%, eluted with benzene), (b) *N,N*-dimethyl-2,2-diphenylacetamide (1.15 g, 23%, mp 128–131° from ligroin, eluted with benzene), and (c) *N*-methyl-2,2-diphenylacetamide (1.95 g, 39%, eluted with 5–50% ether in benzene, mp 164–166° from benzene–ligroin). The identity of each acetamide was shown by comparison of infrared and nmr spectra and mixture melting point with authentic samples prepared from diphenylacetyl chloride and dimethylamine or methylamine, respectively.

This reaction was rerun several times. The yields of the various products varied considerably from run to run, and the reaction time necessary to consume all of the diphenylketene also varied considerably (10–84 hr).

Reaction of Phenyl Isocyanate with Tetramethyl-2-tetrazene.—Tetramethyl-2-tetrazene (2.86 g, 25 mmol) and phenyl isocyanate (2.98 g, 25 mmol) were stirred together in 75 ml of carbon tetrachloride for 48 hr in a flask fitted with a reflux condenser and drying tube. There was no band for phenyl isocyanate (4.5 μ) in the infrared spectrum of the reaction mixture after this time.

The solution was filtered to remove a yellow precipitate which was shown to be crude 1-phenyl-3,3-dimethylurea by its infrared spectrum. This material was recrystallized once from a benzene–pentane mixture to give material of mp 120–131°. The mother liquor from this recrystallization and the reaction mixture were combined. After removal of the solvents, the residue was chromatographed on a column of Florisil.

Early fractions, eluted with benzene, afforded a low-melting solid, which was rechromatographed on a column of alumina. Elution with 1% ether in benzene yielded 146 mg of a material, mp 61–72°. This was recrystallized from a benzene–pentane mixture to mp 69–73°. The structure 8 was suggested by the spectra of this material: ir (Nujol) 3.04 (w, N–H), 6.00 (m, urea carbonyl), 6.23 (m), 7.43 (m), 7.68 (m), 8.14 (m), 8.43 (m), 8.67 (s), 8.98 (w), 9.54 (w), 9.81 (m), 10.65 (m), 11.02 (m), 11.73 (m), 12.22 (m), 13.14 (m), 13.75 (w), and 14.33 μ (m); nmr and uv in text.

The major product of the Florisil chromatography, eluted with ether, was 3,3-dimethyl-1-phenylurea (total yield 3.86 g, 94%, mp 129–132.5°). The identity of this urea was shown by comparison of its infrared and nmr spectra with those of authentic material which was prepared from phenyl isocyanate and dimethylamine.

When this reaction was rerun in a flask with a low actinic coating (spectral transmission varies between 0 at 300 nm and 4% at 500 nm), the yield of urea was reduced to 59%. Also isolated by chromatography on neutral alumina (eluted with methanol) was an oil whose nmr indicated that it contained 1,3,5-trimethylhexahydro-1,3,5-triazine.

The reaction was rerun on a vacuum line, and the evolved gas was collected and shown by its mass spectrum to be nitrogen (92% yield).

(6) W. S. Wadsworth and W. D. Emmons, *J. Org. Chem.*, **32**, 1279 (1967).

(7) E. Renouf, *Ber.*, **13**, 2169 (1880).

(8) H. Wieland and H. Fressel, *Justus Liebigs Ann. Chem.*, **392**, 144 (1912).

(9) We are grateful to Dr. J. C. Martin, Tennessee Eastman Co., for sending us details of this preparation.

Reaction of p-Toluenesulfonyl Isocyanate with Tetramethyl-2-tetrazene.—Tetramethyl-2-tetrazene (2.95 g, 25 mmol) was dissolved in 50 ml of Spectrograde carbon tetrachloride and placed in a flask fitted with reflux condenser, drying tube, and syringe septum. p-Toluenesulfonyl isocyanate (5.00 g, 25 mmol) dissolved in 25 ml of Spectrograde carbon tetrachloride was introduced gradually into the tetrazene solution by syringe. The solution immediately turned orange and then yellow, and a solid separated out. Enough heat was evolved to cause the solution to reflux. The mixture was stirred for 0.5 hr. An infrared spectrum of the reaction mixture at this time showed no band for p-toluenesulfonyl isocyanate (4.4 μ). Methylene chloride was added to dissolve the precipitated solid, and the resulting mixture was extracted with three 50-ml portions of saturated aqueous sodium bicarbonate solution. These extracts were acidified with 2 N hydrochloric acid and extracted with three 50-ml portions of methylene chloride. Drying the latter extracts over magnesium sulfate and evaporation left 3.72 g (62%) of 1-(p-toluenesulfonyl)-3,3-dimethylurea (7) as a white solid, mp 146–160° dec. In another run, 7 was collected by filtration of the acidified sodium bicarbonate extracts. On standing the filtrate precipitated further solid, which was collected and dried, giving 0.28 g (5%) of 1-(p-toluenesulfonyl)-3-methylurea (9): mp 160–171° dec (lit.[10] mp 170–172°); ir (Nujol) 2.97 (m, N–H), 6.02 (s, C=O), 6.39 (m), 7.50 (m, –SO₂–), 8.59 (s, –SO₂–), 9.16 (w), 10.42 (m), 11.07 (m), 11.37 (m), and 12.27 μ (m); nmr (DMSO-d_6) δ 2.34 (s, 3 H), 2.60 (s, 3 H), 7.39 (d, 2 H), 7.93 (d, 2 H).

Anal. Calcd for C₁₀H₁₄N₂O₃S: C, 49.58; H, 5.78; N, 11.57; S, 13.22. Found: C, 49.30; H, 5.91; N, 11.70; S, 12.99.

Melting of 7 was accompanied by evolution of a gas, presumably dimethylamine, which turned wet pH paper blue-green.

Reaction of Phenyl Isocyanate with Tetrabenzyltetrazene.—Tetrabenzyltetrazene (4.20 g, 0.010 mol) and phenyl isocyanate (1.12 g, 0.009 mol) were dissolved in 75 ml of carbon tetrachloride in a 125-ml erlenmeyer flask fitted with a reflux condenser and drying tube, and rubber septum fitted to a small side arm for ir sampling. After 11.5 days of stirring at room temperature, the isocyanate was consumed, as judged by ir. The solvent was stripped off, and the residue was chromatographed on silica gel. This yielded (a) unreacted tetrabenzyltetrazene (0.94 g, 23%), eluted with pentane–benzene mixtures) and (b) a pale yellow solid, eluted with benzene, mp 156–158° after recrystallization from ethanol (0.248 g, 6%), identified as 10 by its ir and nmr spectra (see text).

Anal. Calcd for C₂₈H₂₇N₅O: C, 74.83; H, 6.01; N, 15.59; mol wt, 449. Found: C, 75.51, 75.20; H, 5.99, 6.16; N, 15.72; mol wt, 420 (osmometric in chloroform).

The residue from evaporating the mother liquor from the recrystallization of 10 gave 0.145 g (5%) of benzaldehyde 2,4-dinitrophenylhydrazone on treatment with 2,4-dinitrophenylhydrazine reagent.

Further elution of the chromatography column with ether-benzene mixtures yielded (c) 1,1-dibenzyl-3-phenylurea, 0.243 g, (8%), mp 126–128° after recrystallization from benzene–ligroin (lit.[11] mp 125°).

(10) H. Ruschig, *Arzneim.-Forsch.*, **8**, 448 (1958); *cf. Chem. Abstr.*, **53**, 1316i (1959).

(11) T. Mukaiyama, S. Ozaki, and Y. Hobayashi, *Bull Chem. Soc Jap.*, **29**, 51 (1956).

Reduction of Tertiary Halides to Hydrocarbons with Sodium Borohydride in Sulfolane

Robert O. Hutchins,* Robert J. Bertsch,[1a] and David Hoke[1b]

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

The use of sodium borohydride in polar aprotic solvents as convenient systems for the selective removal of aliphatic halides and tosylates was recently reported from our laboratories[2a] and also independently by Bell and coworkers,[2b] and more recently, by Vol'pin, Dvolaitzky, and Levitin.[2c] In the course of our study, the tertiary halide cumyl chloride was observed to undergo dehydrohalogenation followed by hydroboration. The intermediate alkylborane could be converted to the expected alcohol with alkaline peroxide or to isopropylbenzene by refluxing with valeric acid. This latter procedure results in overall reduction of tertiary halides to the hydrocarbon as shown in Scheme I.

Scheme I
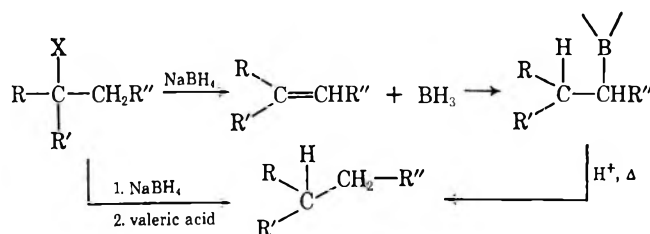
This note describes the utility of sodium borohydride in sulfolane as a convenient one-step procedure for direct removal of tertiary halides by way of elimination, hydroboration, and protonolysis. Recently, Jacobus[3] has reported use of the procedure (in DMSO) to reduce 3-chloro-3,7-dimethyloctane to 2,6-dimethyloctane in unspecified yield.

After conducting some preliminary experimentation, the general reaction conditions represented in Table I were chosen to provide adequate yields with reasonable reaction times. The use of a large excess of borohydride does not appear to be necessary as borohydride/compound ratios of 1:1 to 2:1 were entirely sufficient. Using temperatures of 120° for reaction with borohydride (100° for the benzyl halide, cumyl chloride) and 190–200° (reflux) for the subsequent protonolysis, a total reaction time of about 20 hr was realized. The reaction mixtures were worked up by simply pouring into water and extracting with cyclohexane or ether. Isolation is easily accomplished by washing the organic solution with water and dilute carbonate, drying, and removing the solvent.

The ease of the reductive procedure coupled with the good to excellent yields obtainable recommends the

(1) (a) Undergraduate Research Participant, 1969–1970; (b) Undergraduate Research Participant, 1968–1969.

(2) (a) R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969); (b) H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969); (c) M. Vol'pin, M. Dvolaitzky, and H. Levitin, *Bull. Soc. Chim. Fr.*, 1526 (1970).

(3) J. Jacobus, *Chem. Commun.*, 338 (1970).

Compd	Registry no.	$NaBH_4$/compd, mol/mol	T (NaBH$_4$), °C	Time[a] (NaBH$_4$)	Yield of hydrocarbon[b]
3-Chloro-3-methyloctane	28320-88-9	1.0	100	2.5	45
		1.5	120	2.5	74
3-Chloro-3-ethylheptane	28320-89-0	2.0	120	2.5	84
1-Chloro-n-butylcyclohexane	28320-90-3	1.2	120	2.5	89
tert-Cumyl chloride	934-53-2	1.1	100	2.0[c]	78[d]
		6	100	2.0	9.5[d,e]
Triphenylmethyl chloride[f]	76-83-5	6	85	1.5	90.4[d,e]

[a] Reaction with borohydride followed by treatment with valeric acid at 190–200° for 18 hr. [b] Yields determined by glpc using standard solutions of the products. [c] Treatment with valeric acid for 2.5 hr at 190–200°. [d] Data from ref 2a. [e] Yield without valeric acid treatment. [f] Reaction in DMSO solvent.

method for synthetic applications. In addition, unlike corresponding reductions with lithium aluminum hydride[4] or sodium borohydride in aqueous diglyme,[5] the products are free of contaminating alkene side products. The reduction is not limited to tertiary halides containing an α hydrogen as illustrated by the reduction of triphenylmethyl chloride to triphenylmethane (Table I). In this case the reaction probably occurs by initial ionization followed by hydride capture.[6]

Experimental Section

Materials.—The materials were either obtained commercially and purified or synthesized by standard procedures. Sulfolane was distilled from calcium hydride and stored over 4A molecular sieves. Sodium borohydride was used as received from Alfa Inorganics, Inc.

General Reduction Procedure.—A solution of the tertiary chloride (0.009–0.015 mol) and NaBH$_4$ (0–1.0 mol excess) in 50 ml of sulfolane was prepared in a 500-ml one-neck flask equipped with a magnetic stirrer and a condenser attached at the top to a small Dry Ice–acetone trap which in turn was protected by a drying tube. The solution was heated at 100 or 120° for 2–2.5 hr. A tenfold molar excess of valeric acid was then cautiously added through the top of the condenser, and the temperature was raised to 190–200° and maintained for 18 hr. The solution was cooled, poured into water, and extracted thoroughly with cyclohexane. Yields were determined by diluting the cyclohexane solution to 100 ml and analyzing by glpc[7] (average of three to five determinations). The procedure is illustrated below for the reduction of 3-chloro-3-ethylheptane.

Reduction of 3-Chloro-3-ethylheptane.—The apparatus described above was charged with a solution of 3-chloro-3-ethylheptane (2.27 g, 0.0139 mol) and sodium borohydride (1.07 g, 0.0282 mol) in 50 ml of sulfolane and heated in an oil bath at 120° for 2.5 hr. Valeric acid (28.2 g, 0.282 mol, 30 ml) was slowly added through the top of the condenser and the oil bath temperature raised to 190–200° and maintained there for 18 hr. The mixture was cooled, poured into *ca.* 250 ml of water, and extracted several times with small portions of cyclohexane. The apparatus was washed with a few milliliters of cyclohexane and the combined organic solution diluted to 100 ml with cyclohexane. The product yield (84%) was determined by glpc[7] using a column

temperature of 95° and a standard solution of 3-ethylheptane (Aldrich Chemical Co.). The cyclohexane solution was washed with two 100-ml portions of water and two 50-ml portions of 10% aqueous Na$_2$CO$_3$ and dried (MgSO$_4$). Solvent was removed on a rotary evaporator and the residue distilled at atmospheric pressure to obtain 1.1 g of 3-ethylheptane, bp 135–36°, n^{28}D 1.4076 [lit.[8] bp 143.1° (760 mm), n^{20}D 1.4090]. The ir spectrum was identical with that of an authentic sample.

(8) F. C. Whitmore and H. P. Orem, *J. Amer. Chem. Soc.*, **60**, 2573 (1938).

A Simple, Partial Resolution of
trans-Cyclooctene

WILLIAM L. WATERS

Department of Chemistry, University of Montana, Missoula, Montana 59801

Although one satisfactory asymmetric synthesis[1] and one complete resolution[2] of optically pure *trans*-cyclooctene have appeared in the literature, it should be reported that a more expeditious method of producing up to 20% optically pure olefin *via* Brown's asymmetric destruction method[3,4] is possible.

(−)-*sym*-Tetraisopinocampheyldiborane was prepared in triglyme at −10°. To this asymmetric hydroborating reagent was added an excess of racemic *trans*-cyclooctene, which was later partially recovered in optically enriched form by flash evaporation followed by silver nitrate extraction. Thus, based on starting (±)-*trans*-cyclooctene, it was possible to recover approximately 40% of the olefin in greater than 98% isomeric purity and up to 20% optical purity.

The data collected from many different runs suggest

(4) L. W. Trevoy and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 1675 (1949).

(5) H. M. Bell and H. C. Brown, *ibid.*, **88**, 1473 (1966).

(6) S. Matsumura and N. Tokura, *Tetrahedron Lett.*, 363 (1969), have reported the reduction of aralkyl and triaryl tertiary halides to hydrocarbons with diborane or diisocamphenylborane in nitromethane. In this manner, the authors accomplished reduction of *tert*-cumyl and trityl chlorides to the hydrocarbons in 82 and 95–96% yields, respectively. The reactions were attributed to initial ionization followed by hydrogen capture and, at least in part for cumyl chloride, to elimination followed by hydroboration and subsequent protonation to the hydrocarbon by hydrogen chloride generated in the reaction. Our failure to observe substantial hydrocarbon formation in the absence of valeric acid treatment may be due to the destruction of HX by excess borohydride. See also, S. Matsumura and N. Tokura, *ibid.*, 4703 (1968).

(7) All glpc analyses were performed using Hewlett-Packard Model 5250B thermal conductivity chromatograph coupled to an Leeds & Northrup Model W recorder equipped with a Disc integrator. In all cases a 6-ft ¹/₈-in. 10% OV-1 on 80–100 mesh Chromosorb W column was used.

(1) E. J. Corey and J. I. Shulman, *Tetrahedron Lett.*, 3655 (1968).

(2) A. C. Cope, C. R. Ganellin, H. W. Johnson, T. V. Van Auken, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, **85**, 3276 (1963).

(3) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 397 (1964), and references cited therein.

(4) For other examples of partial resolution by destructive asymmetric hydroboration, see S. I. Goldberg and F. L. Lam, *J. Org. Chem.*, **31**, 240 (1966); J. Furukawa, T. Kakuzen, H. Morikawa, R. Yawamoto, and O. Okuno, *Bull. Chem. Soc. Jap.*, **41**, 155 (1968); P. S. Wharton and R. A. Kretchmer, *J. Org. Chem.*, **33**, 4258 (1968); W. L. Waters and M. C. Caserio, *Tetrahedron Lett.*, 5233 (1968).

that the reaction is indeed complex.[5,6] However, it was found that lower temperatures, longer reagent preparation time, and smaller reaction volumes enhanced the resultant rotatory power of the partially resolved *trans*-cyclooctene.[7]

The overall results of these experiments indicate that partial resolution of *trans*-cyclooctene by kinetic asymmetric destruction (*via* asymmetric hydroboration) can be a valuable alternate[3] path to the optical enrichment of this unique olefin.

Experimental Section

Instrumentation.—All gas chromatographic analyses were performed on a Varian Aerograph Model 90-P instrument. Optical rotations were measured with a Ruldolph Model 80 polarimeter.

Materials.—(+)-α-Pinene (Aldrich) was distilled from crushed calcium hydride and collected at 152–155° (670 mm) [lit.[9] bp 156.2° (760 mm)], $[\alpha]^{27}$D +57.1 ± 0.4° (*c* 5, CHCl₃). Boron trifluoride etherate (Eastman) was purified by distillation at 73° (59 mm) [lit.[9] bp 67° (43 mm)]. Triglyme (Ansul) was distilled at 216–217° (670 mm) [lit.[9] bp 220° (760 mm)] from LiAlH₄.

Preparation of (±)-*trans*-Cyclooctene.—The racemic olefin was prepared according to Cope's procedure[10] except that the *N*,*N*,*N*-trimethylcyclooctylammonium iodide was synthesized in one step from cyclooctylamine (Aldrich) using excess methyl iodide and base. In a typical run cyclooctylamine (50 g, 0.394 mol) was reacted with methyl iodide (228 g, 1.6 mol) in 200 ml of methanol. After the initial reaction had subsided, potassium carbonate (55 g, 0.4 mol) was carefully added and the mixture refluxed for 24 hr. After filtering, partially stripping, and cooling, the solution yielded 112 g (0.376 mol, 96%) of the tetraalkylammonium iodide. Following Cope's procedure,[10] 50 g (0.168 mol) of the iodide yielded 14.1 g (0.128 mol, 76%) of a 3:2 mixture of *trans*- and *cis*-cyclooctene, respectively. Extraction of the mixture with a 20% silver nitrate solution[10] yielded 7.2 g (0.065 mol, 37% overall yield from cyclooctylamine) of >98% pure (gc, 20 ft × ³/₈ in., 20% DEGS) *trans*-cyclooctene.

Partial Resolution of (±)-*trans*-Cyclooctene.—In a typical run, the asymmetric hydroborating reagent was prepared by mixing 0.379 g (0.01 mol) of NaBH₄ (12.0 ml of a 0.83 *M* solution in triglyme) and 2.68 g (0.197 mol) of (+)-α-pinene [[α]²⁷D +57.1 ± 0.4° (*c* 5, CHCl₃)] with 30 ml of dry triglyme. The solution was placed in a three-necked round-bottom flask, covered by N₂, and kept at −10°. Through a dropping funnel 1.39 g (0.0098 mol) of BF₃·Et₂O (in 5 ml of triglyme) was slowly added to the rapidly stirred triglyme solution of NaBH₄ and α-pinene. After addition of the reagent was complete, the entire mixture was stirred an additional 30 hr at −10° after which 2.024 g (0.0184 mol) of (±)-*trans*-cyclooctene (containing 2.024 g of pentane as a gc standard) was added.

This mixture was stirred 4 hr at −10° and then flash distilled at 50° (5 mm) into a Dry Ice–acetone trap until no more cyclooctene (by gc) remained in the reaction pot. Gc analysis of the raw flash distillate showed the presence of 0.87 g (0.0079 mol) of *trans*-cyclooctene. This raw yield represents 92% of the theoretically recoverable trans olefin.[11] Some *cis*-cyclooctene[12] and α-pinene[13] was also observed in the flash distillate.

Finally, the *trans*-cyclooctene was recovered in pure form from the flash distillate by the usual 20% AgNO₃ extraction.[10] After destruction of the silver complex with ammonium hydroxide, 0.685 g (0.0062 mol, 72%[10]) of *trans*-cyclooctene was obtained as a pentane solution. Removal of the pentane by distillation gave the pure trans olefin with $[\alpha]^{25}$D −95.5 ± 0.5° (*c* 7, CHCl₁). Comparing the rotation in CH₂Cl₂ with that of Cope's[2] gives an optical purity of 20.8% for the partially resolved olefin.

Registry No.—(±)-*trans*-cyclooctene, 28541-65-3; (−)-*trans*-cyclooctene, 22770-27-0.

(11) Generally, half of the *trans*-cyclooctene should have been returned unreacted.

(12) The exact origin of the cis olefin is unknown. However, gc analysis of the reaction mixture immediately after addition of the racemic olefin indicated almost immediate formation of this less strained alkene.

(13) α-Pinene has been found in varying amounts as a side product from the asymmetric hydroboration of bulky olefins, thereby inferring a preequilibrium between tetraisopinocampheyldiborane and triisopinocampheyldiborane plus α-pinene. See ref 7.

Catalysis by Molecular Sieves in the Preparation of Ketimines and Enamines[1]

KAZUO TAGUCHI AND F. H. WESTHEIMER*

James Bryant Conant Laboratory of the Chemistry Department of Harvard University, Cambridge, Massachusetts 02138

Ketimines and enamines can conveniently be prepared in high yield by the reaction of the appropriate ketones and amines in the presence of molecular sieves. The method is quite general and can be applied successfully even to medium-sized ring ketones and camphor, which are rather hindered. Since the method is so mild, it might be employed where more vigorous reagents (such as zinc chloride,[2a] titanium tetrachloride,[2b] or aluminum chloride[3]) may cause side reactions; since it is so simple, it may prove preferable to the use of acetals,[4] 1-amino-1-cyanoalkanes,[5] thioketones,[6] gem dichlorides,[7] or iminophosphorus compounds[8] etc.,[9]

(1) After this note had been submitted for publication, the authors saw the paper by E. P. Kyba, *Org. Prep. Proceed.*, **2**, 149 (1970), on "An Improved Synthesis of Ketimines." Dr. Kyba used molecular sieves to shift the equilibrium in favor of the formation of six ketimines, three from acetone with various amines and three from methylamine with various methyl ketones. The present work extends that of Kyba to hindered ketones and further, in particular, reports the catalytic effects of molecular sieves in the formation of ketimines.

(2) (a) J. H. Billman and K. M. Tai, *J. Org. Chem.*, **23**, 535 (1958); (b) W. A. White and H. Weingarten, *ibid.*, **32**, 213 (1967).

(3) K. Taguchi, unpublished results.

(4) J. Claisen, *Ber.*, **29**, 2931 (1926); J. Hoch, *C. R. Acad. Sci.*, *Ser. C*, 199, 1428 (1934).

(5) W. C. Bain, P. D. Richie, and A. E. Wright, *J. Chem. Soc.*, 1454 (1964); J. S. Walia, L. Heindl, H. Lader, and P. S. Walia, *Chem. Ind. (London)*, 155 (1968).

(6) A. Schoenberg and W. Urban, *J. Chem. Soc.*, 530 (1935).

(7) M. Pauly, *Justus Liebigs Ann. Chem.*, **187**, 196 (1877); D. Y. Curtin and J. W. Hausser, *J. Amer. Chem. Soc.*, **83**, 3474 (1961).

(8) R. Appel and A. Hauss, *Ber.*, **93**, 405 (1960); W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **84**, 1316 (1962).

(9) P. A. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. I, W. A. Benjamin, New York, N. Y., 1965, p 295.

(5) As with some of the more hindered olefins of Brown's, there is some ambiguity as to the exact nature of the asymmetric hydroborating species. See ref 6 and 7.

(6) D. J. Pasto, V. Balasubramaniyan, and P. W. Wojtkowski, *Inorg. Chem.*, **8**, 594 (1969). The authors proved that five different disproportionating equilibrium reactions exist simultaneously in certain alkylborane solutions.

(7) H. C. Brown and G. J. Klender, *ibid.*, **1**, 204 (1962). The authors showed that an appreciable equilibrium exists between tetraisopinocampheyldiborane and triisopinocampheyldiborane when the reagent is prepared in tetrahydrofuran. The trialkyldiborane is thought to be the cause of the reduced degree of resolution in the case of certain sterically hindered olefins. See H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 1071 (1964). In diglyme the tetraalkyldiborane appears to precipitate, thereby shifting the equilibrium toward the more highly substituted diborane. Results in this lab indicate that this borane is more soluble in triglyme than in diglyme and that a more concentrated solution is required to effect precipitation.

(8) Since the synthesis of *dl*-*trans*-cyclooctene is relatively simple and inexpensive, loss of part of the trans olefin should not be objectionable. Moreover, the amount of the olefin "lost" can be reduced by the use of less hydroborating reagent. Of course, this would also result in lowered optical activity of the resolved *trans*-cyclooctene.

(9) D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, "Purification of Laboratory Chemicals," Pergamon Press, New York City, N. Y., 1966.

(10) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, **75**, 3212 (1953). The near-quantitative extraction procedure described by Cope has not yet been reproduced in this laboratory. Recovery of *ca.* 80% *trans*-cyclooctene by the AgNO₃ method represents this laboratory's best efforts.

TABLE I
IMINES AND ENAMINES[a]

Ketone	Amine	Yield, %	Mp or bp, °C (mm)	Calcd, %			Found, %		
				C	H	N	C	H	N
Cyclooctanone	Aniline	88	107–108 (0.25)	83.53	9.51	6.96	83.47	9.47	6.96
Cycloheptanone	Aniline	85	97–98 (0.4)	83.37	9.15	7.48	83.00	9.12	7.53
Cyclohexanone	Aniline	74	85–86 (0.4)						
Cyclohexanone	*m*-Toluidine	77	90–92 (0.25)	83.37	9.15	7.48	83.36	9.00	7.22
Camphor-*d*	Aniline	81	17	84.53	9.31	6.16	84.66	9.36	6.19
Benzophenone	Aniline	85	114–115						
Acetophenone	Aniline	75	40–41						
Acetophenone	*m*-Toluidine	78	124–126 (0.4)						
Cyclooctanone	Pyrrolidine[a]	82	79–81 (0.25)						
Cyclooctanone	Morpholine[a]	88	90–92 (0.4)	73.80	10.84	7.17	73.72	10.93	7.14
Cycloheptanone	Pyrrolidine[a]	80	64–65 (0.4)						
Cycloheptanone	Morpholine[a]	87	75–76 (0.25)						
Cyclohexanone	Diethylamine[a]	78	52.5–53.5 (1.25)						
Acetophenone	Pyrrolidine[a]	77	75–76 (0.25)						
Bicyclo[4.3.1]decan-10-one	Aniline	81	48.5–49.5	84.53	9.31	6.16	84.70	9.36	5.88
Ketopinic acid	Aniline	70	130–131	74.68	7.44	5.44	74.54	7.44	5.26
Bicyclo[4.2.1]nonan-9-one-1-carboxylic acid[b]	Aniline	41	119.5–121.0	74.68	7.44	5.44	74.68	7.56	5.29
Bicyclo[3.3.1]nonan-9-one-1-carboxylic acid[c]	Aniline	64	174–175.5	74.68	7.44	5.44	74.44	7.61	5.19

[a] The product is an enamine. In all other cases, the product is an imine (see Table II). [b] J. R. Wiseman, H. F. Chan, and C. J. Ahola, *J. Amer. Chem. Soc.*, **91**, 2812 (1969). [c] E. W. Colvin and W. Parker, *J. Chem. Soc.*, 5764 (1965).

as intermediates or as special reagents. Ketimines and enamines are frequently prepared by azeotropic distillation of a mixture of ketone and amine with benzene or toluene; further, in some instances the distillate has been dried effectively with molecular sieves.[10] Bonnett and Emerson[11] previously used the method discussed in this note for the preparation of the *n*-butylketimine at the 17 position of androsterone, but they did not report that the sieves serve as catalyst as well as dehydrating agent. The generality of the method and especially its application to hindered ketones are reported here. The method is of interest in this laboratory for the preparation of ketimines in connection with researches on these compounds as intermediates in enzymic decarboxylation.[12]

Results

The half-time for the condensation of aniline and acetophenone, in the presence of molecular sieves under the conditions described in the Experimental Section (about 0.15 *M* reagents in benzene at room temperature), is about 15 min. In the absence of molecular sieves or other catalyst, the reaction is quite slow, with no detectable formation of ketimine in 50 hr.

Catalysis by aniline hydrochloride is ineffective in benzene as solvent because of the insolubility of the salt, but the reaction can be strongly catalyzed by soluble acids, such as acetic acid. However, in the absence of a dehydrating agent, the reaction is incomplete, with yields of less than 10%. Molecular sieves serve simultaneously as a dehydrating agent and as a catalyst that can be removed at the end of the reaction simply by filtration.

(10) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 217 (1965).

(11) R. Bonnett and T. R. Emerson, *J. Chem. Soc.*, 4508 (1965).

(12) F. H. Westheimer, *Proc. Chem. Soc.*, 253 (1963); *Search*, **1**, 34 (1970).

The anils and enamines, prepared by the method here described, are reported in Table I. Particular attention is directed to the anils of camphor and of cyclooctanone, which are not easily prepared in such high yields by other methods. On the other hand, the anils of the keto acids could be prepared in the absence of molecular sieves; apparently carboxyl groups supply the needed acid catalysis, although the preparation of the anil from ketopinic acid gave a slightly better yield, and in less time, in the presence of molecular sieves.

Experimental Section

General Procedure.—About 40 g of molecular sieves (Linde 5A) are added to 0.10 mol of ketone and 0.12 mol of aromatic amine in 40 ml of benzene or ether. The reaction mixture is shaken until almost no free ketone can be detected in the supernatant liquid by ir or nmr spectroscopy (1–30 hr at room temperature for unhindered ketones), and the corresponding absorption for the ketimine is maximized. The mixture is then filtered from the molecular sieves which are washed with solvent. Solvent is removed from the filtrate and washings by rotary evaporation, and the product purified by vacuum distillation or crystallization.

Cyclooctanone anil, cycloheptanone anil, cyclohexanone-*m*-toluid, and acetophenone *m*-toluid were prepared in the above-described manner, employing benzene as solvent. The anil of benzophenone was prepared in this way in benzene as solvent except that the crude imine was crystallized from ethanol rather than subjected to distillation; the anil from acetophenone was crystallized from petroleum ether (bp 37–49°). The enamines from cyclooctanone and from cycloheptanone with pyrrolidine, the enamine from cyclohexanone with diethylamine, and that from cycloheptanone with morpholine were prepared by the standard procedure, using ether rather than benzene as solvent. The enamine from cyclooctanone and morpholine, prepared in ether as solvent, required 4 days at room temperature until the ir band of the ketone had nearly disappeared.

Camphor-*d* anil was prepared similarly, but the reaction is slow, with a half-time in benzene solution at room temperature of 2 days; to obtain a good yield, the reaction required 2 weeks at room temperature or 10 hr of refluxing. Similarly, the anil of

TABLE II

Compd	Registry no.	Ir, C=N or =C—N, μ^a	Nmr, δ in ppm relative to TMS[b,c]	Ref
N-Cyclooctylideneaniline	13683-44-8	6.06	1.0–2.7 (m, 14 H), 6.4–7.3 (m, 5 H)	
N-Cycloheptylideneaniline	13683-43-7	6.08	1.3–2.2 (m, 12 H), 6.4–7.3 (m, 5 H)	5
N-Cyclohexylideneaniline	1132-38-3	6.01	1.3–2.5 (m, 10 H), 6.4–7.3 (m, 5 H)	d
N-Cyclohexylidene-m-toluidine	28627-51-2	6.01	1.3–2.5 (m, 10 H), 2.25 (s, 3 H), 6.2–7.2 (m, 5 H)	
Camphor-d anil	28627-52-3	5.94	0.81 (s, 3 H), 0.91 (s, 3 H), 1.05 (s, 3 H), 1.1–2.4 (m, 7 H), 6.5–7.2 (m, 5 H)	d
Benzophenone anil	574-45-8	6.20[e]	6.5–7.8 (m, 15 H)	d
Acetophenone anil	1749-19-5	6.14[e]	2.10 (s, 3 H), 6.5–8.0 (m, 10 H)	d
N-(1-Methylbenzylidene)-m-toluidine	28627-55-6	6.13	2.15 (s, 3 H), 6.5–8.0 (m, 10 H)	d
1-Pyrrolidenyl-1-cyclooctane	28627-56-7	6.14	1.2–3.2 (m, 20 H), 4.08 (t, 1 H, J = 8 Hz)	f
1-Morpholinyl-1-cyclooctene	17344-01-3	6.21	1.45 (br, 8 H), 1.8–2.4 (br, 4 H), 2.5–2.8 (m, 4 H), 3.4–3.7 (m, 4 H) 4.50 (t, 1 H, J = 8 Hz)	g
1-Pyrrolidenyl-1-cycloheptene	28627-58-9	6.12	1.2–3.2 (m, 18 H), 4.37 (t, 1 H, J = 7 Hz)	f
1-Morpholinyl-1-cycloheptene	7182-08-3	6.09	1.2–2.3 (m, 10 H), 2.5–2.7 (m, 4 H), 3.5–3.7 (m, 4 H), 4.08 (t, 1 H, J = 8 Hz)	10
1-Diethylamino-1-cyclohexene	10468-24-3	6.10	0.95 (t, 3 H, J = 8 Hz), 1.2–2.3 (m, 8 H), 2.90 (q, 2 H, J = 7 Hz), 4.40 (t, 1 H, J = 3 Hz)	h
α-Pyrrolidinyl styrene	3433-56-5	6.21	1.5–2.0 (m, 4 H), 2.2–3.1 (m, 4 H), 3.80 (s, 1 H), 3.87 (s, 1 H), 7.0–7.5 (m, 5 H)	i
10-Phenyliminobicyclo[4.3.1]decane	28627-61-4	6.14[e]	1.1–2.2 (m, 14 H, 2.85 (br, 2 H), 6.4–7.3 (m, 5 H)[j]	
2-Phenylimino-7,7-dimethylbicyclo-[2.2.1]heptane-11-carboxylic acid	28627-62-5	6.00[e]	1.20 (s, 3 H), 1.33 (s, 3 H), 1.5–2.5 (m, 12 H), 2.6 (br, 1 H), 6.8–7.6 (m, 5 H), 14.03 (s, 1 H)[j]	
9-Phenyliminobicyclo[4.2.1]nonane-1-carboxylic acid	28627-63-6	6.00[e]	1.0–2.7 (m, 12 H), 3.00 (br, 1 H), 6.7–7.7 (m, 5 H), 13.45 (s, 1 H)[j]	
9-Phenyliminobicyclo[3.3.1]nonane-1-carboxylic acid	28627-64-7	6.07[e]	1.0–2.8 (m, 12 H), 2.90 (br, 1 H), 6.7–7.6 (m, 5 H), 14.90 (s, 1 H)[j]	

[a] Infracord (±0.02 μ); liquid film unless otherwise noted. [b] In CCl_4 unless otherwise noted. [c] s, singlet; t, triplet; q, quartet; m, multiplet; br, broad. [d] G. Reddelien, *Ber.*, **42**, 4759 (1909); *ibid.*, **43**, 2476 (1910); *ibid.*, **46**, 2712 (1913); G. Reddelien and O. Meyn, *Ber. Deut. Chem. Gesell. B*, **53**, 345 (1920); *Justus Liebigs Ann. Chem.*, **388**, 187 (1912). [e] In KBr. [f] M. E. Kuhne, *J. Amer. Chem. Soc.*, **81**, 5400 (1959). [g] G. Opitz and A. Griesinger, *Justus Liebigs Ann. Chem.*, **665**, 101 (1965). [h] E. P. Blanchard, Jr., *J. Org. Chem.*, **28**, 1397 (1963). [i] P. Nelson and A. Pelter, *J. Chem. Soc.*, 5142 (1965). [j] Approximately 15% solution in $CDCl_3$.

ketopinic acid was prepared by refluxing the acid and aniline in chloroform solution in the presence of molecular sieves for 15 hr. The anils of the other keto acids here reported (bicyclo[4.2.1]- and bicyclo[3.3.1]nonan-9-one-1-carboxylic acids) are formed with 3 hr of refluxing and with 3 hr of shaking at room temperature, respectively.

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