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Cyclization of Anthranilamide–Acetylenedicarboxylate Adducts. A Facile Synthesis of 1,4-Benzodiazepine-3,5-diones[1]

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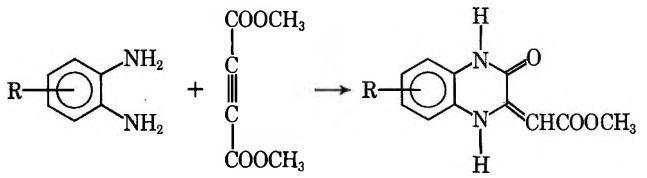
Anthranilamides have been found to react with dimethyl acetylenedicarboxylate to produce fumarate Michael adducts which ring close to 2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5(1H,4H)-diones. These benzodiazepines undergo alkoxide-catalyzed rearrangement to yield mixtures of maleimides and quinazolinones. The maleimides obtained from the benzodiazepines can also be prepared by the ammonolysis of (2-carbomethoxyanilino)fumarates in a mechanistic pathway shown to involve geometric isomerism of the enamine double bond.

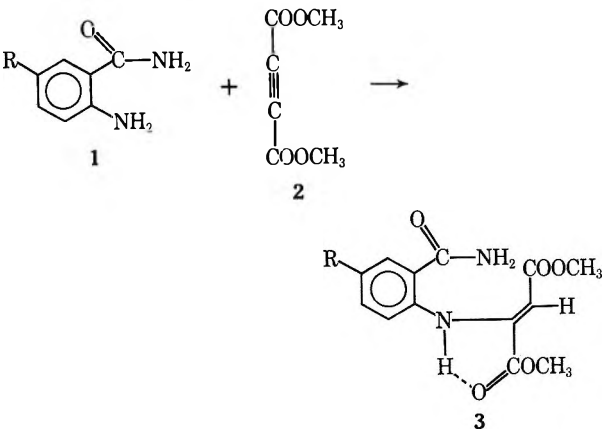
Numerous examples have appeared in the recent literature demonstrating the synthetic utility of amine–acetylenedicarboxylate adducts as convenient precursors for a variety of five-[2-4] and six-membered[4-8] heterocyclics. The facile reaction of *o*-phenylenediamines with acetylenedicarboxylate as a quinoxalone synthesis[3] has prompted us to explore the reaction of



2

anthranilamides (1) with 2 as a potential route to benzodiazepinediones.

The reaction of anthranilamides (1) with dimethyl acetylenedicarboxylate (2) occurs spontaneously in methanol to give 71–84% yields of adducts (3). It is apparent that these adducts represent amine to acetylene addition, since aniline reacts under similar conditions,[9] but benzamide requires elevated temperatures and strong base catalysis.[10] Further, these



1 2 3

R = H, Cl, Br, CH_3

anthranilamide adducts (3) give a negative test for a free amine function and display ir spectra which lack the characteristic primary amine stretching absorptions. Primary aromatic amine adducts of 2 have been reported to exhibit exclusive fumarate geometry. The nmr criterion established by the previous workers[9,11,12] for isomeric homogeneity, namely a single vinyl proton resonance, was satisfied by all our crystalline adduct intermediates. The enamines (3) all possessed a single =C—H absorption in the range δ 5.42–5.67 ppm. Additional support for the transoid geometry was provided by the appearance of chelated ester bands at 1670 ± 10 cm^{-1} characteristic of analogous fumarate systems.[13,14]

Cyclization of Anthranilamide–Acetylenedicarboxylate Adducts.—When the adducts 3 were treated with

(1) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968. For previous papers in this series, see N. D. Heindel, I. S. Bechara, T. F. Lemke, and V. B. Fish, *J. Org. Chem.*, **32**, 4155 (1967), and references cited therein.

(2) D. S. James and P. E. Fanta, *ibid.*, **27**, 3346 (1962).

(3) G. M. Brooke and R. J. D. Rutherford, *J. Chem. Soc., C*, 1189 (1967).

(4) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(5) J. W. Lown and T. C. N. Ma, *Can. J. Chem.*, **45**, 939 (1967).

(6) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 1666 (1967).

(7) E. C. Taylor and N. D. Heindel, *ibid.*, **32**, 3339 (1967).

(8) Y. Iwanami, *Nippon Kagaku Zasshi*, **83**, 161 (1962); *Chem. Abstr.*, **59**, 3920 (1963).

(9) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(10) A. W. Johnson, "The Chemistry of the Acetylene Compounds," Vol. II, Longmans, Green and Co., New York, N. Y., 1950, p 133.

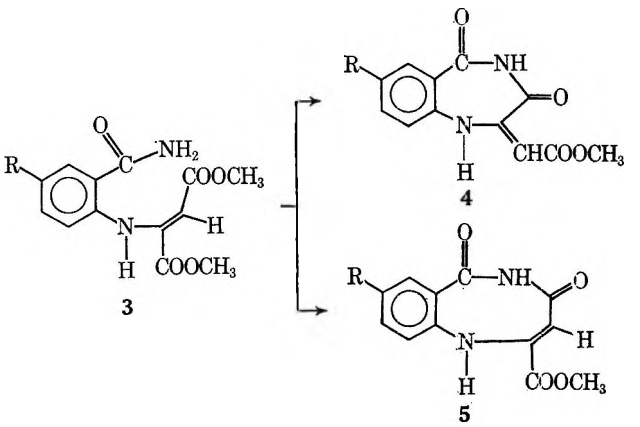
(11) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

(12) E. Winterfeldt, *Angew. Chem. Intern. Ed. Engl.*, **6**, 423 (1967).

(13) Y. Iwanami, *Nippon Kagcku Zasshi*, **83**, 593 (1962); *Chem. Abstr.*, **59**, 5153 (1963).

(14) Y. Iwanami, S. Isoyama, and Y. Kenjo, *Bull. Chem. Soc. Jap.*, **37**, 1745 (1964); *Chem. Abstr.*, **62**, 7755 (1965).

sodium methoxide in xylene at reflux for 1 hr, they yielded products whose elemental analyses indicated the loss of a single molecule of methanol. Molecular models indicate that two possible modes of cyclization exist for the adducts **3**; namely, the amide nitrogen can displace upon either of the two nonequivalent methyl esters of the fumarate portion. Displacement upon the α carbomethoxy would generate a carbomethoxymethylenebenzodiazepine (**4**), while attack upon the β ester would yield a carbomethoxybenzodiazocine (**5**).

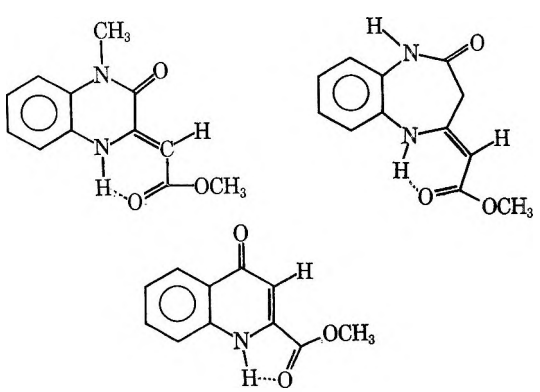


3 **4** **5**

Discrimination between alternatives **4** and **5** could not be effected by instrumental means alone, although support for structure **4** could be derived from comparison of nmr and ir data with those of model systems. Mass spectral examination was of little assistance, for the predominant high mass fragements could be rationalized with either isomeric possibility: parent at 246 amu; P − 32, loss of CH_3OH; and P − 59, loss of $\cdot CO_2CH_3$.

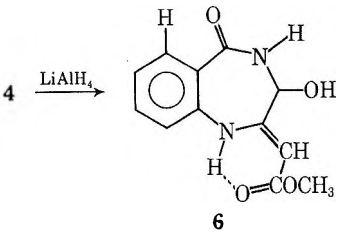
The nmr (DMSO-d_6) spectrum of the product (from **3** with R = H) could have been consistent with either isomer: singlet at δ 3.80 ppm, three protons; singlet at 5.88, one proton; aromatic multiplet at 7.0–8.2, four protons; and two broad NH singlets at 11.16 and 11.78 each integrating for a single proton.

A close analogy to the proposed benzodiazepine structure **4** is provided by the N-methylquinoxalone[15] shown below in which the vinyl resonance occurred at δ 5.82 ppm and the methyl resonance at 3.77. The ester carbonyl stretching frequencies of this model compound and those of our unknown material were likewise identical (1690 cm^{-1}) and in excellent agreement with the carbonyl assignment (1686 cm^{-1}) in a similar 2-carbomethoxymethylene-1,5-benzodiazepinone.[16] These C=O stretching frequencies are lower than the normal α,β-unsaturated esters and indicative of intramolecular chelation.[17]



Appropriate models which can be used to predict the ester C=O absorption in alternative structure **5** must reflect molecular situations in which the NH of a vinylogous amide and the carbonyl of an ester could be involved in a five-membered bonded cycle. It is of interest in this regard that 2-carbomethoxy-4(1H)-quinolones, see above, display carbonyl absorptions at 1730 ± 5 cm^{-1} which are only slightly shifted from normal ester bands.[18] In general terms it has been noted that intramolecular hydrogen bonding is most significant when a six-membered cycle is generated.[19]

The strongest support for the assignment of structure **4** to the ring-closed product is based on the results of its reduction with $LiAlH_4$. The employment of the technique of inverse addition (hydride slurry in THF added to compound in THF) yielded a product whose combustion and spectral analyses revealed it to be a hydrobenzodiazepinone (**6**). The ir spectrum displayed strong hydroxy absorption at 3395 cm^{-1}, which had been absent in the starting material. In addition, its nmr spectrum, obtained in DMSO-d_6 in order to detect splitting through the O—H bond,[20] could be rationalized only as being due to a partially reduced benzodiazepinedione.



6

The OH appeared as a doublet (J = 4 Hz) at δ 6.78 ppm coupled to a carbinyl proton at 5.10. This carbinyl proton was similarly coupled to an NH proton (J' = 6 Hz) at 9.00 ppm and therefore appeared as a double doublet (J = 4 Hz and J' = 6 Hz). When the spectrum was run in C_5D_5N, a solvent which accelerates hydroxyl proton exchange, the OH resonance collapsed to a singlet and the carbinyl resonance to a doublet. Upon addition of D_2O, the NH and OH signals disappeared and the carbinyl proton remained as a singlet.

The additional resonances appeared as expected in the nmr spectrum, including the vinyl singlet at δ 4.98 ppm, which had shifted to higher field as a consequence of the reduction of its flanking and deshielding carbonyl, the ester methyl at 3.85 ppm, and the chelated NH at 10.33 ppm. Further support for the fact that reduction occurred at the carbonyl in position 3 of the parent benzodiazepine and not at position 5 is obtained by examination of the signal of the aromatic proton at C-6, *i.e.*, *peri* to the carbonyl attached to the ring. This proton appears downfield at 7.83 ppm as a quartet

(15) D. D. Chapman, *J. Chem. Soc., C*, 806 (1966).

(16) E. Müller, R. Haller, and K. W. Merz, *Ann.*, **697**, 197 (1966).

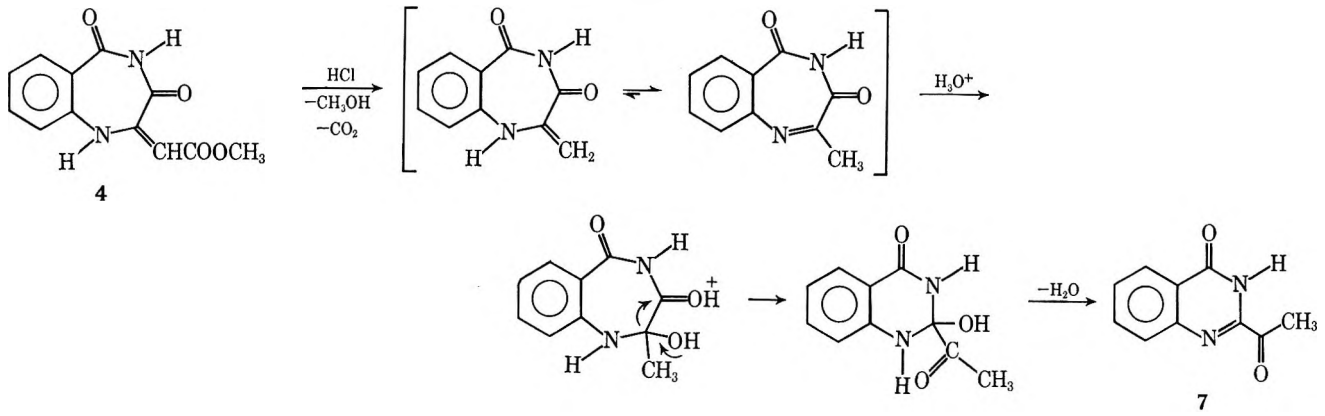
(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1964, pp 184, 185.

(18) N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocycl. Chem.*, **3**, 222 (1966).

(19) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden Publishers, New York, N. Y., 1959, p 30.

(20) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

SCHEME I



(J_o = 8 Hz, J_m = 2 Hz) coupled to its *ortho* and *meta* neighbors. Budzikiewicz and coworkers have commented in detail on this "peri-doublet" effect.[21]

The partial $LiAlH_4$ reduction of an amide carbonyl to a stable *gem*-amino alcohol is unusual but not without precedent in the literature. Hydride reduction of certain 2-oxoquinoxalines and 3-oxomorpholines has been reported to yield the carbinol amines[22] and similar precedent exists for the preparation of stable 3-hydroxy-1,4-benzodiazepines.

Ring-Contraction Reactions of the Benzodiazepines (4).—When treated with 6 *N* hydrochloric acid, the benzodiazepine (**4**, R = H) underwent a decarbomethoxylation ring contraction leading to 2-acetyl-4(3H)-quinazolinone (**7**). The acid-catalyzed contraction of diazepines has been observed on numerous occasions in a wide variety of compounds.[23] In our case, the ring contraction adds additional weight to the structure assignment of the diazepine **4** since a more plausible mechanism can be evoked for transformation of **4** into **7** than can be written for a **5** to **7** contraction. See Scheme I.

The characterization of **7** rests on nmr and ir spectral data (*vide infra*) and on the fact that a 2,4-dinitrophenylhydrazone derivative and a positive iodoform test could be obtained. Further, the uv spectrum of **7** was virtually superimposable on that of authentic 2-carboxy-4(3H)-quinazolinone[24] and also on a variety of other 4-quinazolinones reported in the literature.[25]

When treated with sodium methoxide in methanol, the 2-carbomethoxymethylene-1,4-benzodiazepine-3,5-diones (**4**) were transformed into mixtures of two heterocyclic materials by an interesting base-catalyzed rearrangement. The two products, 2-carbomethoxymethyl-2-carbomethoxy-2,3-dihydro-4(1H)-quinazolinone (**11**) and 2-carbomethoxyanilinomaleimide (**9**) can be rationalized as arising from methoxide ion attack at the two carbonyls of the imide linkage. Imides are in general known to undergo similar nucleophilic ring opening.[26] See Scheme II.

In a previous publication from our laboratories it was incorrectly reported that condensation of anthranilamides (**1**) and dimethyl acetylenedicarboxylate (**2**) in sodium methoxide–methanol gave rise to the benzodiazepinediones (**4**). The products described in that report as the seven-membered heterocycles were in reality the isomeric maleimides (**9**), the least soluble components of their respective product mixtures. The quinazolinones (**11**), the other components produced in the reaction, can be isolated in a pure state only with difficulty because of their higher solubility and tendency to crystallize with entrained traces of maleimide and starting material.

The authentic benzodiazepinediones (**4**), which can be prepared from the amide adducts (**3**) only in alcohol-free media, are very labile in the presence of alcoholic alkoxide. They are converted into the rearranged products **9** and **11** in the same ratio in which these materials are obtained from the direct combination of the acetylene diester and the anthranilamide in methanol–sodium methoxide. A plausible mechanistic possibility, therefore, is that transient formation of the benzodiazepine intervenes even in the presence of alcohol. In particular it is likely that the maleimide **9** is formed through the intermediacy of **4** because benzamide does not undergo significant methanolysis to methyl benzoate under the reaction conditions.

Geometric Isomerization of the Vinyl Linkage. Maleimide Formation.—Since it is probable that the amide adduct **3** has the fumarate arrangement for its diester side chain and since, presumably, the benzodiazepine (**4**) has a transoid geometry[27] (*i.e.*, $COOCH_3$ to C-3 carbonyl), it is apparent that formation of the maleimide has required an isomerization of the C=C double bond. Unfortunately, the proposed methyl anthranilate adduct of the half-amide–half-ester of acetylenedicarboxylic acid (**8**) could not be isolated from the reaction medium for stereochemical correlation. It is known, however, that the barrier to rotation about the enamine double bond is considerably lower[28] than that of a normal olefinic linkage; hence, such *trans–cis* isomerization is plausible. Further, we have

(21) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron*, **19**, 1011 (1963).

(22) N. C. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, New York, N. Y., 1956, pp 600–626.

(23) See, for example, R. K. Bly, E. C. Zoll, and J. A. Moore, *J. Org. Chem.*, **29**, 2129 (1964), J. A. Moore and W. J. Theuer, *ibid.*, **30**, 1887 (1965), and L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *ibid.*, **29**, 332 (1964), all of whom reported on the 1,4-benzodiazepine to quinazoline contraction. J. A. Barltrop, C. G. Richards, and D. M. Russell, *J. Chem. Soc.*, 1423 (1959), have studied the contraction of 1,5-benzodiazepines to quinoxalines. R. L. Williams, J. Schuller, and D. Lloyd, *J. Heterocycl. Chem.*, **5**, 147 (1968), have reported a similar conversion of 1,5-benzodiazepines into benzoimidazoles.

(24) M. T. Bogert and R. A. Gortner, *J. Amer. Chem. Soc.*, **32**, 119 (1910).

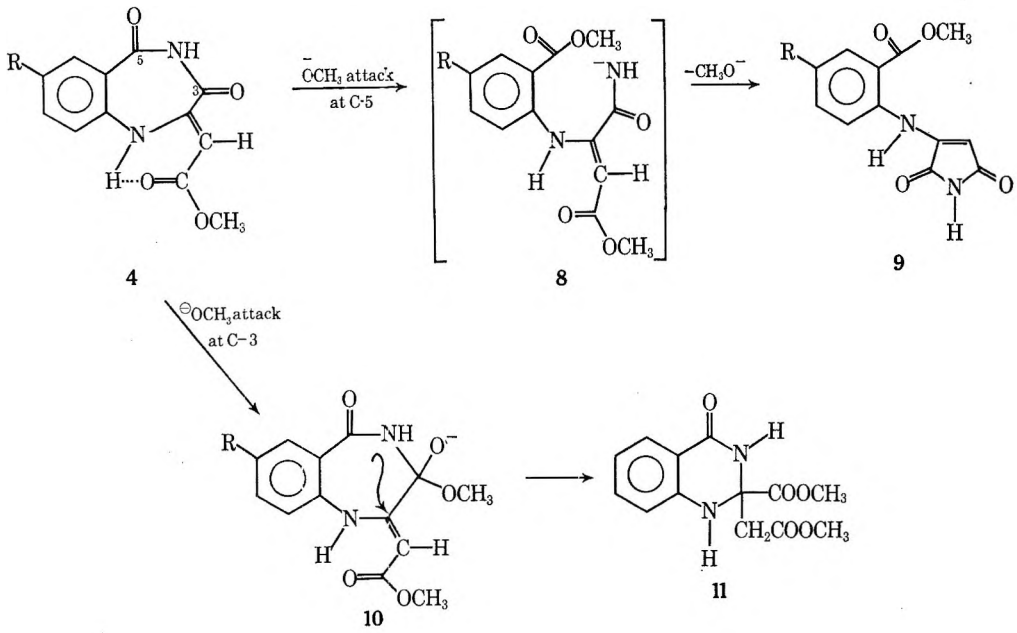
(25) See spectra 1041–1047 in L. Lang, "Absorption Spectra in the Ultraviolet and Visible Region," Vol. VI, Academic Press, New York, N. Y., 1965.

(26) C. D. Hurd, *J. Chem. Educ.*, **44**, 454 (1967).

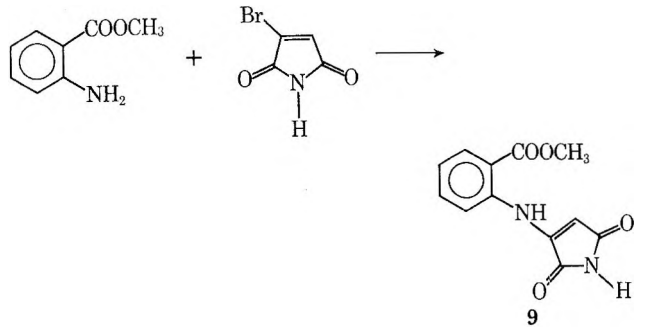
(27) This hypothesis is in accord with the chelated ester carbonyl observed in the ir spectra of **4** and is in agreement with similar observations by others; see ref 13 and 14.

(28) Y. Shvo, E. C. Taylor, and J. Bartulin, *Tetrahedron Lett.*, 3259 (1967).

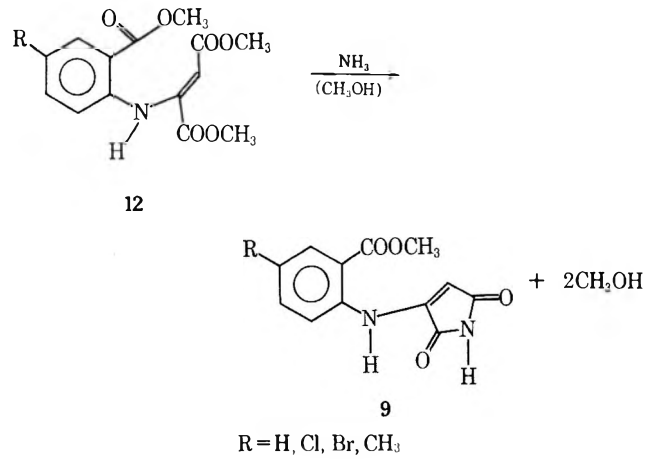
SCHEME II



demonstrated that dimethyl anilinofumarate[9] and dimethyl (2-carbomethoxyanilino)fumarate,[7] when treated with anhydrous ammonia in cold methanol, generate anilinomaleimide[29] and 2-carbomethoxyanilinomaleimide (**9**), respectively. The latter compound, **9**, was prepared in an independent synthesis by allowing methyl anthranilate to react with 3-bromomaleimide, thereby confirming its structure. The fumarate–



maleate isomerization induced by methoxide attack on **4** or by ammonolysis of the anilinofumarate clearly demonstrates the geometric lability of the enamine double bond.[30] We have ammoniated several methyl anthranilate adducts of acetylenedicarboxylate (**12**) and in all cases have obtained the maleimide products identical with those obtained by methoxide ring opening of **4**. The maleimide structure was recognized by the characteristic high-frequency imide carbonyls, 1765 and 1710 ± 15 cm^{-1}. The possibility that these materials might, in fact, be other imides (*i.e.*, benzodiazepines or benzodiazocines) linking either of the side-chain carbonyls with the carbonyl of the carboxylate on the *ortho* ring position was effectively eliminated when the ethyl ester of **9** (R = H) was ob-



tained from the treatment of the adduct of ethyl anthranilate–dimethyl acetylenedicarboxylate with ammonia.

The cyclization of the anthranilamide adduct **3** or its anionic analog (**10**) has excellent precedent in the observed ring closure of the dimethyl acetylenedicarboxylate adduct of thiosalicylamide to a 2-carbomethoxymethyl-2-carbomethoxy-1,3-benzothiazin-4-one.[31] As observed in the ring closure of the thiosalicylamide adduct, these anthranilamide adducts require trace alkoxide catalysis, presumably to enhance the nucleophilicity of the amide.

Alkylation of the benzodiazepine in the presence of excess methyl iodide occurred at the number 4 nitrogen. The site of alkylation was conveniently established when, during an attempted recrystallization of the alkylated benzodiazepine (**13**) from methanol, it was observed to take up the elements of CH_3OH. This product **14**, obtained when **13** was refluxed with methanol, was identical with the adduct formed from **2** and *o*-amino-N-methylbenzamide (**16**). See Scheme III.

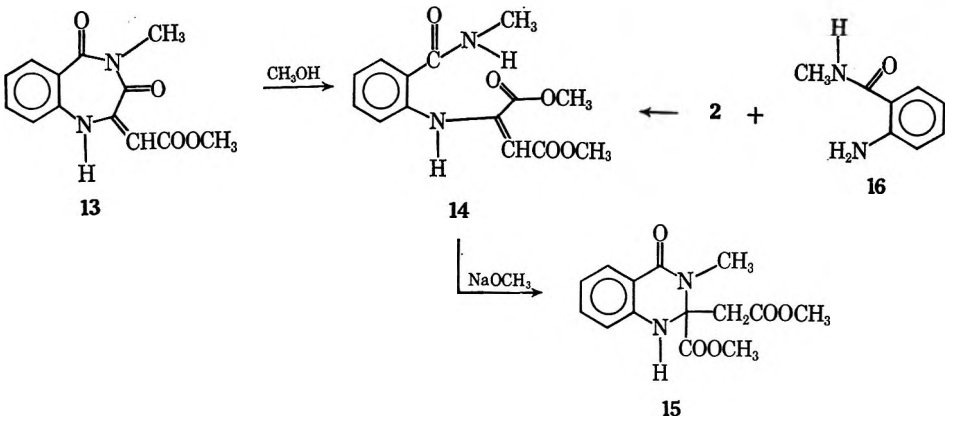
When the N-methyl amide adduct (**14**) was treated with methoxide–methanol, it gave rise to 3-methyl-

(29) S. J. Davis and C. S. Rondestvedt, Jr., *Chem. Ind.* (London), 845 (1956).

(30) J. de Wolf and L. van de Straete have shown that both dimethyl fumarate and dimethyl maleate undergo ammonolysis to their respective diamides, but the latter ester undergoes considerable isomerization to fumaramide. See *Bull. Sci. Acad. Roy. Belge*, **21**, 216 (1935).

(31) N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *J. Org. Chem.*, **32**, 2678 (1967).

SCHEME III



2-carbomethoxymethyl-2-carbomethoxydihydroquinazolin-4-one (**15**) but no trace of maleimide product. This result indicates that there are conceivably two pathways for transformation of amide adducts to quinazolinones: one which involves cyclization to a benzodiazepinedione which then suffers nucleophilic ring opening at both imide carbonyls to give maleimides plus quinazolinones, and the other which involves direct nucleophilic attack of the amide nitrogen upon the enamine double bond. Since **14** does not generate the corresponding diazepine **13**, even on reaction in the methoxide–xylene system, but instead yields only **15**, the presence of the N methyl apparently contributes a steric retardation to amide displacement upon the α carbomethoxy.

Structure Proof of the Quinazolinone Products.—The major products obtained upon methoxide–methanol ring opening of the benzodiazepinediones and upon direct reaction of the anthranilamide adducts in methoxide–methanol have been described herein as quinazolinone diesters (*viz.*, **11** and **15**).

The available spectral data are entirely in accord with this assignment. The ir spectra, for example, of these quinazolinone esters invariably displayed two slightly different, nonconjugated, carbonyl absorptions in the range 1715–1740 cm^{-1}. The nmr spectrum (for **11**, R = H and R = Cl) showed the two methyl singlets at δ 3.73–3.68 ppm and the unsplit methylene at 3.17–3.41 in excellent accord with the published spectrum of a similar benzothiazinone diester.[31]

Saponification of **11** (R = H) in 0.3 *M* sodium carbonate produced an unstable dicarboxylic acid which evolved CO_2 and acetic acid on attempted drying of an analytical sample. When the diacid was melted or sublimed, it was converted quantitatively into quinazolinone itself. A thermal gravimetric analysis of the diacid[32] revealed a nonconcomitant evolution of the CO_2 and acetic acid. The mass equivalents of the thermal gravimetric plateaus corresponded to the removal of a 60-amu fragment (HOAc) at 145–155° and a 44-amu species (CO_2) at 158–180°.

The mass spectra of the quinazolinone diesters displayed two competing fragmentation courses involving side-chain cleavages of methyl formate and methyl acetate moieties in excellent parallel with the thermal cleavages from the diacid. The full mass spectral data for **11** are reported in the Experimental Section, but it is of interest to note that the parent ion, *m/e* 278, undergoes fragmentation by loss of methyl acetate to a 204-amu species which loses $-COOCH_3$ to produce a quinazolinone ion, 145 amu. In a parallel pathway the parent ion evolves methyl formate to a 218-amu daughter, which in several successive cleavages fragments the methyl acetate side chain.

Encouraged by the variety of intriguing reaction pathways displayed by anthranilamide, methyl anthranilate, thiosalicylamide, and methyl thiosalicylate with acetylenedicarboxylate, we are extending these studies to salicylic acid analogs.

Experimental Section[33]

Preparation of Anthranilamides (1).—The ammonolysis procedure of Staiger and Wagner[34] for ring opening of the isatoic anhydrides was employed to obtain the anthranilamides from the 5-chloro-,[35] 5-bromo-,[36] 5-methyl-,[37] and the unsubstituted anhydrides.[35] Isatoic anhydride was treated with methyl amine by the procedure of Wedige[38] to give *o*-amino-N-methylbenzamide.

Dimethyl (2-Carboxamidoanilino)fumarate (3, R = H).—Reaction of equimolar quantities of anthranilamide and dimethyl acetylenedicarboxylate in methanol (0.1 mol/100 ml of solvent) produced a 91% yield of the crude adduct after 1 hr of reflux. Recrystallization from methanol provided yellow crystals of pure **3** (R = H): mp 153–153.5°; ir (Nujol mull) 3480 and 3370 ($CONH_2$), 3265 (chelated NH), 1718 (ester C=O), 1675 (chelated C=O), and 1658 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 11.0 (s, 1, NH), 6.8–8.0 (m, 4), 5.42 (s, 1, C=CH), 3.55 (s, 3, CO_2CH_3), and 3.68 ppm (s, 3, CO_2CH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07. Found: C, 56.12; H, 5.11.

Dimethyl (4-Chloro-2-carboxamidoanilino)fumarate (3, R = Cl).—The reaction of 5-chloroanthranilamide with **2** as before yielded 84% crude adduct which was recrystallized twice from methanol to afford the pure adduct **3** (R = Cl): mp 156–158°; ir (Nujol mull) 3455, 3395, 3365, and 3260 (NH), 1738, 1697, 1680, and 1662 cm^{-1} (C=O); nmr ($DCCl_3$) δ 10.93 (s,

(32) We are grateful to Professor Harold C. Beachell of the University of Delaware for performing this analysis on a Du Pont Model 950 thermal gravimetric analyzer under nitrogen atmosphere.

(33) All ir spectra reported in this work were obtained on a Perkin-Elmer 257 spectrophotometer as Nujol-mulled materials. Nmr spectra are reported in parts per million (δ units) and were carried out on a Varian A-60 calibrated against internal TMS. Combustion analyses were performed by one of us (V. B. F) in these laboratories or were obtained from Dr. George I. Robertson, Microanalytical Laboratories, Florham Park, N. J. Mass spectral analyses were carried out on a Hitachi-Perkin-Elmer RMU-6E instrument equipped with a direct solids inlet system. We gratefully acknowledge the assistance of National Science Foundation Departmental Major Equipment Grants which enabled us to obtain the nmr and mass spectrometer facilities.

(34) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **18**, 1427 (1953).

(35) These compounds were graciously provided by the Maumee Chemical Co., Toledo, Ohio.

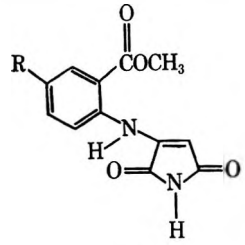
(36) R. Adams and H. R. Snyder, *J. Amer. Chem. Soc.*, **60**, 1411 (1938).

(37) W. Panaotovic, *J. Prakt. Chem.*, [2] **33**, 58 (1886).

(38) H. Weddige, *ibid.*, [2] **36**, 150 (1887).

TABLE I

(2-CARBOMETHOXYANILINO)MALEIMIDES



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R	Method[a]	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	A	48	234–235.5	$C_{12}H_{10}N_2O_4$	58.53	4.08	11.38	58.81	4.16	11.17
	B	23								
Br	A	33	297	$C_{12}H_9BrN_2O_4$	44.33	2.79	8.62	44.25	2.81	8.75
	B	33								
Cl	A	21	291–292	$C_{12}H_9ClN_2O_4$	51.35	3.23	9.98	51.24	3.38	10.26
	B	33								
CH_3	A	57	264–265	$C_{13}H_{12}N_2O_4$	60.00	4.65	10.76	59.87	4.55	10.86
	B	39								
I	A	61	281–283	$C_{12}H_9IN_2O_4$	38.73	2.44	7.53	39.04	2.84	7.53

[a] Method A refers to the synthesis by ammonolysis of the adducts of 2 and methyl anthranilates. Method B refers to the products obtained by methoxide–methanol treatment of anthranilamide adducts of 2.

1, NH), 7.7–6.5 (m, 3), 6.52 (very broad, undefined, 2, NH_2), 5.63 (s, 1, C=CH), and 3.77 ppm (s, 6, OCH_3).

Anal. Calcd for $C_{13}H_{13}ClN_2O_5$: C, 49.92; H, 4.19; N, 8.96. Found: C, 49.92; H, 4.20; N, 8.73.

Dimethyl (4-Methyl-2-carboxamidoanilino)fumarate (3, R = CH_3).—By the method described above, an 84% yield of the adduct was obtained from 2 and 5-methylanthranilamide, mp 134–135°.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.59. Found: C, 57.64; H, 5.67; N, 9.43.

Dimethyl (4-Bromo-2-carboxamidoanilino)fumarate (3, R = Br).—A 71% yield, mp 162.5–164°, was obtained from 2 and 5-bromoanthranilamide.

Anal. Calcd for $C_{13}H_{13}BrN_2O_5$: C, 43.71; H, 3.67; N, 7.84. Found: C, 43.90; H, 3.78; N, 7.87.

Dimethyl (2-N-Methylcarboxamidoanilino)fumarate (14).—To a solution of 18.5 g (0.123 mol) of 2-amino-N-methylbenzamide in 250 ml of methanol was added 17.55 g (0.123 mol) of dimethyl acetylenedicarboxylate. The reaction mixture was heated on a steam bath for 0.5 hr, concentrated to 125 ml, and cooled to 0°. The precipitated material was collected by filtration. The crude product (mp 164–168°, 26.3 g, 73%) was recrystallized twice from methanol to produce yellow crystals of pure 14: mp 166–168°; ir (Nujol mull) 3340 (NH), 3165 (chelated NH), 1725 (ester C=O), and 1690 cm^{-1} (chelated C=O); nmr ($DCCl_3$) δ 10.20 (s, 1, NH), 6.7–7.7 (m, 4), 6.55 (broad undefined, s, 1, CH_3N—H), 5.57 (s, 1, C=CH), 3.83 (s, 3, CO_2CH_3), 3.80 (s, 3, CO_2CH_3), and 3.02 ppm (d, 3, J = 5 Hz, $HNCH_3$).

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.81; H, 5.58; N, 9.88.

Dimethyl (2-Carbomethoxy-4-R-anilino)fumarates (12).—These compounds (R = H, Br, CH_3, Cl, and I) were prepared as we have described previously.[7] The 2-carbethoxy isomer, prepared by the reaction of ethyl anthranilate and 2, was a liquid: bp 195–197° (22 mm) and 162–164° (0.075 mm) [lit. bp 224° (0.1 mm)];[39] ir (thin film) 3250 (chelated NH), 1733 (methyl ester C=O), and 1686 cm^{-1} (ethyl ester C=O); nmr ($CDCl_3$) δ 11.42 (s, 1, NH), 8.2–6.6 (m, 4), 5.63 (s, 1, C=CH), 4.45 (q, 2, J = 7 Hz, OCH_2CH_3), 3.71 (s, 3, OCH_3), and 1.40 ppm (5, t, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.62; H, 5.58; N, 4.56. Found: C, 58.56; H, 5.47; N, 4.84.

(39) During the preparation of this manuscript, S. K. Khetan, J. G. Hiriyakkanavar, and M. W. George, *Tetrahedron*, **24**, 1567 (1963), reported physical data for the same compound which were not entirely in accord with what we observed. A reexamination of the reaction yielded data consistent with our original results but not entirely in agreement with the recorded boiling point and ir and nmr data.

Cyclizations of 3 in Methoxide–Xylene System. Preparation of 2-Carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = H).—A 2.0-g (0.072 mol) sample of dimethyl (2-carboxamidoanilino)fumarate (3) was dissolved in boiling xylene (dried over Dri-Na) and treated with a catalytic amount (less than 0.1 g) of sodium methoxide. The evolved methanol was allowed to escape from the refluxing solution. The reaction mixture was stirred and refluxed for 2 hr and then cooled to room temperature. The yellow crystals (1.35 g, 76%, mp 218–230°) that precipitated were collected by filtration and washed with hexane. A sample of these crystals was sublimed (170°, 0.1 mm) to provide the pure benzodiazepine 4 (R = H): mp 230–232°; ir (Nujol mull) 3185 (NH) and 1657 cm^{-1} (chelated ester C=O); nmr (DMSO-d_6) δ 11.78 (s, 1, NH), 11.16 (s, 1, NH), 7.0–8.2 (m, 4), 5.88 (s, 1, C=CH), and 3.80 ppm (s, 3, CO_2CH_3); mass spectrum (80 eV), m/e 246 (P).

Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.50; H, 4.09; N, 11.43. Found: C, 58.76; H, 4.06; N, 11.39.

Preparation of 7-Chloro-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = Cl).—Reaction of 10.0 g (32.0 mmol) of the chloro adduct (3, R = Cl) with methoxide in xylene as above yielded 6.10 g (63%) of the crude product, which was sublimed to give the pure 4 (R = Cl): mp 233–234°; ir (Nujol mull) 3210 (chelated NH) and 1696 cm^{-1} (chelated C=O).

Anal. Calcd for $C_{12}H_9ClN_2O_4$: C, 51.35; H, 3.23; N, 9.98. Found: C, 51.63; H, 3.41; N, 9.98.

Preparation of 7-Bromo-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = Br).—Employing the above procedure an 81% yield of this product was obtained: mp 239–240.5°; ir (Nujol mull) 3190 (chelated NH) and 1690 cm^{-1} (sh, chelated CO).

Anal. Calcd for $C_{12}H_9BrN_2O_4$: C, 44.32; H, 2.79; N, 8.62. Found: C, 44.46; H, 2.91; N, 8.68.

Preparation of 7-Methyl-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = CH_3).—An identical method gave a 76% yield of product: mp 240–241.5°; ir (Nujol mull) 3185 (chelated NH) and 1690 cm^{-1} (chelated CO).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.10; H, 4.68; N, 10.79.

Cyclizations of 3 in Methoxide–Methanol System. Reaction of 3 (R = H).—The product isolation step in the preparation of 3 (R = H) was omitted, and a trace amount of $NaOCH_3$ was added to the reaction mixture. Alternatively, the adduct 3 (R = H) can be isolated and treated under these conditions to give the same product distribution. After refluxing for 2 hr, the solution was cooled to room temperature to provide 23% crude maleimide (see Table I, method B) which was then sublimed to afford the pure 9 (R = H): mp 234–235°; ir (Nujol

mull) 3150 (NH), 1765 and 1720 (O=CNC=O), and 1690 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 10.80 (s, 1, NH), 10.68 (s, 1, NH), 7.75–7.3 (m, 4), 5.78 (s, 1, C=CH), and 3.75 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.08; N, 11.38. Found: C, 58.81; H, 4.16; N, 11.17.

Concentration and cooling of the mother liquor provided 71% crude light yellow crystalline quinazolinone, which was appreciably more soluble in methanol than was **9**. Careful recrystallization from methanol afforded white crystals of the pure **11** (R = H): mp 149–150°; ir (Nujol mull) 3375 and 3350 (NH), 1725 and 1715 (ester C=O), and 1675 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 8.1–6.6 (m, 4), 7.35 (s, 1, NH), 5.6 (s, 1, NH), 3.73 (s, 3, OCH_3), 3.73 (s, 3, OCH_3), and 3.17 ppm (s, 2, $-CH_2CO$); mass spectrum (80 eV), *m/e* (rel intensity) 278 (<1), 218 (100), 204 (19), 187 (22), 159 (80), 145 (31), 119 (17), 91 (24).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07. Found: C, 55.92; H, 5.07.

Reaction of 3 (R = Cl).—The reaction can be accomplished by adding $NaOCH_3$ to the preparation of **3** (R = Cl) before work-up or by first isolating the adduct and then treating it with methoxide. The same product distribution is obtained in either case. The more insoluble product (33% yield, see Table I) is the maleimide **9** (R = Cl): mp 291–292°; ir (Nujol mull) 3240 and 3150 (NH), 1765, 1700, and 1685 cm^{-1} (C=O); nmr (DMSO-d_6) δ 10.65 and 10.45 (s, 1, NH), 7.8–7.3 (m, 3), 5.78 (s, 1, C=CH), and 3.81 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_9ClN_2O_4$: C, 51.35; H, 3.23; N, 9.98. Found: C, 51.24; H, 3.38; N, 10.26.

Concentration of the mother liquor provided 40% highly soluble chloroquinazolinone (**11**, R = Cl): mp 189–190°; ir (Nujol mull) 3330 and 3210 (NH), 1730 (ester C=O), and 1675 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 8.38 (s, 1, NH), 7.7–6.8 (m, 3), 7.55 (s, 1, NH), 3.68 (s, 6, OCH_3), and 3.41 ppm (s, 2, $-CH_2-CO$).

Anal. Calcd for $C_{13}H_{13}ClN_2O_5$: C, 49.92; H, 4.19; N, 8.96. Found: C, 50.31; H, 4.41; N, 9.21.

Reaction of 3 (R = Br and CH_3).—An identical product distribution was obtained when either the respective anthranilamide adducts (**3**) or the equimolar quantities (0.01 mol each) of the anthranilamide and **2** were dissolved in 50 ml of methanol and refluxed for 2 hr with approximately 0.10 g of sodium methoxide. The quinazolinones in these two cases could not be isolated owing to their high solubility in the methanol and their tendency to precipitate with traces of maleimide contamination. Evaporation of the methanol to one-fourth of its original volume brought about precipitation of the respective maleimides (**9**, R = Br) and (**9**, R = CH_3). These materials were sublimed to analytical purity. See Table I under method B for physical properties and yields. The mother liquors after removal of the maleimides clearly showed the NH and carbonyl absorptions characteristic of the quinazolinones. The saturated ester side chain on C-2 is clearly evident at 1725 ± 5 cm^{-1}.

Reaction of 4 (R = H).—To the refluxing solution of 3.0 g (12.2 mmol) of **4** (R = H) in 75 ml of methanol was added a trace amount of $NaOCH_3$. The solution was stirred and refluxed for a total of 2 hr, cooled to room temperature, diluted with 2 ml of H_2O, and filtered. The yellow crystals (0.61 g, 25%) obtained were shown by melting point and spectral comparisons to be the maleimide (**9**, R = H). The mother liquor was then concentrated to two-tenths of its volume, cooled, and filtered. The light yellow product (2.15 g, 63%) was identical in all respects with the quinazolinone **11** (R = H). From the resultant mother liquor was obtained 0.20 g (6%) of the open adduct **3** (R = H).

Reaction of 14.—A 3.0-g (10.0 mmol) sample of the adduct **14** in 125 ml of methanol was treated with a trace of $NaOCH_3$ (less than 0.05 g). The reaction mixture was refluxed for 22 hr, cooled, and filtered. The white crystals (2.6 g, 83%) obtained were recrystallized from cyclohexane–benzene to yield the pure 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-3-methyl-4-(1H)-quinazolinone (**15**): mp 116–118°; ir (Nujol mull) 3260 (NH), 1743 and 1736 cm^{-1} (ester CO); nmr ($DCCl_3$) δ 8.1–6.65 (m, 4), 6.00 (s, 1, NH), 3.80 (s, 3, OCH_3), 3.77 (s, 3, OCH_3), 3.24 (q, 2, J = 16 Hz, $-CH_2CO-$), and 3.14 ppm (s, 3, $N-CH_3$). Similar reaction in xylene solvent gave the same product. No trace of the maleimide was observed in either product mixture.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.65; H, 5.66; N, 9.42.

An Alternative Synthesis of the Maleimides. Ammonolysis of Dimethyl (2-Carbomethoxy-4-R-anilino)fumarates (Method A).—In a ground-glass stoppered bottle was placed 0.01 mol of the adduct of **2** and methyl 5-R-anthranilate (R = H, Cl, Br, CH_3, and I)[7] and sufficient methanol (200–300 ml) to bring the adduct into solution. The vessel was chilled to ice-bath temperatures and saturated with anhydrous ammonia. The solution was stirred in a tightly sealed bottle at room temperature for 8 hr. Some of the product precipitated directly, but isolation was facilitated by evaporation to one-tenth of the original volume. Bright yellow crystals separated and were purified by recrystallization from methanol and by sublimation at 210° (0.5 mm). Yields and analyses are summarized on Table I. Each maleimide was spectrally identical with that obtained by methoxide–methanol treatment of the amide adducts (*i.e.*, method B).

Preparation of Dimethyl 2-Anilinofumarate[9] and Its Ammonolysis to Maleimide.—To 6.3 g (67.5 mmol) of freshly distilled aniline in 30 ml of ether was added 9.58 g (67.5 mmol) of **2**. After the vigorous exothermic reaction had ceased, the reaction mixture was heated to remove the remaining solvent. Distillation of the residue gave 11.80 g (75%) of the aniline adduct: bp 105–107° (0.05–0.07 mm) [lit.[9] bp 115–118°, bath temperature (0.001 mm)].

Ammonia (anhydrous) was passed through a solution of 4.70 g (20 mmol) of the anilinofumarate in 40 ml of methanol for 2.5 hr. The solution was then stirred for an additional 18 hr. The yellow crystals that precipitated were collected by filtration, washed with 5 ml of methanol, and dried to give 1.95 g (52%) of crude product which was purified by sublimation to afford the pure maleimide, mp 211–213° (lit.[24] mp 206.5–207°).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.89; H, 4.56; N, 14.79.

Preparation of 3-Bromomaleimide.—A solution of 9.7 g (0.10 mol) of maleimide in 30 ml of glacial acetic acid was heated on a steam cone and subjected to the dropwise addition of 19.2 g (0.12 mol) of bromine dissolved in 25 ml of glacial acetic acid. The reaction mixture was agitated during the entire addition and was heated without agitation for 15 min following the completion of the addition. The acetic acid was evaporated under vacuum to one-tenth of the original volume, and a 5% aqueous sodium bicarbonate solution was added to achieve neutrality. The precipitated crystals were filtered off and recrystallized twice from water to produce white microneedles, mp 155–156.5°, 10.2 g (58%) (lit.[29] mp 153–154°).

Independent Synthesis of (2-Carbomethoxyanilino)maleimide (9, R = H).—Methyl anthranilate (6 ml) and 0.20 g of 3-bromomaleimide were heated at reflux for 10 min. A deep burgundy color developed in the solution. The solution was cooled to room temperature and treated with 5 ml of methanol containing 0.10 g of sodium methoxide. Chilling in an ice bath precipitated yellow crystals, which were filtered off and washed well with cold diethyl ether. The crude crystals, 0.14 g, melted at 226–229° and had an ir spectrum identical with that of the material obtained by methoxide–methanol treatment of **3** and by ammonolysis of dimethyl (2-carbomethoxyanilino)fumarate.

(2-Carbethoxyanilino)maleimide.—A 5.0-g (16.3 mmol) sample of the adduct of ethyl anthraniliate and **2** was treated with NH_3–CH_3OH as before to provide 3.70 g (87%) of the crude product, which was sublimed to afford the pure maleimide: mp 220–224°; ir (Nujol mull) 3150 (chelated NH), 1765 and 1695 (O=C—N—C=O), and 1675 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 10.88 (s, 1, NH), 8.2–7.1 (m, 4), 5.95 (s, 1, C=CH), 4.43 (q, 2, J = 7 Hz, OCH_2CH_3), and 1.40 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.07; H, 4.63; N, 10.76.

Hydride Reduction of the Benzodiazepinedione (4, R = H).—To a stirred solution of 2.46 g (0.010 mol) of **4** in 350 ml of absolute tetrahydrofuran at 0° was added a slurry of 0.40 g of lithium aluminum hydride in 20 ml of absolute tetrahydrofuran over a period of 1.5 hr. The cold reaction mixture was stirred an additional 0.5 hr, treated with a saturated solution of Na_2SO_4, dried over anhydrous Na_2SO_4, and filtered. The solids were washed well with tetrahydrofuran and diethyl ether. The combined filtrates were evaporated to dryness under vacuum, and the crystalline residue was recrystallized from methanol to produce 0.90 g (36%) of pure white **6**: mp 204–206°; ir (Nujol mull) 3395 (OH), 3220 and 3130 (NH), and 1670 cm^{-1} (chelated ester C=O); nmr (DMSO-d_6) δ 10.33 (s, 1, NH), 9.00 (d, 1, J = 6

Hz, NH), 7.83 (q, 1, J_o = 8 Hz, J_m = 2 Hz, -C-6 H), 7.65–7.00 (m, 3, C-7 H, C-8 H), C-9 H), 6.78 (d, 1, J = 4 Hz, OH), 5.10 (q, 1, J = 4 Hz, J = 6 Hz, ≡C—H), 4.98 (s, 1, =C—H), and 3.85 ppm (s, 3, $COOCH_3$).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.21; H, 4.71; N, 11.37.

Methylation of the Benzodiazepinedione System. Preparation of 4-Methyl-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5(1H,4H)-dione (13).—A solution of 12.30 g (0.05 mol) of **4** (R = H) in 150 ml of hot DMF (freshly distilled from P_2O_5) was added to 0.06 mol of NaH in 125 ml of dry benzene. The red-orange solution that resulted was stirred until the evolution of gases ceased (5 min) before the dropwise addition of 6.9 g (0.07 mol) of methyl iodide was initiated. The reaction mixture was then heated at 80° for 45 min, cooled to room temperature, treated with a small amount of methanol–water, and diluted with ice–water until two distinct layers appeared. The aqueous layer was separated and extracted with 150 ml of benzene. The benzene layers were combined, dried (Na_2SO_4), and concentrated. Cooling the residue produced brown-yellow crystals which were triturated with methanol and washed with hexane to afford light yellow crystals (mp 117–124, 4.70 g, 36%). Recrystallization from benzene–cyclohexane produced pure **13**: mp 126–128°; ir (Nujol mull) 1685 cm^{-1} (chelated C=O); nmr ($DCCl_3$) δ 10.93 (s, 1, NH), 6.9–8.1 (m, 4), 5.87 (s, 1, C=CH), 3.80 (s, 3, CO_2CH_3), and 3.47 ppm (s, 3, N—CH_3); mass spectrum (80 eV), *m/e* 260 (P).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.11; H, 4.88; N, 10.64.

Ring Opening of 13 with Methanol.—A 1-g sample of crude **13** was heated in 15 ml of methanol for 15 min. Upon cooling to 0°, the resulting solution precipitated yellow crystals which were collected and dried. By nmr ($DCCl_3$), the yellow crystals appeared to be a mixture of **13** and **14**, in the ratio of 1:2. When the spectrum of this mixture was compared with the nmr spectra of pure **13** and **14**, an exact peak for peak correspondence was obtained. In addition, the ir spectrum of the mixture could be matched peak for peak with the spectra of pure **13** and **14**. No attempt was made to separate the mixture.

Reaction of 4 (R = H) with 6 *N* HCl. Preparation of 7.—A 2.1-g (8.5 mmol) sample of **4** in 100 ml of 6 *N* aqueous hydrochloric acid was stirred and refluxed for 2 hr. After the reaction mixture cooled to room temperature, the precipitated material was collected by filtration, washed with water, and dried. The crude material (1.37 g, 86%) was recrystallized from benzene and was washed with hexane to produce pure **7**: mp 202–205°; ir (Nujol mull) 1708 (acetyl C=O), 1665 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.6–8.4 (m, 4) and 2.68 ppm (s, 3, CH_3CO–); uv max (100% EtOH) 229, 259 sh, 261 sh, and 304 mμ.

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.88. Found: C, 63.97; H, 4.31; N, 14.80.

A positive methyl ketone test (iodoform) was obtained,[40] and a 2,4-dinitrophenylhydrazone, mp 324–326° (from ethanol), was prepared.

Anal. Calcd for $C_{16}H_{12}N_6O_5$: N, 22.81. Found: N, 22.59.

Registry No.—**3** (R = H), 17244-69-8; **3** (R = Cl), 17244-20-1; **3** (R = CH_3), 17244-21-2; **3** (R = Br), 17244-22-3; **4** (R = H), 13187-67-2; **4** (R = Cl), 13214-23-8; **4** (R = CH_3), 17244-25-6; **4** (R = Br), 17244-26-7; **6**, 17244-27-8; **7**, 17244-28-9; **7** dinitrophenylhydrazone, 17244-29-0; **9** (R = H), 17244-30-3; **9** (R = Cl), 17244-31-4; **9** (R = Br), 17244-32-5; **9** (R = CH_3), 17244-33-6; **9** (R = I), 17244-34-7; **11** (R = H), 17244-35-8; **11** (R = Cl), 17244-36-9; **12** (2-carbethoxy isomer), 17244-37-0; **13**, 17244-38-1; **14**, 17244-39-2; **15**, 17244-40-5; (2-carbethoxyanilino)maleimide, 17244-41-6; dimethyl 2-anilinofumarate maleimide, 17244-42-7.

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(40) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 137.

Synthesis of Epindolidione[1,2]

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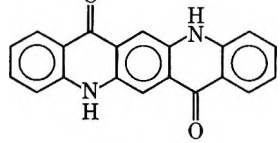
Two new syntheses of epindolidione (**2**) are described. The first synthesis affords **2** and some symmetrically substituted derivatives in good yield and relatively high purity. Dimethyl dihydroxyfumarate (**4**) reacts with aniline to give dimethyl dianilinomaleate (**5**). Evidence for the *cis* structure of **5** is given. The latter ester is cyclized to 2-methoxycarbonyl-3-anilino-4-quinolone (**7a**) which in turn is cyclized to **2**. The second method involves the cyclization of 3-(2-carboxyphenylamino)-4-quinolone (**16**) which is obtained by condensation of 3-amino-4-quinolone with *o*-bromobenzoic acid. Physical and spectral properties of **2** are discussed and evidence for intermolecular hydrogen bonding is presented.

The advent of quinacridone[3] (**1**) as a commercial pigment stimulated research in the synthesis of related structures. A compound of particular interest was dibenzo[*b*,*g*][1,5]naphthyridine-6,12(5,11H)-dione (**2**).



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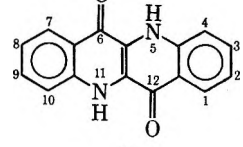


2

The 2,8-dimethyl derivative of **2** was first synthesized by Ainley and Robinson[4] in order to compare its properties with those of indigo, a structural isomer of **2**. These workers coined the name epindolidione for com-

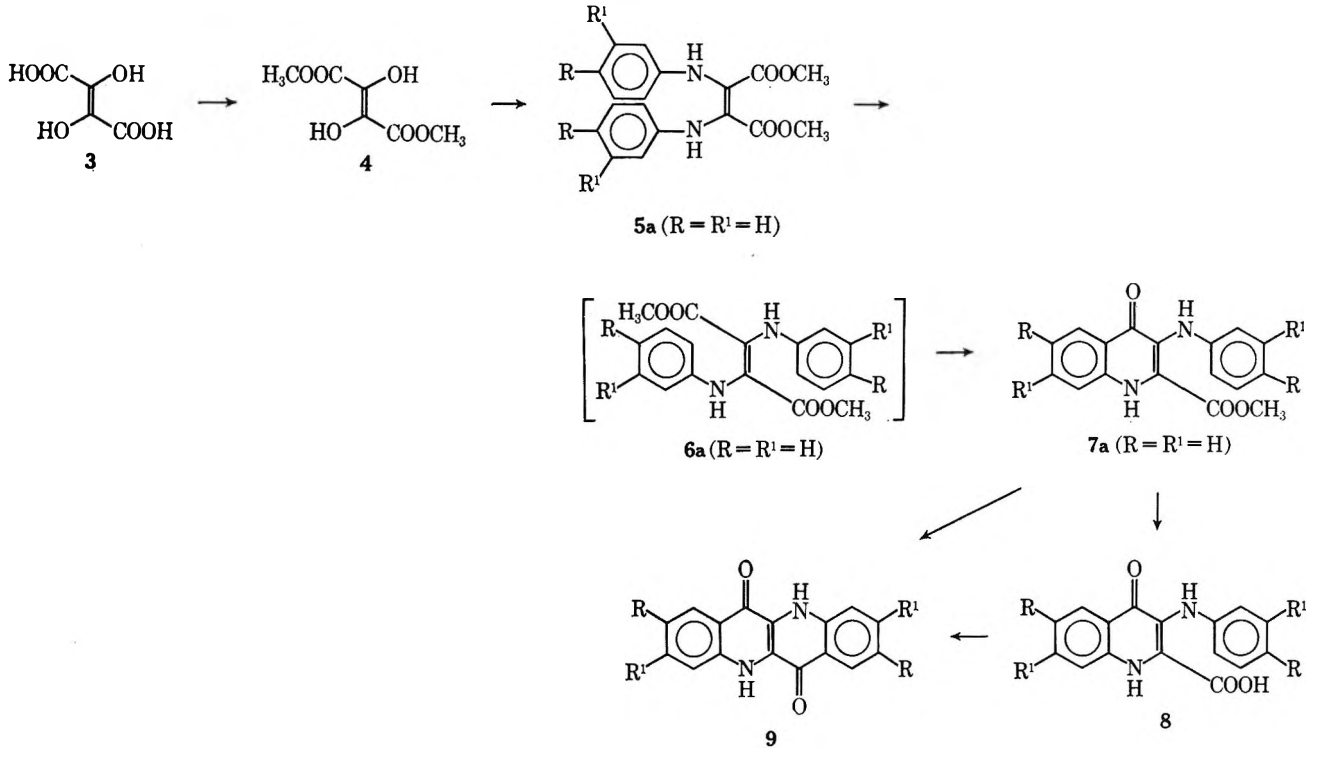
(1) Presented in part at the 3rd Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968.

(2) Included in part in U. S. Patent 3,334,102.

(3) (a) H. Liebermann, *Ann.*, **518**, 245 (1935); (b) W. S. Struve, U. S. Patent 2,821,529; *Chem. Abstr.*, **52**, 10215 (1958); U. S. Patent 2,821,530; *Chem. Abstr.*, **52**, 10216 (1958); (c) S. S. Labana and L. L. Labana, *Chem. Rev.*, **67**, 1 (1967).

(4) A. D. Ainley and R. Robinson, *J. Chem. Soc.*, 1508 (1934).

SCHEME I



pound **2**. The Ainley and Robinson synthesis started with a known but difficultly obtainable compound and gave a poor over-all yield. Subsequently, this synthesis was used for the preparation of the parent compound[5] **2**. This method is not, however, suitable for the preparation of certain substituted derivatives.

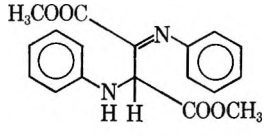
Results and Discussion

We wish to report two new and improved methods for the preparation of **2**. One of these methods gives good yields of **2** and its symmetrically substituted derivatives in relatively high purity. This synthesis is outlined in Scheme I.

Dihydroxyfumaric acid (**3**), whose structure was shown to be *trans* by Goodwin and Witkop,[6] was esterified by a modification of the usual methanol–hydrogen chloride esterification procedure. The simple modification involved conducting the reaction in the presence of anhydrous magnesium sulfate, thus more than doubling the previously reported yield of 45%.[7] The increase in yield is presumably due to removal of product water which favorably affects the esterification equilibrium. Goodwin and Witkop[6] have assigned a *trans* configuration to this ester based on infrared (ir) spectral evidence.

Dimethyl Bis(arylamino)maleates (5).—Dimethyl dihydroxyfumarate (**4**) reacts rapidly with aniline or substituted anilines under acid catalysis to give good yields of dimethyl bis(arylamino)maleates. The maleates which have been prepared in this study along with pertinent data are listed in Table I.

The dianilino compound **5a** was previously prepared by Salmony and Simonis[8] by the reaction of dimethyl dibromomaleate with aniline. The ir spectra showed the product of this reaction to be identical with the compound obtained from the reaction of aniline with **4**. Although Salmony and Simonis formulated the compound as dimethyl dianilinomaleate, they offered no evidence for the assigned structure. This compound can theoretically exist as one or more of three possible structures: **5a**, the maleate; **6a**, the fumarate; and **10**, the anilinophenylimino ester. The nmr spectrum of



10

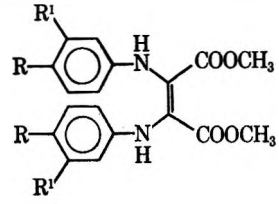
this compound shows a singlet for the ester methyl groups at δ 3.65 (6 H), an aromatic multiplet at 6.68–7.33 (10 H), and a singlet for N–H at 7.72 (2 H). The latter signal disappears upon exchange with heavy water. This evidence unequivocally excludes structure **10** from consideration.

In order to differentiate between the *cis* and *trans* structures the ir and Raman spectra of the compound were examined, and its dipole moment was determined. Between 3 and 6.5 μ the ir spectrum shows bands at 3.02, 3.08, 5.79, 5.96, 6.29, and 6.38 μ. The doublet at 3.02 and 3.08 μ is attributed to coupling of the two N–H frequencies. The doublet in the carbonyl-stretching region at 5.79 and 5.96 μ is believed to be due to the in phase and out of phase stretching vibration of the ester carbonyls. The 6.29-μ band is attributed to an aromatic double-bond vibration, and the strong 6.38-μ band is assigned to the olefinic double-bond stretching vibration as would be expected of the maleate structure. Based on the selection rules,[9] the fumarate isomer

(5) H. de Diesbach, A. Schurch, and G. Cavin, *Helv. Chim. Acta*, **31**, 716 (1948).
(6) S. Goodwin and B. Witkop, *J. Amer. Chem. Soc.*, **76**, 5599 (1954).
(7) E. F. Hartree, *ibid.*, **76**, 6244 (1953).
(8) A. Salmony and H. Simonis, *Ber.*, **38**, 2580 (1905).
(9) F. A. Miller in "Organic Chemistry," Vol. III, H. Gilman, Ed., John Wiley & Sons, Inc., New York, N. Y., pp 131, 132.

TABLE I

DIMETHYL BIS(ARYLAMINO)MALEATES

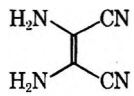


5

5	R	R¹	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Halogen, % Calcd	Halogen, % Found
a	H	H	196–198[a,b]	83.4	$C_{18}H_{18}N_2O_4$	66.24	66.03	5.56	5.38	8.59	8.76		
b	OCH_3	H	135–137[c]	64.9	$C_{20}H_{22}N_2O_6$	62.16	62.08	5.74	5.73	7.25	7.36		
c	CH_3	H	182–184.5[c]	73.2	$C_{20}N_{22}N_2O_4$	67.78	67.80	6.26	6.24	7.91	8.05		
d	F	H	199–200[d]	80.0	$C_{18}H_{16}F_2N_2O_4$	59.66	59.66	4.45	4.54	7.73	7.58	10.49	10.47
e	Cl	H	203–204[d]	85.1	$C_{18}H_{16}Cl_2N_2O_4$	54.70	54.71	4.08	4.03	7.09	7.03	17.94	18.18
f	H	Cl	151–154[d]	99.0	$C_{18}H_{16}Cl_2N_2O_4$	54.70	54.94	4.08	4.03	7.09	7.11	17.94	18.15
g	Cl	Cl	155–156[c]	89.0	$C_{18}H_{14}Cl_4N_2O_4$	46.58	46.82	3.04	2.94	6.04	6.23	30.56	30.68

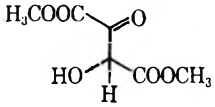
[a] Recrystallized from 1-butanol. [b] Lit.[8] mp 172°. [c] Recrystallized from petroleum ether (bp 90–120°). [d] Recrystallized from methanol.

should show little or no absorption in this region. The relatively long wavelength of this absorption is believed to be due to electronic interaction of the anilino and ester groups. It is noteworthy that the Raman spectrum shows only bands corresponding to those observed in the ir spectrum described above, thus lending support to the assignment of the maleate structure **5a** for this ester. More decisive evidence was obtained when the dipole moment of this compound was determined in dioxane and found to be 3.48 D. This evidence lends important support to the assigned *cis* structure, since the *trans* compound would be expected to have a small dipole moment or none at all. The formation of the *cis* compound is not surprising in view of the fact that the tetramer of HCN (**11**) also exists in the *cis* form. The structural assignment of **11** is conclusively supported by both dipole moment[10] and X-ray diffraction[11] data.



11

The formation of **5** from **4** can theoretically take place by either of the two following acid-catalyzed mechanisms: (a) protonation of the keto tautomer of dimethyl dihydroxyfumarate (**12**), followed by reaction with aniline, elimination of water, a second keto tautomer formation, and a repetition of the above steps; (b) acid-catalyzed addition of aniline to the double bond of **4**, followed by elimination of water, and repetition of these steps on the monoanilino compound.



12

Mechanism a is favored because dimethyl diacetoxyfumarate[6] failed to react with aniline under the acid-catalyzed conditions under which **4** reacted readily. Were mechanism b operative, the diacetoxy compound would have been expected to undergo the addition–elimination reaction. The favored mechanism a is analogous to the one proposed for the acid-catalyzed reaction of aniline and substituted anilines with benzoins.[12]

2-Methoxycarbonyl-3-arylamino-4-quinolones (7).—Since the discovery of the cyclization of alkyl β-anilinoacrylates to 4-quinolones by Conrad and Limpach[13] this reaction has been widely applied to the synthesis of 4-quinolones.[14] Assuming that **5** could isomerize to the corresponding geometric isomer **6**, the latter could be expected to undergo the Conrad–Limpach cyclization. Dimethyl bis(arylamino)maleates (**5**) were actually found to readily undergo cyclization in boiling Dowtherm A[15] to give high yields of the corresponding quinolones **7**. Although good yields can be obtained by simple boiling of Dowtherm A solutions of **5**, controlled addition of **5** to boiling Dowtherm A increased the yield of the quinolones **7**. This is believed to be due to the favoring of the monomolecular cyclization by operating at higher dilution. The quinolones **7** which have been prepared, along with pertinent data are listed in Table II.

It is well-known that 4-quinolones exist predominantly in the vinologous amide rather than the 4-hydroxyquinoline form. Nmr and ir spectra of **7a** similarly support the 4-quinolone structure for these compounds. The nmr spectrum of 7a shows a singlet for the ester methyl group at δ 3.65 (3 H), an aromatic multiplet at 6.66–7.12 (9 H), a singlet for the anilino N–H at 7.48 (1 H), and a broad singlet for the quinolone N–H centered at 12.00 (1 H). The latter two signals disappear upon exchange with heavy water. The corresponding N–H singlet in the parent compound, 4-quinolone, was found to be centered at δ 12.06. The ir spectrum shows bands at 5.82 and 6.18 μ attributed to the ester and quinolone carbonyls, respectively. In addition, a band attributed to the anilino N–H at 2.98

(10) R. L. Webb, S. Frank, and W. C. Schneider, *J. Amer. Chem. Soc.*, **77**, 3491 (1955).

(11) B. R. Penfold and W. N. Lipscomb, *Acta Crystallogr.*, **14**, 589 (1961).

(12) E. F. Pratt and M. J. Kamlet, *J. Org. Chem.*, **28**, 1366 (1963).

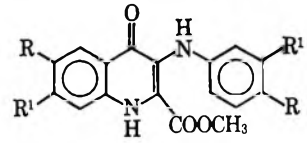
(13) M. Conrad and L. Limpach, *Ber.*, **20**, 1944 (1887); **21**, 521(1888).

(14) R. C. Elderfield in "Heterocyclic Compounds," R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1952, pp 1–343; R. H. Reitsema, *Chem. Rev.*, **43**, (1948).

(15) Dowtherm A is an azeotropic mixture of 26.5% biphenyl and 73.5% diphenyl ether.

TABLE II

2-METHOXYCARBONYL-3-ARYLAMINO-4-QUINOLONES



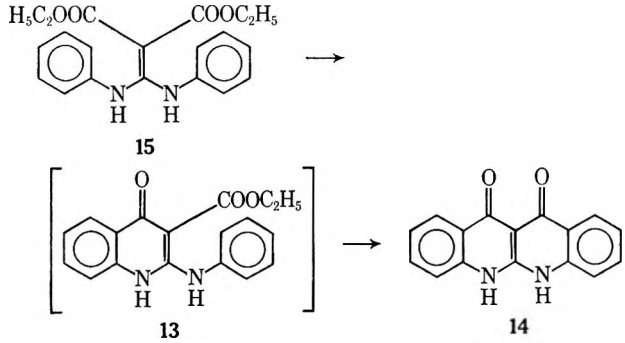
7

7	R	R¹	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Halogen, % Calcd	Halogen, % Found
a	H	H	201.5–203[a]	87.6	$C_{17}H_{14}N_2O_3$	69.37	69.18	4.79	4.82	9.52	9.46		
b	OCH_3	H	222–225[b]	87.0	$C_{19}H_{18}N_2O_5$	64.40	64.54	5.12	5.04	7.91	8.14		
c	CH_3	H	219–220[b]	82.6	$C_{19}H_{18}N_2O_3$	70.79	70.96	5.63	5.52	8.69	8.77		
d	F	H	223–226[a]	79.3	$C_{17}H_{12}F_2N_2O_3$	61.82	61.94	3.66	3.68	8.48	8.43	11.51	11.65
e	Cl	H	247–248.5[a]	89.4	$C_{17}H_{12}Cl_2N_2O_3$	56.21	56.33	3.33	3.37	7.71	7.88	19.52	19.56
f	H	Cl	225–226[b]	97.1[c]	$C_{17}H_{12}Cl_2N_2O_3$	56.21	55.98	3.33	3.27	7.71	7.95	19.52	19.40
g	Cl	Cl	251–253[b]	90.0[d]	$C_{17}H_{10}Cl_4N_2O_3$	47.25	47.25	2.33	2.46	6.48	6.73	32.82	32.40

[a] Recrystallized from methanol. [b] Recrystallized from acetic acid. [c] The crude product may have been a mixture of the 7-chloro and some of the 5-chloro isomer. [d] The crude product may have been a mixture of the 6,7-dichloro and some of the 5,6-dichloro isomer.

and a shoulder at 3.15 μ believed to be due to the pyridone N–H were found.

As previously stated, formation of **7** from maleates **5** requires prior isomerization to the fumarates **6**.[16] Cyclization of **6a** under conditions of the Conrad–Limpach reaction occurs in high yield to give **7a**, but there the reaction stops. All attempts to effect the cyclization of **7a** to **2** by pyrolytic means have not been successful. This is in contrast to the behavior of 2-anilino-3-ethoxycarbonyl-4-quinolone (**13**), which undergoes pyrolytic cyclization to the isomer of epindolidione, dibenzo[*b*,*g*][1,8]naphthyridine-11,12-(5,6H)-dione (**14**). In fact, pyrolysis of diethyl dianilinomethylenemalonate (**15**) proceeds directly to **14**, presumably *via* **13**.[17] An explanation of this difference in behavior is not readily apparent.

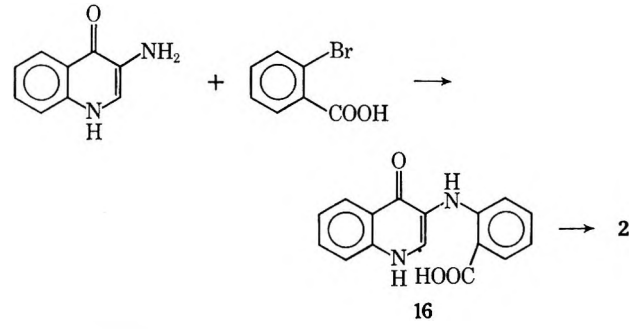


15 13 14

Epindolidiones (9).—Cyclization of **7** in polyphosphoric acid at 150° gave excellent yields of **9**. Although direct cyclization of **7** is the preferred method, the corresponding acids **8** can be similarly cyclized in polyphosphoric acid. The feasibility of the latter route was demonstrated in the synthesis of **2**. This route is actually preferred in the preparation of 2,8-dimethoxyepindolidione (**9**, R = OCH_3; R^1 = H) in order to take advantage of the more facile cyclization of the acid relative to the ester to avoid demethylation. A similar cyclization was effected by Ainley and Robinson[4] in boiling 60% sulfuric acid in the preparation of 2,8-dimethylepindolidione (**9**, R = CH_3; R^1 = H), although in lower yield. The cyclization of **8** (R^1 = R = H) in the preparation of **2** was carried out by de Diesbach, *et al.*,[5] with phosphorus pentoxide in nitrobenzene in undisclosed yield.

Table III gives pertinent data for epindolidione and its substituted derivatives.

Synthesis *via* 3-(2-Carboxyphenylamino)-4-quinolone.—One of the routes which were followed by Ainley and Robinson[4] in their attempt to synthesize epindolidione involved the preparation of 3-(2-carboxyphenylamino)-4-quinolone (**16**). This acid was obtained in unspecified yield from N-benzoyl-2,3-dihydro-4-quinolone and ethyl *o*-nitrosobenzoate. Many attempts by these workers to cyclize acid **16** or its acid chloride under a variety of conditions were unsuccessful. We have prepared acid **16** by a more convenient route involving the copper-catalyzed reaction of 3-amino-4-quinolone[18] with *o*-bromobenzoic acid in 69% yield. This acid was found to undergo cyclization to epindolidione in nearly quantitative yield in an aluminum chloride–sodium chloride eutectic melt at 200°. Similarly, the acid underwent cyclization in hot polyphosphoric acid, although in lower yield. The



16

failure of Ainley and Robinson to effect cyclization of **16** to **2** was due to their use of insufficiently active catalysts such as 60% sulfuric acid, zinc chloride, and stannic chloride.

Structure and Properties of Epindolidione.—The epindolidiones range from greenish yellow to orange microcrystalline powders, which in most cases exhibit the phenomenon of polymorphism. They do not melt or decompose up to 400° and are very sparingly soluble

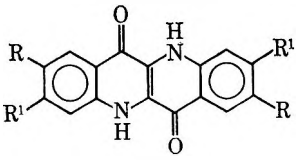
(16) Attempts to detect isomerization prior to cyclization by differential thermal analysis have not been successful.

(17) Subsequent to the completion of this work, this observation has been reported by R. Gompper and R. Kuntz, *Ber.*, **98**, 1391 (1965).

(18) B. B. Bachman, D. E. Welton, G. L. Jenkins, and J. E. Christian, *J. Amer. Chem. Soc.*, **69**, 365 (1947).

TABLE III

EPINDOLIDIONES[a]



9

9	R	R¹	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Halogen, % Calcd	Halogen, % Found	λ_{max} in concd H_2SO_4, mμ
a	H	H	$C_{16}H_{10}N_2O_2$	73.27	73.55	3.84	3.89	10.68	10.96			500
b	OCH_3	H	$C_{18}H_{14}N_2O_4$	67.07	66.96	4.38	4.42	8.69	8.74			542
c	CH_3	H	$C_{18}H_{14}N_2O_2$	74.46	74.14	4.86	4.96	9.65	9.65			515
d	F	H	$C_{16}H_8F_2N_2O_2$	64.43	64.69	2.70	2.70	9.40	9.33	12.74	12.48	502
e	Cl	H	$C_{16}H_8Cl_2N_2O_2$	58.03	57.97	2.43	2.43	8.46	8.39	21.41	21.20	514
f	H	Cl[b]	$C_{16}H_8Cl_2N_2O_2$	58.03	58.10	2.43	2.41	8.46	8.70	21.41	21.30	494
g	Cl	Cl[c]	$C_{16}H_6Cl_4N_2O_2$	48.03	48.10	1.51	1.71	7.00	7.01	35.45	35.20	511

[a] Without exception, the yields of **9** were essentially quantitative. Because of the very low solubility of these compounds in organic solvents, they were purified by precipitation of their sulfates in H_2SO_4. An example of this method is given in the Experimental Section. [b] The crude product may have been a mixture of the 2,8-dichloro and some of the 1,8-dichloro isomer. [c] Experimental evidence suggests that the crude product may have been a mixture of the 2,3,8,9-tetrachloro and some of the 1,2,8,9-tetrachloro isomer.

in organic solvents. This low solubility may be attributed to strong intermolecular hydrogen bonding between the carbonyl oxygen and the N–H hydrogen atoms which are favorably situated for such bonding. Support for strong intermolecular bonding in the solid state is derived from a comparison of the visible spectra in the solid state with that of a solution in N,N-dimethylformamide. The visible absorption spectrum of epindolidione in solution is characterized by three bands increasing in intensity with increasing wavelength as shown in Table IV. The spectrum in the solid state

TABLE IV

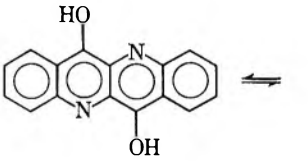
VISIBLE ABSORPTION MAXIMA OF EPINDOLIDIONE

λ, mμ Solid state[a]	λ, mμ Solution in DMF	Molar extinction coefficient in DMF
494	444	20,200
462	419	13,200
429	398	5,200

[a] Obtained from a reflectance spectrum on a dispersion of solid in an alkyd resin film.

is similar to that of the solution spectrum but shows a strong bathochromic shift which for the major absorption band is 50 mμ. A shift of this magnitude can be attributed to intermolecular hydrogen bonding in the solid state. A similar shift was shown in the case of indigo, by Weinstein and Wyman,[19] who concluded that, in the solid state, indigo is associated by means of intermolecular hydrogen bonding. Furthermore, the positions of the carbonyl and N–H stretching frequencies in the ir spectrum (see below) lend additional support to the suggestion that the epindolidiones are intermolecularly hydrogen bonded. Lüttke and Klessinger[20] came to the same conclusion based on similar findings in an ir spectral investigation of indigo and its substituted derivatives.

As shown earlier by nmr and ir spectral data, **7a** exists in the quinolone rather than the tautomeric hydroxyquinoline form. Unfortunately, the insolubility of the epindolidiones does not permit measurement of their nmr spectra. However, the ir spectra of **9** show a band at 6.10–6.28 μ attributed to the carbonyl groups and similar to that shown by **7** and 4-quinolone. In addition, the spectra of **9** show a band at 3.13–3.16 μ attributed to the N–H stretching frequencies. Based on these data it is concluded that epindolidione exists in the ketonic form **2**, not the enolic form **17**.



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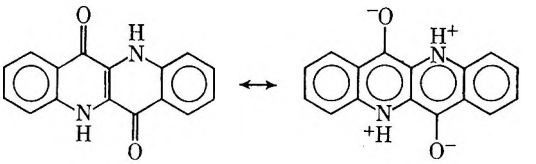
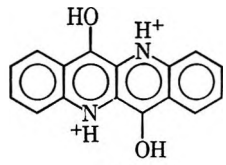


2 18

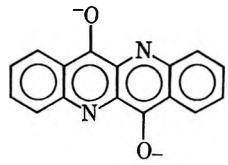
The extent of contribution of the resonance form **18** to the structures of epindolidione is difficult to assess. X-ray structural determinations of peptides and related substances has shown that the zwitterionic form contributes about 40% to the structure of the amide group.[21] Since epindolidione is a vinologous amide, the zwitterionic form **18** in which both pyridone moieties are in the charge-separated form, as well as the resonance form in which only one pyridone group is so affected, will make a significant contribution to the structure of epindolidione. It is noteworthy that the spectrum of **2** in 96% sulfuric acid is similar to that of naphthacene in N,N-dimethylformamide solution but shows a strong bathochromic shift relative to the visible spectrum of **2** in N,N-dimethylformamide. This is to be expected if the degree of aromatic character of the molecule is increased on protonation. The spec-

(19) J. Weinstein and G. M. Wyman, *J. Amer. Chem. Soc.*, **78**, 2387 (1956).
(20) W. Lüttke and M. Klessinger, *Ber.*, **97**, 2342 (1964).
(21) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, pp 281, 282.



19

trum is best interpreted on the basis of structure **19** where protonation has taken place on the oxygen rather than the nitrogen atoms. This is in agreement with the work of Katritzky and Jones[22] who have shown by an nmr study that protonation of pyridones and quinolones takes place on oxygen. Likewise, the spectrum of **2** in methanolic N-benzyltrimethylammonium hydroxide[23] shows similarity to the spectrum of the diprotonated species, although the relative peak intensities are different and the spectrum in basic solution shows a bathochromic shift. This suggests that the visible spectra in strongly basic as well as strongly acidic solutions are due to the same chromophore.[3c,24] The spectrum in methanolic N-benzyltrimethylammonium hydroxide is, therefore, indicative of an aromatic structure which is best formulated as the dianion **20**.



20

Experimental Section[25]

Dimethyl Dihydroxyfumarate (4).—To a solution of 222 g (1.5 mol) of dihydroxyfumaric acid[26] in 1.2 l. of methanol in a flask equipped with a stirrer, thermometer, a gas inlet tube, and means for external cooling, was added 300 g (2.5 mol) of anhydrous magnesium sulfate. The mixture was stirred and cooled to 0–5°, treated with a stream of anhydrous hydrogen chloride for 4.5 hr, and thereafter kept at room temperature for 3 days. The solid was collected by filtration, washed with a small amount of methanol, and reslurried in 3 l. of cold water. The product was promptly filtered and washed with cold water until free of acid and sulfate. After drying at 60° the yield of ester was 245.7 g (93.2%), mp 168–172° (lit.[6] mp 165–173°).

Dimethyl Bis(arylamino)maleates (5).—To a suspension of 17.6 g (0.10 mol) of **4** in 80 ml of methanol was added 0.22 mol of an arylamine followed by 1.0 ml (*ca.* 0.012 mol) of concentrated hydrochloric acid, and the mixture refluxed for 6 hr. Alternatively, an equivalent amount of dry arylamine hydrochloride can be used as catalyst. Upon refluxing, a clear solution formed, which became deeper in color, and eventually the product precipitated out of solution. The slurry was cooled to 5–10°; the product was separated by filtration, washed sparingly with methanol, and dried at 60°. Yields, melting points, recrystallization solvents, and elemental analyses are given in Table I.

2-Methoxycarbonyl-3-arylamino-4-quinolones (7).—In a 3-l. round-bottom flask, equipped with a stirrer, thermometer, heated addition funnel, and Dean–Stark tube, 400 ml of Dowtherm A was brought to reflux. To the gently refluxing solvent was added a hot (120–130°) solution of 100 g of **5** in 1 l. of Dowtherm A over a period of 0.5 hr. After completion of the addition, refluxing was continued for another 15 min. A mixture of methanol and Dowtherm A was collected in the Dean–Stark tube. The solution was cooled to room temperature, and the precipitated yellow to orange crystalline solids were separated by filtration. After thorough washing with petroleum ether (bp 60–90°) the products were dried at 60°. Yields, melting points, recrystallization solvents, and elemental analyses are given in Table II. A simplified procedure for the cyclization of **5** entails simple reflux of a solution of this ester in Dowtherm A with provision for removal of product methanol. The isolation procedure is the same, but the yields are somewhat lower.

The ester **7a** was isolated in two forms: a yellow form when the Dowtherm A solution was cooled rapidly, and a brown form when the solution was cooled slowly. Both forms showed essentially the same ir spectra and chemical reactions but had distinctive X-ray diffraction patterns. They are, therefore, believed to be different polymorphic forms of this compound.

2-Carboxy-3-anilino-4-quinolone (8, R = R¹ = H).—A mixture of 200 ml of 5% sodium hydroxide, 50 ml of ethanol, and 10 g of **7a** was refluxed for 2 hr. The solution was cooled to room temperature, filtered, and carefully acidified with 6 *N* hydrochloric acid. The resultant yellow solid was collected by filtration, washed free of acid with water, and dried at 60°. The yield was 7.5 g (78.8%). A sample was recrystallized from acetic acid. The colorless material showed mp 224–225° (lit.[5] mp 220–221°).

2-Carboxy-3-(*p*-anisidino)-6-methoxy-4-quinolone (8, R = OCH_3; R^1 = H).—A mixture of 960 ml of 10% sodium hydroxide and 49.2 g of **7** (R = OCH_3; R^1 = H) was refluxed for 2 hr. The solution was cooled to 0–5° and carefully acidified to a pH of 4 with 6 *N* hydrochloric acid. The resultant yellow solid, which turned colorless after several minutes, was collected by filtration, washed free of acid with water, and dried at 60°. The yield was 45.0 g (95.4%). A sample was recrystallized from acetic acid: mp 234–235°.

Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.62; H, 4.64; N, 8.28.

Epindolidiones (9).—To 790 g of stirred polyphosphoric acid protected from atmospheric moisture was added 79 g of **7**, and the mixture was heated over 1 hr to 150° and then maintained at 145–150° for 2 hr. After it cooled to 40–50°, water was slowly added, maintaining the temperature at about 50°, until the vigorous hydrolysis reaction had ceased, after which an excess of water was added. The products were separated by filtration, then washed with water until free of acid, and dried at 80°. The yields were found to be essentially quantitative. The procedure does not apply to the preparation of **9** (R = OCH_3; R^1 = H). The compounds were conveniently purified by a procedure, an example of which follows.

In a flask equipped with a stirrer, drying tube, and thermometer 1380 g of 100% sulfuric acid was cooled to 8–10°. With stirring, 50 g of crude, pulverized **9** (R = Cl; R^1 = H) was added at 8–10°. The mixture was stirred at this temperature for 15–30 min or until complete solution was obtained as judged by microscopic examination. At this point water was added dropwise at a temperature not exceeding 20° until precipitation of the sulfate was nearly complete, in this case occurring at 94%. The latter value varied depending on the substituents and the concentration of **9** in the sulfuric acid. The sulfate was collected by filtration on a sintered-glass funnel and washed with sulfuric acid, the concentration of which was 5% below the concentration at which precipitation occurred, in this case 89%. The solid was transferred to 500 ml of ice–water, then heated to 90–100°, collected by filtration, and washed free of acid with hot water. After drying at 80°, the yield was 45.0 g (90% recovery).

Cyclization of 2-Carboxy-3-anilino-4-quinolone to 2.—Using a procedure analogous to that described for the cyclization of the esters **7**, a 92.6% yield of product was obtained. The ir spectrum of this material was identical with that of epindolidione obtained from the cyclization of the ester **7a**.

2,8-Dimethoxyepindolidione (9, R = OCH_3; R^1 = H).—To 100 g of stirred polyphosphoric acid protected from atmospheric moisture was added 10 g of **8** (R = OCH_3; R^1 = H), and the mixture heated over 1 hr to 100° and then maintained at 100–105° for 6 hr. The isolation procedure was analogous to that de-

(22) A. R. Katritzky and R. A. Y. Jones, *Proc. Chem. Soc.*, 313 (1960); A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961).

(23) Triton B was supplied by Rohm and Haas Co.

(24) A similar relationship of two visible spectra in the anthraquinone series was suggested to be due to the same chromophore by J. Weinstein and C. Merritt, Jr., *J. Amer. Chem. Soc.*, **81**, 3759 (1959).

(25) All melting points are uncorrected. The ir spectra were determined by the Nujol mull technique on a Perkin-Elmer Model 137 or 21 recording spectrophotometer. A Varian Associates A-60 instrument was used for recording the nmr spectra in deuterated dimethyl sulfoxide, employing tetramethylsilane as an internal standard. Visible spectra were measured on a Beckman DK or DU spectrophotometer. The Raman spectrum was recorded on a Cary Model 81, laser spectrophotometer. The dipole moment was determined by Dr. H. Eatough of the Central Research Department, E. I. du Pont de Nemours and Co.

(26) J. H. H. Fenton, *J. Chem. Soc.*, **87**, 811 (1905).

scribed for the preparation of **9** from **7**. The yield was quantitative, and the purification procedure was analogous to that described for **9** (R = Cl; R¹ = H). Elemental analysis is given in Table III.

Dibenzo[*b*,*g*][1,8]naphthyridine-11,12(5,6H)-dione (14), Isomer of Epindolidione.—To 250 ml of boiling Dowtherm A was added 25 g of diethyl dianilinomethylenemalonate[27] in small portions over a period of 15 min. By the use of a Dean–Stark tube, provision was made for the removal of product ethanol. After completion of the addition, reflux was continued for 1 hr. After the mixture cooled to room temperature, the product was removed by filtration, washed with ethanol, and dried at 60°. The yield was 17.4 g (96.5%). A sample was recrystallized from acetic acid and found not to melt up to 400°.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.30; H, 4.00; N, 10.84.

3-(2-Carboxyphenylamino)-4-quinolone (16).—A mixture of 30.4 g (0.19 mol) of 3-amino-4-quinolone, 38.0 g (0.19 mol) of *o*-bromobenzoic acid, 50.5 g (0.38 mol) of potassium carbonate, 0.5 g of spongy copper,[28] and 500 ml of amyl alcohol was refluxed for 4 hr and then steam distilled to remove the amyl alcohol. The resultant mixture was filtered hot, and the cooled filtrate was acidified with concentrated hydrochloric acid. The product was collected by filtration, then extracted with 500 ml of boiling water, filtered, washed free of acid, and dried at 80°. The yield was 34.7 g (69%). After recrystallization from methanol the melting point was 255–256° (lit.[4] mp 255°). Calcd: neut equiv, 280. Found: neut equiv, 278.

Epindolidione *via* 16. Aluminum Chloride Method I.—An intimate mixture of 70 g of aluminum chloride and 7 g of sodium chloride was heated to 130–135°. To the stirred molten mass was added 5.6 g of **16** in small portions. The mixture was heated at 200° for 3 hr, cooled to 130–135°, and cautiously poured over a mixture of 500 g of ice and 100 ml of concentrated hydrochloric acid. The slurry was heated at 95–100° for 15 min, and the yellow product was collected by filtration and washed free of acid and chloride ion with water. The wet solid was extracted with 100 ml of boiling 10% sodium carbonate, filtered, washed base free, and dried at 80°. The yield was 5.0 g (96.3%). The product showed an ir spectrum identical with that of **2** prepared *via* **5a**.

Epindolidione *via* 16. Polyphosphoric Acid Method II.—A mixture of 50 g of polyphosphoric acid and 5.0 g of **16** was heated with stirring at 200° for 6 hr. After it cooled to 40–50°, water was slowly added, maintaining the temperature at 50°, until the vigorous hydrolysis reaction had ceased, after which an excess of water was added. The mixture was heated to boiling and filtered hot. The product was washed free of acid with hot water. The wet solid was extracted with 100 ml of boiling 10% sodium carbonate, filtered, washed base free, and dried at 80°. The yield was 3.0 g (64.2%). The product showed an ir spectrum identical with that of **2** prepared *via* **5a**.

(27) W. Traube and A. Eyme, *Ber.*, **32**, 3176 (1899).

(28) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 446.

Registry No.—**2**, 17352-37-3; **5a** (Table I), 17540-23-7; **5b**, 17540-24-8; **5c**, 17540-25-9; **5d**, 17540-26-0; **5e**, 17540-27-1; **5f**, 17540-28-2; **5g**, 17540-29-3; **7a** (Table II), 16377-52-9; **7b**, 16479-61-1; **7c**, 17540-32-8; **7d**, 17540-33-9; **7e**, 16377-54-1; **7f**, 16427-99-9; **7g**, 16377-56-3; **8** (R = OCH_3; R′ = H), 16377-61-0; **9b** (Table III), 17352-38-4; **9c**, 17540-39-5; **9d**, 17341-72-9; **9e**, 17470-44-9; **9f**, 17352-60-2; **9g**, 17341-73-0; **14**, 3048-67-7.

Acknowledgment.—We are indebted to Dr. G. S. Hammond, Dr. R. C. Lord, and Dr. J. C. Sheehan for helpful comments.

Azecino[2,1-*a*]tetrahydroisoquinolines and Related Compounds. I. Reaction of 3,4-Dihydroisoquinolines with Nonenolizable β Diketones

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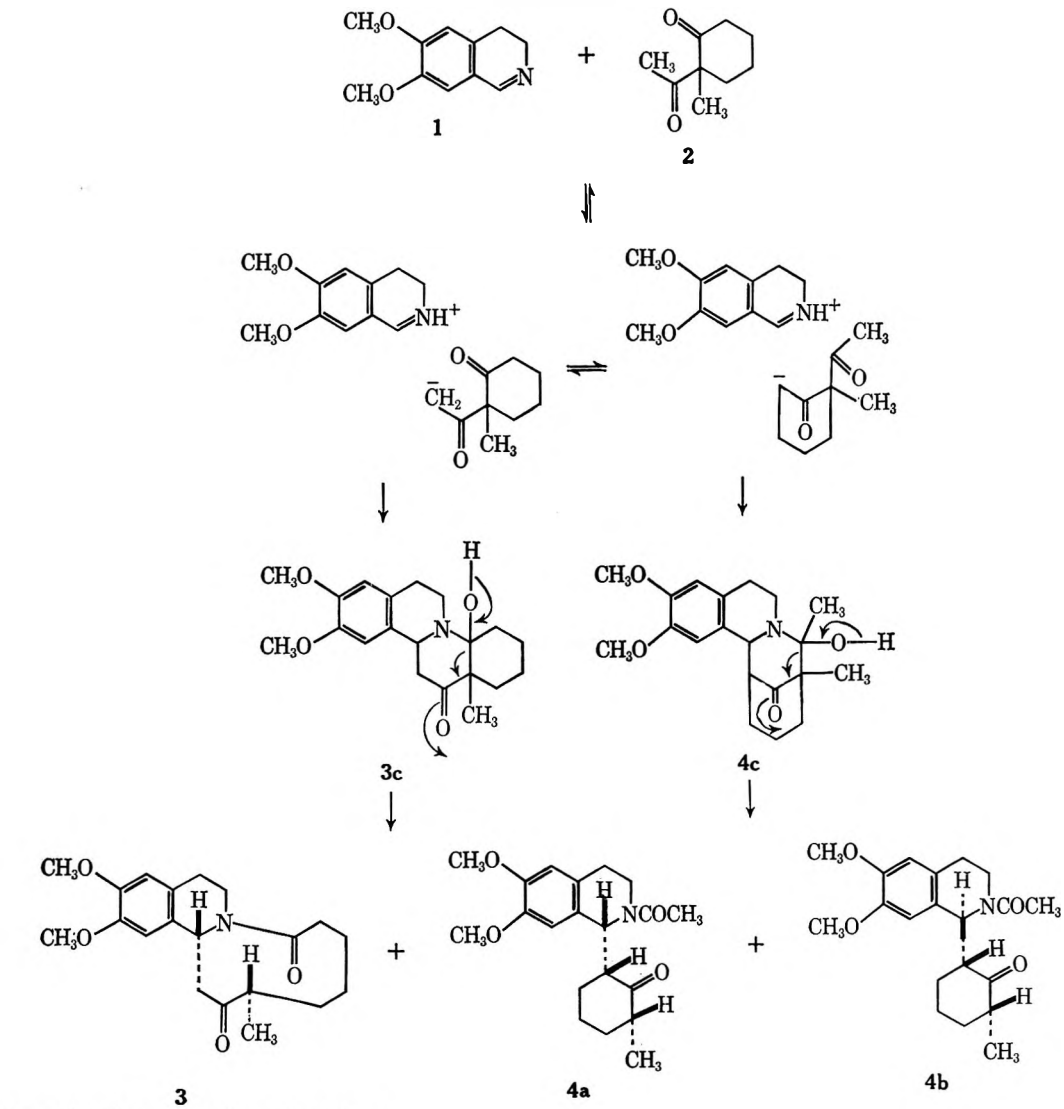
3,4-Dihydroisoquinolines react with nonenolizable β diketones to give 1-(2-oxoalkyl- or -cycloalkyl)-N-acyl-1,2,3,4-tetrahydroisoquinolines (type **4** and **9**), and azecino[2,1-*a*]isoquinolines (type **3**), or other related large-ring compounds (**8**).

Recently, we have described the synthesis of benzo[*a*]quinolizines and dibenzo[*a*,*f*]quinolizines by the condensation of 3,4-dihydroisoquinolines with enolizable β diketones.[1] The present communication is concerned with the reaction of 3,4-dihydroisoquinolines with nonenolizable β diketones (Scheme I). In the course of this reaction the β diketone is cleaved, and the resulting oxoalkyl (or oxocycloalkyl) and acyl fragments alkylate and acylate the isoquinoline reactant at C-1 and N, respectively. Linear β diketones yield 1-(2-oxoalkyl)-N-acyl-1,2,3,4-tetrahydroisoquinolines (**9**, **10**), whereas β diketones of the acylcycloalkanone type give 1-(2-oxocycloalkyl)-N-acyltetrahydroisoquinolines (type **4a**, **b**) and azecino[2,1-*a*]isoquinolines (type **3**), or other related, large-ring compounds (**8**). For example, the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) with 2-acetyl-2-methylcyclohexanone (**2**) gave 5,6,10,11,12,13,15,15a-octahydro-2,3-dimethoxy-13-methyl-9H-azecino[2,1-*a*]-isoquinoline-8,14-dione (**3**) and two of the four possible stereoisomeric 2-acetyl-1-(3-methyl-2-oxocyclohexyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines (**4a**, **b**). The pH dependence (the reaction is inhibited by alkali and strong acid) and the solvent dependence (rate increases with solvent polarity) are analogous to those observed in the reaction of 3,4-dihydroisoquinolines and enolizable β diketones.[1] This suggests that both reactions proceed by related mechanisms. Extension of this reaction to other dihydroisoquinolines and to 3,4-dihydro-β-carboline is summarized in Table I. The table also includes 3-phenyl-2,4-pentanedione (**10**), which in contrast to the other enolizable β diketones did not yield a benzo[*a*]quinolizine. Instead, it was cleaved analogously to nonenolizable β diketones. This may be a consequence of stabilization of the resulting anion by the phenyl group.

The structure of the large-ring compounds is based on the following evidence. The ultraviolet spectra are characteristic of the parent tetrahydroisoquinoline chromophores. The infrared spectra show bands typical of a ketone (1700–1705-cm^{-1} region) and an amide carbonyl (1620–1633-cm^{-1} region). The mono-

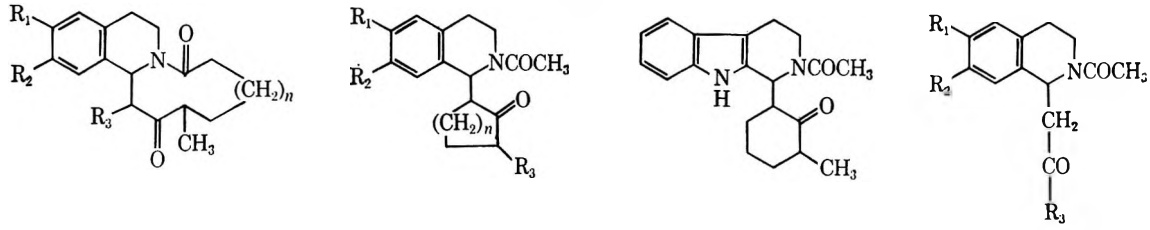
(1) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1965).

SCHEME I[a]



[a] The configurational assignments are tentative.

TABLE I



Compound	Starting β diketone	Type	Product R1	Product R2	Product R3	n	Mp, °C	% yield	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
3	2-Acetyl-2-methylcyclohexanone	A	CH_3O	CH_3O	H	2	240–244	35	69.54	7.88	4.05	69.52	7.96	4.24
4a	2-Acetyl-2-methylcyclohexanone	B			CH_3	2	158–158.5	3.5	69.54	7.88	4.05	69.72	8.06	4.35
4b	2-Acetyl-2-methylcyclohexanone	B	CH_3O	CH_3O	CH_3	2	135–137	1	69.54	7.88	4.05	69.77	7.95	4.34
5	2-Acetyl-2-carbethoxycyclohexanone	B	CH_3O	CH_3O	$COOC_2H_5$	2	144–152	5	65.49	7.25	3.47	65.34	7.04	3.30
6	2-Acetyl-2-methylcyclopentanone	B	CH_3O	CH_3O	CH_3	1	134–139	28	68.86	7.60	4.23	69.03	7.64	4.47
7	2-Methoxyacetyl-2-methyleyclohexanone	A	CH_3O	CH_3O	CH_3O	2	161.5–163	12	67.18	7.79	3.73	67.09	7.68	4.00
8	2-Acetyl-2-methylcyclododecanone	A	CH_3O	CH_3O	H	8	129–130	25	72.69	9.15	3.26	72.88	9.10	3.18
9	3,3-Diethyl-2,4-pentanedione	D	CH_3O	CH_3O	$(C_2H_5)_2CH$		139–140	6.5	69.13	8.41	4.03	69.39	8.63	4.27
10	3-Phenyl-2,4-pentanedione	D	CH_3O	CH_3O	$C_6H_5CH_2$		124–126	68	71.92	6.86	3.81	71.79	6.92	3.97
11	2-Acetyl-2-methylcyclohexanone	A	CH_3O	H	H	2	189–191	14	72.35	7.99	4.44	72.44	8.01	4.53
12	2-Acetyl-2-methylcyclohexanone	B	CH_3O	H	CH_3	2	168–171	1	72.35	7.99	4.44	72.26	7.73	4.56
13	2-Acetyl-2-methylcyclohexanone	A	H	H	H	2	151–153	2	75.75	8.12	4.91	75.60	8.03	4.80
14	2-Acetyl-2-methylcyclohexanone	C					250–252	50	74.04	7.46	8.64	73.91	7.43	8.57

molecular formula was confirmed by Rast molecular weight determination. A Kuhn–Roth assay indicated the presence of one C–CH_3 group. The corresponding pmr signals are found as a doublet in the 1.10–1.13-ppm region. In addition, the spectra show four signals corresponding to one proton in the 5.63–5.80-ppm region constituting the X part of the H-15a–H_2-15 ABX system. (Compound 7 having only one hydrogen

TABLE II

THE PMR OF KETO AMIDES (TABLE I)

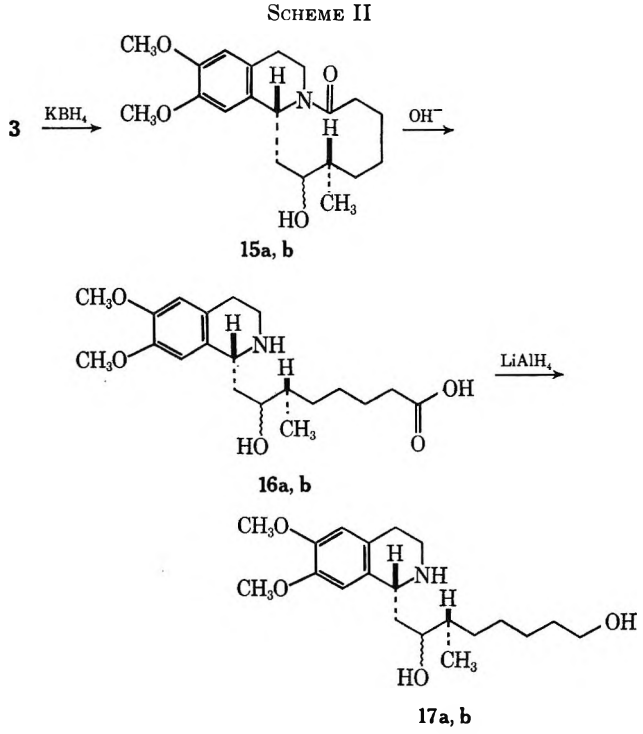
Compound	>CH–CH₃[a]	Ar–CH–N	Multiplicity of Ar–CH–N (*J*, cps)	CH₃CON<	Solvent
3	1.13	5.63	Quadruplet (12, 6)		$CDCl_3$
7	1.13	5.15	Doublet (9)		$CDCl_3$
8	1.10	5.6–6.1	Multiplet		$CDCl_3$
11	1.10	5.78	Quadruplet (12, 5)		$CDCl_3$
13	1.12	5.80	Quadruplet (12, 5)		$CDCl_3$
4a	1.02, 0.96	5.50, 6.24	Two doublets (10)	2.13	$CDCl_3$
4a	0.95	5.78	Doublet (9)	2.02	$(CD_3)_2SO$, 140°
4b	0.98	6.04	Doublet (12)	2.03	$CDCl_3$
5	1.14	5.77, 5.10	Two doublets (9)	1.98	$(CD_3)_2SO$
6	1.0	5.78, 5.32	Two doublets (5)	2.09	$(CD_3)_2SO$
6	1.0	5.63	Doublet (5)	2.10	$(CD_3)_2SO$, 130°
9	0.83	6.00, 5.51	Two triplets (6)	2.22 (2.12)	$CDCl_3$
10		5.88, 5.42	Two triplets (7)	2.15 (2.24)	$CDCl_3$
10		5.63	Triplet (7)	2.03	$(CD_3)_2SO$, 140°
12	0.88	6.08, 5.38	Two doublets (10)	2.02	$(CD_3)_2SO$
14	1.2	5.98	Doublet (7)	2.6	CF_3COOH

[a] Shifts expressed in parts per million (δ) from tetramethylsilane (TMS).

at C-15 gives this signal as a doublet at 5.15 ppm.) The cyclic nature of the amide was established by the fact that no carbon was lost upon hydrolysis of the amide bond.

Since attempted hydrolysis of **3** itself was attended by β elimination,[2] it was decided to reduce the carbonyl function prior to hydrolysis. KBH_4 reduction of the ketone amide **3** gave a stereoisomeric mixture of amide alcohols **15a, b**[2] which was hydrolyzed to a noncrystalline mixture of amino acids **16a, b**. The latter was characterized by its amphoteric properties, by the

SCHEME II



ir spectrum of the derived mixture of hydrochlorides which displayed a carboxyl band at 1710 cm^{-1}, as well as by reduction to the crystalline aminodiol mixture **17a, b** (Scheme II above).

(2) The elimination reactions as well as the separation of the mixture of epimers **15a, b** is described in the accompanying paper: M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 4015 (1968).

The structure of compounds of type **4** is based on the following evidence. Similarly, as in the large-ring compounds, the uv and the ir spectra are characteristic of the parent tetrahydroisoquinoline chromophore (tetrahydro-β-carboline in the case of **14**), and of the amide and ketone functions. The Kuhn–Roth assay indicates the presence of two C–CH_3 groups. The pmr spectra display the signals of these groups as a singlet ($CH_3CON<$) in the 1.98–2.22-ppm region and a doublet (>CH–CH_3) in the 0.88–1.03-ppm region. In place of the latter signal, the spectrum of the carbethoxy-substituted compound **5** shows a triplet at 1.14 ppm. In contrast to the finding in the large-ring compounds, the proton at the tetrahydroisoquinoline C-1 is shown as a doublet (rather than a quartet) in the 5.50–6.24-ppm region. Hydrolysis of the amido alcohol **18**, prepared by the KBH_4 reduction[3] of the keto amide **4a**, gave the amino alcohol **19**. The loss of the acetyl group in the course of hydrolysis proves the noncyclic nature of the amide. Compounds not subjected to the reduction–hydrolysis sequence were classified as cyclic (type **3**) or noncyclic (type **4**) amides on the basis of their pmr spectra, using as criteria the presence or absence of the N-acetyl proton signals, and the multiplicity (doublet or quartet) of the tetrahydroisoquinoline H-1 signal. (See Table II.)

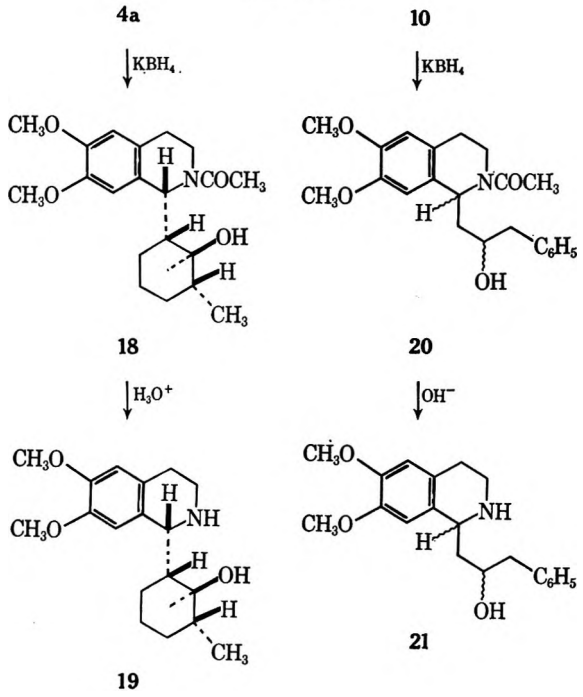
The structures of compounds **9** and **10** are based on their uv (6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline chromophore), ir (ketone and amide carbonyl bands), and pmr spectra (tetrahydroisoquinoline H-1 triplet; N-acetyl) and on the hydrolysis of the amido alcohol **20**[3] to the amino alcohol **21** (Scheme III).

Stereochemical Considerations.—The assignments of configurations were based upon consideration of Dreiding models and pmr spectra. Because of lack of basic knowledge in the literature[4] about relative conforma-

(3) (a) The KBH_4 reduction gave predominantly one of the two expected epimers, the small amount of the second one being lost upon crystallization. (b) The reduction prior to hydrolysis was necessary because, under the reaction conditions, **4a** suffered β elimination as evidenced by the isolation of 3,4-dihydro-6,7-dimethoxyisoquinoline.

(4) For discussion of stereochemistry of ten-membered rings, see J. Sicher in "Progress in Stereochemistry," part 3, de la Mare and Klyne, Ed., Butterworth and Co. Ltd., London, 1962, p 202; J. Sicher, M. Svoboda, J. Zavada, R. B. Turner, and P. Goebel, *Tetrahedron*, **22**, 659 (1966); R. M. Moriarty, *J. Org. Chem.*, **29**, 2748 (1964); L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965).

SCHEME III



tional stabilities of azecines having an amide and a keto function, *these assignments must be considered as tentative.*

Analogies in the pmr spectra (Table II) of the azecino-[2,1-*a*]isoquinolines indicate a common stereochemistry for **3**, **11**, and **13** (Figure 1). The following discussion of the pmr spectrum of **13** is therefore pertinent to the other compounds of this series. The H-15a signal appears as the X part of an ABX system at 5.8 ppm, (four equally intense signals with observed splittings of 12 and 5 cps). The large chemical shift of this proton indicates its position in the plane of the aromatic ring as well as in the plane of the amide group.[5] Consequently, the 15a–15 bond is pseudoaxial with respect to the tetrahydropyridine ring. The splitting pattern of the H-15a signal and magnitude of the coupling constants are best explained by assumption of approximately 180 and 60° dihedral angles with the two protons at C-15.[6] Spin decoupling of the methyl group hydrogens permits the location of the H-13 signal at 3.28 ppm. This unusual low-field position cannot be explained by proximity of the carbonyl group alone (H-2 in 2-methylcyclohexanone resonates at *ca.* 2.5 ppm). Inspection of models suggests that, in the *trans* configuration (referring to the H-15a,H-13 relationship), H-13 may be located either in the diamagnetic zone of the amide group or outside of its magnetic field. In contrast, in the *cis* configuration, the conformation with the least amount of interactions (Figure 1), H-13 appears to be located in the paramagnetic zone of the amide.[7] The *cis* configuration is therefore assigned to **3**, **11**, and **13**.

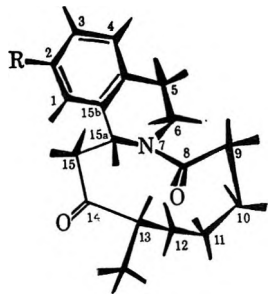


Figure 1.—Suggested conformation of azecino[2,1-*a*]isoquinolines **3**, **11**, and **13**. [The model is viewed approximately perpendicular to the 15b–15a–15–14–(H-13) segment.]

The pmr spectra of the compounds of type **4a** (including **9** and **10**) show a double set of signals. For example, the spectrum of **4a** in $CDCl_3$ displays two overlapping doublets at 0.96 and 1.02 ppm (CH–CH_3), two half-proton doublets at 5.50 and 6.24 ppm (tetrahydroisoquinoline H-1), one proton singlet at 6.62 ppm, and two half-proton singlets at 6.7 and 7.11 ppm (aromatic hydrogens). This doubling is explained by the presence of two conformations, in relatively slow equilibrium similar to those observed by Dalton, *et al.*,[8] in the case of 2-acetyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines. Upon heating to 130–140° in $(CD_3)_2$-SO solution the two sets of signals coalesce to a simple spectrum: a doublet at 0.95 ppm (CH–CH_3), a doublet at 5.87 ppm (tetrahydroisoquinoline H-1), and two singlets at 6.67 and 6.87 ppm (aromatic hydrogens).

The difference in the chemical shifts of the two aromatic hydrogens suggests that the tetrahydroisoquinoline H-8 is deshielded by the carbonyl group. Examination of the models shows that the proximity of the tetrahydroisoquinoline H-8 to the carbonyl group is possible only in the *erythro*[9] configuration, providing that the tetrahydroisoquinoline H-1 and the cyclohexanone H-2 are predominantly *anti* periplanar, as suggested by their coupling constant (J = 10 cps). The *erythro* configuration is therefore assigned to **4a** and the *threo* configuration to **4b** which has both aro-

(5) F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 2435 (1965), report a chemical-shift difference of 2.4 ppm for the geminal protons at C-6 of 4-oxoquinolizidine. The low-field resonance (4.63 ppm) of the equatorial H-6 is attributed to its position in the plane of the lactam group.

(6) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(7) (a) The argument is crucially dependent on the assumption that H-15a is axial and the C-15a–C-15 bond is equatorial. A referee has suggested that there may actually be fast ring inversion at C-15a and that we may be observing an averaged conformation in the nmr. However, our C-15a proton signals in **3**, **11**, and **13** at 5.63–5.80 ppm are uniquely compatible with the *equatorial* proton signals (5.60–5.65 ppm) reported in ref 8b. (b) For a detailed study of the magnetic anisotropy of the amide group see H. Paulsen and K. Todt, *Chem. Ber.*, 100, 3385 (1967). (c) No evidence is available regarding the configuration at C-13 in **7**. In contrast to the spectrum of **3**, that of **7** displays the aromatic protons at different fields (H-1, 7.08; H-4, 6.67 ppm) indicating that H-1 is in the field of the aliphatic methoxy group. (For correlation of chemical shifts of the aromic hydrogens with the spatial arrangement of the aliphatic methoxy group in a similar molecule, see ref 1.) The signal of H-15 is a sharp doublet (J = 9 cps) at 3.7 ppm and the corresponding H-15a doublet is displayed at 5.15 ppm. The magnitude of the coupling constant[6] as well as the H-1–CH_3O-15 interaction suggest an *anti*-periplanar arrangement for H-15 and H-15a. The smaller chemical shift of the H-15a signal, compared with the corresponding resonance of **3**, suggests that H-15a, while being in the deshielding zones of the aromatic ring and the amide carbonyl, is not in their plane. This finding, as well as the H-1–CH_3O-15 interaction, points to a pseudoequatorial arrangement of the C-15a–C-15 axis with respect to the tetrahydropyridine ring.

(8) (a) D. R. Dalton, M. P. Cava, and K. T. Buck, *Tetrahedron Lett.*, 2687 (1965). (b) G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Amer. Chem. Soc.*, **89**, 329 (1967). These authors observe Ar–CH–N signals at 4.72–4.77 and 5.60–5.65 ppm which they ascribe to axial and equatorial protons at C-1, respectively, the benzyl substituent at C-1 flipping slowly from the equatorial to the axial position. The signals observed by us are at lower field; in view of this difference, as well as the different geometry, at least of our series B, we feel that the two conformations observed by us are due to a different change, probably a rotation of the amide ($CH_3CON<$) grouping.

(9) The terms *threo* and *erythro* refer to spatial arrangement around the tetrahydroisoquinoline C-1–cyclohexanone C-2 axis. The *threo* configuration has the ketone carbonyl and the amide group on opposite sides of the plane dissecting the eclipsed hydrogens; the *erythro* configuration has these groups on the same side.

matic hydrogens resonating at approximately the same field (6.74 and 6.77 ppm). Since formation of compounds of type **4** from the cage intermediate (**4c**) probably involves enolization at cyclohexanone C-6, the end product is likely to have the preferred *cis* (diequatorial) configuration of the two cyclohexanone substituents.[10] This was confirmed by equilibration of **4a** and **4b** by Na_2CO_3 in methanol. Since this equilibration involves epimerization at C-2, it is likely that it also leads to labilization of the chiral center at C-6; consequently, the relative configuration of C-2 and C-6 in both **4a** and **4b** is the more stable one, *i.e.*, *cis*. At equilibrium, **4a** (*erythro*) predominated over **4b** (*threo*) in a ratio of about 10:1 (by tlc estimations) presumably because of steric (or dipolar) repulsion of the cyclohexanone carbonyl and acetamide functions in the preferred (H-1,H-2 *anti*) conformation of **4b**.[11]

The greater crowding of the N-acetyl group in **4b** apparently restricts the amide to a single conformation, since the pmr spectrum of **4b** does not show the doubling of signals, observed with compounds of type **4a**.

In summation, *erythro,cis* configuration is assigned to **4a** and compounds with analogous pmr spectra **5**, **6**, and **12**, and *threo,cis* configuration is assigned to **4b**.

Since KBH_4 reduction of **4a** might be expected to give as the major product, the more stable alcohol,[3a,12] the *erythro,cis,trans* [*erythro* (isoquinoline C-1,cyclohexanol C-2), *cis* (cyclohexanol C-2,C-6), and *trans*(cyclohexanol C-2, C-1)] configuration is assigned to **18** and **19**.

The configurations of compounds **8**, **14**, **20**, and **21** were not determined.

The separation of the alcohols **15a** and **15b** together with the assignments of their configurations were carried out within the study of the chemical reactions of azecino[2,1-*a*]isoquinolines and are described in part II of this series.

Experimental Section[13]

Preparation of Keto Amides (Table I).—A mixture of 0.1 mol of a 3,4-dihydroisoquinoline (or 3,4-dihydro-β-carboline) and 0.1 mol of a suitable β diketone in 500 ml of water (100 ml of ethanol for **10**, and 900 ml of 75% ethanol for **14**) was refluxed for 20 hr (34 hr for **8**, 7.5 hr for **9**, and 48 hr for **10**). In the case of **10** and **14**, the product crystallized on chilling. In the case of **3**, after chilling of the reaction mixture, the aqueous layer was decanted, and the oily residue was crystallized by boiling in 100 ml of acetonitrile. In all other cases, the mixture was extracted with chloroform. The extracts were freed from basic material by washing with 2 *N* HCl, dried over Na_2SO_4, and evaporated at reduced pressure. The residual gum was crystallized directly (**5**, **8**, **11**, and **13**) or chromatographed on Florisil (1 g:40 g) using ethyl acetate as the eluent (**6**, **7**, and **9**). Concentration of mother liquors of **3** gave **4a**. Chromatography of mother liquors of **4a** and **11** gave **4b** and **12**, respectively. The products were crystallized from acetonitrile (**3**), ethyl acetate (**6**, **7**, **9**, **10**, **11**, **4a**, and **4b**), 2-propanol (**5**, **13**), ethanol (**8**), 95% ethanol (**12**), and acetic acid (**14**). The analytical and the pmr data of the keto amides are listed in Tables I and II, respectively.

KBH_4 Reduction of Keto Amides.—A solution of 2 g of a keto amide (**3**, **4a**, **10**) in 100 ml of 1:1 methanol–chloroform was treated portionwise with 2 g of KBH_4 and stirred for 6 hr at room temperature. The solvents were evaporated at reduced pressure, and the residue was dissolved in 25 ml of chloroform and 10 ml of water. The organic layer was separated, dried over Na_2SO_4, and evaporated to yield 90–95%. The analytical samples were obtained by a twofold crystallization from ethyl acetate.

5,6,9,10,11,12,13,14,15,15a-Decahydro-14-hydroxy-2,3-dimethoxy-13-methyl-8H-azecino[2,1-*a*]isoquinolin-8-ones (15a, b)[2] had mp 163–194°; ν_{max}^{Nujol} 1515 (s), 1605 (s), 3350 (w), and 3500 (w) cm^{-1}; λ_{max}^{EtOH} 282 mμ (ϵ 4300).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 68.92; H, 8.54; N, 4.03.

2-(2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)-6-methylcyclohexanol (18)[3a] had mp 199–200.5°; λ_{max}^{EtOH} 283 mμ (ϵ 4000); ν_{max}^{Nujol} 1515 (s), 1615 (vs), and 3470 (s), cm^{-1}.

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41; N, 4.03. Found: C, 69.36; H, 8.48; N, 3.90

α-[(2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)-methyl]phenethyl alcohol (20)[3a] had mp 157–159°; ν_{max}^{Nujol} 1510 (m), 1620 (s), and 3400 (m) cm^{-1}; λ_{max}^{EtOH} 281 mμ (ϵ 4000).

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.38; H, 7.38; N, 3.59.

Hydrolysis of the Amido Alcohols. 2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolyl)-6-methylcyclohexanol (19).—A solution of 1.5 g of **18** in 15 ml of concentrated HCl was heated on a steam bath for 1 hr. After dilution with 85 ml of water, the reaction mixture was washed with ethyl acetate, made basic with 10% NaOH, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to give 0.81 g (61%) of **19**. The analytical sample was obtained by crystallizations from ether and from ethyl acetate: mp 137–142°.

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.49; H, 8.95; N, 4.72.

2-[(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolyl)methyl]-phenethyl Alcohols (21).—A solution of 1 g of **20** in 10 ml of 95% ethanol was treated with 3 g of KOH, refluxed for 2 hr, diluted with 85 ml of water, and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to give 0.7 g (80%) of **21**: mp 123.5–125.5; ν_{max}^{Nujol} 1515 (s), 1610 (w), and 3300 (m) cm^{-1}.

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.42; H, 7.81; N, 4.33.

6-Methyl-8-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)-1,7-octanediol (17a, b).—A solution of 0.78 g of **15a, b** and 2.1 g of KOH in 25 ml of 95% ethanol was refluxed for 3.5 hr, chilled, acidified with ethanolic 3 *N* HCl, filtered, and concentrated *in vacuo* to give the hydrochloride of the amino acids (**16a, b**).

A solution of the latter in 50 ml tetrahydrofuran was treated with 1 g of $LiAlH_4$ and refluxed for 4.5 hr. Excess $LiAlH_4$ was destroyed by dropwise addition of water. The mixture was filtered and the collected solids were extracted with tetrahydrofuran. The combined filtrate and extracts were evaporated *in vacuo*. The residue was dissolved in chloroform, and the resulting solution was extracted with 2 *N* HCl. The aqueous portion was made basic with 10% NaOH and extracted with chloroform. The chloroform extracts were dried over Na_2SO_4 and evaporated to give 0.65 g (67%) of **17a, b**. The analytical sample was prepared by a twofold crystallization from CH_3CN: mp 97–99°; ν_{max}^{Nujol} 3300 (s) cm^{-1}.

Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.56; H, 9.49; N, 4.01.

(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 52.

(11) The *anti*-periplanar (H-1,H-2) conformation is confirmed by the observation that J = 12 cps for the protons. An attempt was made to confirm the equatorial conformation of the C-6 methyl group in **4a** and **4b** by studying the effect of benzene on the chemical shifts. According to N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 165, the resonance of an axial methyl group adjacent to carbonyl suffers an upfield shift of 0.2–0.3 ppm on passing from $CDCl_3$ to benzene solution, whereas the resonance of an equatorial methyl suffers a small downfield shift. Our results ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$ = 0.02 for **4a** and −0.2 ppm for **4b**) were not conclusive probably because of effects of the amide and the aromatic ring. If anything, they suggest the equatorial conformation [hence *cis* (cyclohexanone C-2,C-6) configuration] of the methyl group in **4b**.

(12) D. J. Cram and F. D. Greene, *J. Amer. Chem. Soc.*, **75**, 6005 (1953); D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(13) Melting points were determined using the Thomas–Hoover capillary melting point apparatus. The uv and ir spectra were recorded, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated, the former were determined as solutions in 95% ethanol and the latter as Nujol mulls. The nmr spectra were obtained in deuterated chloroform using a Varian A-60 spectrometer with tetramethylsilane as an internal standard. Tlc was carried out on silica gel G according to Stahl (Merck, Darmstadt), using ethyl acetate or 95% ethanol as the eluent. The chromatograms were developed by spraying with either dilute aqueous $KMnO_4$ or ethanolic iodine (4%) solutions.

Registry No.—**3**, 17628-44-3; **4a**, 17628-45-4; **4b**, 17628-46-5; **5**, 17628-47-6; **6**, 17628-48-7; **7**, 17692-13-6; **8**, 17628-99-8; **9**, 17628-94-3; **10**, 17628-95-4; **11**, 17628-49-8; **12**, 17652-45-8; **13**, 17628-50-1; **14**, 17628-96-5; **15a, b**, 17628-51-2; **17a, b**, 17628-52-3; **18**, 17628-53-4; **19**, 17628-54-5; **20**, 17628-97-6; **21**, 17628-98-7.

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Azecino[2,1-*a*]tetrahydroisoquinolines and Related Compounds. II. Preparation of Isoquino[2,1-*a*][1,5]diazacycloundecine and Benzazacyclotetradecine Derivatives, Transannular N → O Acyl Migration, and Other Reactions

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Received December 1, 1967

Conversions of azecino[2,1-*a*]tetrahydroisoquinolines into isoquino[2,1-*a*][1,5]diazacycloundecine and benzazacyclotetradecine derivatives *via* Beckmann rearrangement and by intramolecular β elimination, respectively, are recorded. Transannular N → O acyl migration leading to the formation of a 1-isoquinolineoctanoic acid γ-lactone derivative and other reactions are described.

In the preceding paper[1] we have described the preparation of azecino[2,1-*a*]tetrahydroisoquinolines by the reaction of nonenolizable β diketones with 3,4-dihydroisoquinolines. In the course of the transformations carried out to prove the structure of I,[2] its chemical properties were explored in some detail.

KBH_4 reduction of I (Scheme I) gave an epimeric mixture of amido alcohols (IIa, b)[3] which had a broad melting point and was inseparable on tlc. However, on treatment of this mixture with acid, one of the alcohols (IIa) underwent N → O acyl migration to give the labile amino lactone III, whereas the other alcohol (IIb) was recovered in pure form. Under the reaction conditions (HCl in chloroform), lactone III reacted immediately with the ethanol present in the commercial chloroform to give the ethyl ester IV. The sensitivity of lactone III toward traces of water or alcohol thwarted all attempts at its preparation in pure form. The presence of a lactone, however, was indicated by a 1710-cm^{-1} band in the ir spectrum of the crude product obtained from the reaction in washed and dried chloroform. The high reactivity of the lactone is apparently due to the proximity of the carboalkoxy group to the amine function, which may promote intramolecular base catalysis of transesterification with alcohols. Tosylation of IIa, b eliminated this proximity effect and gave a mixture of a stable lactone V (from IIa) along with the expected O-tosylation product VI (from IIb). When IIb alone was allowed to react with TsCl, under identical conditions, complete conversion into VI took place indicating that the lactone-forming reaction is stereoselective in that it requires a favorable orientation of the hydroxy group in the amido alcohol II.

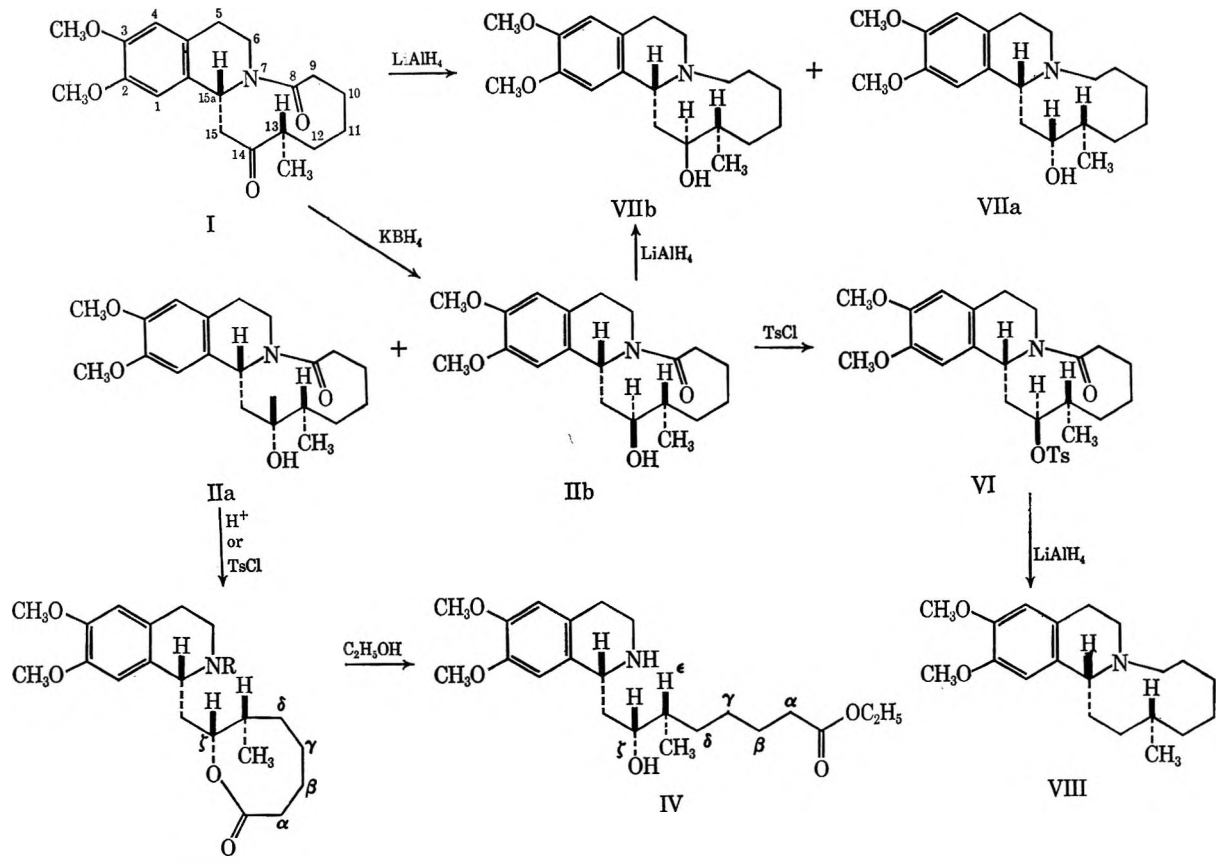
$LiAlH_4$ reduction of I gave two amino alcohols (VIIa and VIIb) which were separable on tlc and by column chromatography. One of the alcohols VIIb was shown to be identical with the alcohol prepared by the $LiAlH_4$ reduction of the amido alcohol IIb. Reduction of the tosyloxy amide VI with $LiAlH_4$ gave the amine VIII.

Treatment of I with base (Scheme II) caused an intramolecular β elimination of the amide group resulting in the formation of an unsaturated 14-membered-ring compound IX. The structure of IX was assigned on the basis of the following evidence. The uv spectrum [λ_{max} 222 mμ (ϵ 11,700), 246 (11,200), 305 (11,700) plateau, and 339 (16,000)] resembles that of veratralacetone [λ_{max} 224 mμ (ϵ 7500), 244 (9500), 298 (10,500) shoulder, and 335 (17,500)]. The ir spectrum showed bands characteristic of amide carbonyl (1640), amide NH (3330), and α,β-unsaturated ketone (1662 cm^{-1}). In contrast to I, the pmr spectrum of IX displays no signals in the 5–6.5-ppm region, indicating that position 15a was involved in the chemical transformation. In the low-field region, in addition to the signals of the two aromatic protons (6.87 and 7.27 ppm), there is now displayed an AB quartet (6.56, 6.83, 7.54, and 7.81 ppm) indicative of the two olefinic hydrogens.

With hydroxylamine I readily formed the oxime X, which on treatment with polyphosphoric acid underwent the Beckmann rearrangement to give the 11-membered cyclic diamide XI. That the nitrogen was inserted between the carbonyl carbon and the carbon carrying the methyl group was confirmed by identification of 1,2,3,4-tetrahydroisoquinoline-1-acetic acid among the fragments resulting from a vigorous acid hydrolysis of XI. Reduction of XI by $LiAlH_4$ at room temperature gave the amine amide XII. That the tertiary amide was reduced, in preference to the secondary, was indicated by the ir spectrum of XII which displayed an amide NH at 3280 cm^{-1}. The $LiAlH_4$ reduction at room temperature of the amide oxime X gave an amine oxime XIII which, according to its ir spectrum, had no carbonyl functions. The near-ir spectrum indicated absence of NH and presence of OH. The latter was confirmed by O acetylation (XIIIa). The assumption that the amide group was reduced in preference to the oxime was confirmed by

(1) M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Org. Chem.*, **33**, 4010 (1968).
(2) Compound **3** of preceding paper.[1]
(3) Compounds **15a, b** of preceding paper.[1]

SCHEME I[a]



[a] The configurational assignments are tentative.

the Beckmann rearrangement of XIII to XII. On treatment with HCl, XIII readily gave compound XIV, the uv spectrum of which [λ_{max} 220 mμ (ϵ 13,250), 242 (12,250), 295 (16,100), and 325 (17,250)] closely resembles the veratralacetone chromophore of IX. The presence of OH and NH groups, indicated by near-ir spectroscopy, was confirmed by the preparation of diacetyl derivative XIVa. The uv spectrum of the latter compound [λ_{max} 224 mμ (ϵ 13,500), 242 (14,250), 305 (13,250), and 335 (16,900)] was nearly identical with the spectrum of IX. In agreement with the assigned structure, the pmr spectra of XIV and XIVa showed signals corresponding to four protons in the low-field region.

Stereochemical Considerations.—In the preceding paper[1] compound I was tentatively assigned the *cis* (C-13,C-15a) configuration. Therefore, its derivatives VIII, X, XIII, and XIIIa are presumably also *cis*. Since the Beckmann rearrangement is known to proceed with retention of configuration of the migrating carbon,[4] the *cis* configuration is assigned to XI and XII.

The configuration assignment of the amido alcohols II is based on the ability of one of the isomers (IIa) to form a lactone. Consideration of Dreiding models indicates that both the *threo* and the *erythro* forms (the *threo* and *erythro* prefixes refer to the spatial arrangement at positions 13 and 14) appear *a priori* to be capable of lactone formation. However, lactone formation from the *erythro* isomer appears more facile because (in one of the preferred conformations) its hydroxyl points in the direction of the amide N–C bond and, on conformational inversion around the N–C-15a axis, can approach the carbonyl carbon within bonding distance, at a favorable angle and without serious interactions. The model of the intermediate is free of crowding. On this basis the *cis,threo* [(C-13,C-15a),-(C-13,C-14)] configuration may tentatively be assigned to IIb, VI, and VIIb and the *cis,erythro* [(C-13,C-15a),-(C-13,C-14)] configuration to IIa, VIIa, V, and IV. (The configuration of the alcohols VII follows from the conversion of IIb into VIIb by $LiAlH_4$ reduction.)

(4) E. S. Gould, "Mechanism and Structure in Organic Chemistry," pp 618–621, M. Holt and Co., New York, N. Y., 1959.

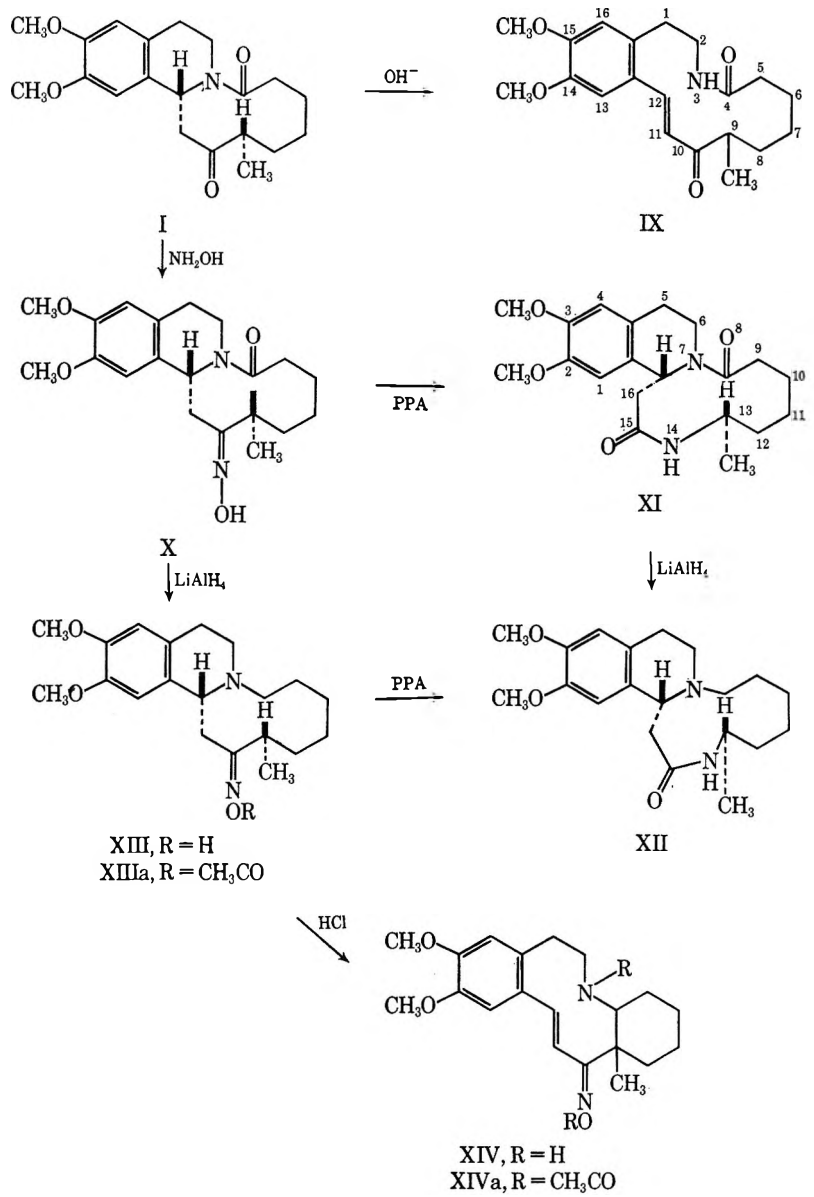
Experimental Section[5]

Treatment of Amido Alcohols IIa, b with HCl.—A slow stream of dry HCl was passed for 40 min through a solution of 7.2 g of IIa, b[1] in 350 ml of chloroform. The mixture was allowed to stand overnight, and the solvent was removed *in vacuo* at room temperature (rotary evaporator). Chloroform was added, and the evaporation was repeated. The glossy residue was treated with 200 ml of ethyl acetate. The crystalline precipitate was filtered off, and the filtrate was extracted with three 70-ml portions of water.

The aqueous extracts were combined, made basic with saturated sodium bicarbonate solution, and extracted with chloroform. The chloroform extracts were dried and evaporated, and

(5) Melting points were determined using the Thomas–Hoover capillary melting point apparatus. The uv and ir spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated, the former were determined as solutions in 95% ethanol and the latter as Nujol mulls. The nmr spectra were determined in deuterated chloroform using a Varian A-60 spectrometer with tetramethylsilane as an internal standard. Tlc was carried out on silica gel G according to Stahl (Merck, Darmstadt), using ethyl acetate as the eluent. The chromatograms were developed by spraying with either dilute aqueous $KMnO_4$ or ethanolic iodine (4%) solutions.

SCHEME II



I IX X XI XIII, R = H XIIIa, R = CH₃CO XII XIV, R = H XIVa, R = CH₃CO

the residue was recrystallized from ethyl acetate to give 2.68 g (39%) of **ethyl 1,2,3,4-tetrahydro-ζ-hydroxy-6,7-dimethoxy-ε-methyl-1-isoquinoline octanoate (IV)**: mp 82–83°; ν_{max} 1520 (vs), 1610 (ms), 1730 (vs), 3100 (m), and 3300 cm^{-1} (m); λ_{max} shoulder 223 mμ (ε 3100), 282 (3800), and 286 (3800); δ 0.88 (d, CH_3–CH), 1.22 (t, CH_3–CH_2), 3.83 (CH_3O), 4.12 (q, CH_3CH_2), 4.39 (t, isoquinoline H-1), and 6.56, 6.60 ppm (aromatic H).

Anal. Calcd for $C_{22}H_{35}NO_5$: C, 67.14; H, 8.97; N, 3.56. Found: C, 67.42; H, 9.02; N, 3.63.

The initial crystalline precipitate and the concentrated ethyl acetate solution (marked with asterisk) yielded 3.17 g (44%) of **5,6,9,10,11,12,13,14,15,15a-decahydro-14-hydroxy-2,3-dimethoxy-13-methyl-8H-azecino[2,1-a]isoquinolin-8-one (IIb)**: mp 211–216°; ν_{max} 3430 (m), and 1600 cm^{-1} (s); δ 1.01 (d, CH_3–CH), 3.86 (CH_3O), 4.8–5.3 (2 H, m, H-15a and equatorial H-6), and 6.60, 6.68 ppm (aromatic H).

Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.02; H, 8.52; N, 4.00.

Reaction of IIa, b with *p*-Toluenesulfonyl Chloride.—A solution of 10 g (0.029 mol) of IIa, b in 250 ml of pyridine was treated dropwise (45 min) with a solution of 11.4 g (0.06 mol) of *p*-toluenesulfonyl chloride in 100 ml of pyridine and was stirred at room temperature for 22 hr. The reaction mixture was concentrated under reduced pressure at temperatures not exceeding 40°. The residue was dissolved in 250 ml of chloroform and was washed consecutively with dilute HCl, 5% sodium hydroxide solution, and H_2O. Drying and evaporation of the chloroform solution gave 13.2 g of residue. Crystallization from 100 ml of 2-propanol afforded 3 g (21%) of **5,6,9,10,11,12,13,14,15,15a-decahydro-14-hydroxy-2,3-dimethoxy-13-methyl-8H-azecino[2,1-a]isoquinoline-8-one *p*-toluenesulfonate (VI)**. Crystallization from ethyl acetate yielded analytical material: mp 165–166°; R_f 0.5; ν_{max} 1635 (s), 1520 (m), and 915 cm^{-1} (vs).

Anal. Calcd for $C_{27}H_{35}NO_6S$: C, 64.65; H, 7.03; N, 2.79. Found: C, 64.70; H, 7.15; N, 3.06.

A second crop of crystalline material from the 2-propanol mother liquor of VI gave on recrystallization from ethyl acetate 0.88 g (6%) of **1,2,3,4-tetrahydro-ζ-hydroxy-6,7-dimethoxy-ε-methyl-2-(*p*-tolylsulfonyl)-1-isoquinolineoctanoic acid ζ-lactone (V)**: mp 189–190°; R_f 0.8; ν_{max} 1720 cm^{-1} (s); δ 0.93 (d, CH_3–CH), 2.27 (CH_3–C_6H_4), 3.73, 3.84 (CH_3O), 4.3–4.8 (2 H, m, equatorial H-3, ζ-H), 5.15 (H-1, q, J_{ab} = 12 cps, J_{ab} = 3.5 cps), 6.28, 6.57 (dimethoxybenzene aromatic H's), and 6.98, 7.12, 7.48, 7.63 ppm (toluene aromatic H's).

Anal. Calcd for $C_{27}H_{35}NO_6S$: C, 64.65; H, 7.03; S, 6.30. Found: C, 64.88; H, 7.05; S, 6.28.

5,6,9,10,11,12,13,14,15,15a-Decahydro-2,3-dimethoxy-13-methyl-8H-azecino[2,1-a]isoquinolin-14-ols (VIIa and VIIb).—A solution of 8.7 g of IIa,b in 500 ml of tetrahydrofuran was treated with 8 g of $LiAlH_4$, refluxed for 8 hr, and allowed to stand overnight. Excess $LiAlH_4$ was destroyed with water, and the solids were filtered off and washed with tetrahydrofuran. Combined filtrate and washings were concentrated to dryness under reduced pressure. The residue was dissolved in ethyl acetate and extracted with 3 *N* HCl. The acid solution was made basic with

10% NaOH and extracted with chloroform. Evaporation of the chloroform solution gave 6.32 g (80%) of crude isomeric mixture.

Chromatography of a portion of the crude product on Florisil (40 g/g) with ethyl acetate afforded isomer VIIa (R_f 0.7) which was dissolved in dilute HCl and treated with an excess of 17% perchloric acid. The precipitated perchloric acid salt was recrystallized from 2-propanol: mp 160°; ν_{max} 3400 (m), 3100 (w), 1610 (w), and 1525 cm^{-1} (m).

Anal. Calcd for $C_{20}H_{31}NO_3 \cdot HClO_4$: C, 55.36; H, 7.43; N, 3.23; Cl, 8.17. Found: C, 55.62; H, 7.33; N, 3.47; Cl, 8.39.

Chromatography of a portion of the crude product on silica gel (100 g/g) with ethyl acetate afforded chromatographically pure VIIb as a gum (R_f 0.85). The hydrochloride salt, prepared by dissolving the gum in ethyl acetate and treating it with ethereal hydrogen chloride, was crystallized from 2-propanol three times to give the analytical sample: mp 183–185°; ν_{max} 3300 (s), 2550 (m), 1610 (w), and 1520 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{31}NO_3 \cdot HCl$: C, 64.94; H, 8.72; N, 3.79; Cl, 9.58. Found: C, 65.06; H, 8.88; N, 4.09; Cl, 9.35.

Preparation of VIIb from IIb.—A mixture of $LiAlH_4$ (2.7 g) and IIb (2.74 g) in 125 ml of tetrahydrofuran was refluxed for 6.5 hr. Excess reagent was destroyed with water. The mixture was filtered, and the solids were washed with tetrahydrofuran. Combined filtrate and washings were evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was extracted with 2 *N* HCl. The aqueous extracts were made basic with 10% NaOH and extracted with chloroform. On drying and evaporation of the chloroform solution VIIb base was obtained (R_f 0.85). The gummy product was dissolved in ether, and the solution was treated with ethereal HCl. The precipitated hydrochloride was filtered off and recrystallized from acetonitrile to yield 1.9 g (65%), mp 181–183°.

5,6,9,10,11,12,13,14,15,15a-Decahydro-2,3-dimethoxy-13-methyl-8H-azecino[2,1-*a*]isoquinoline Perchlorate (VIII).—A solution of 3 g of VI in 250 ml of tetrahydrofuran was treated with 3 g of $LiAlH_4$ and refluxed for 4 hr. Excess $LiAlH_4$ was destroyed by addition of water. The solids were filtered off and washed with hot tetrahydrofuran. Combined filtrate and washings were concentrated under reduced pressure. The oily residue was dissolved in ether and extracted with 2 *N* HCl. The acid solution was made basic with 10% NaOH and extracted with $CHCl_3$. Drying and evaporation of the $CHCl_3$ solution yielded the crude product. Chromatography on 30 g of Florisil with ethyl acetate as the eluent afforded chromatographically pure material (R_f 0.9), which was dissolved in 10 ml of methanol and treated with 2 ml of 70% perchloric acid. After evaporation of the methanol, the residue was triturated with cold water and crystallized from 2-propanol to yield 1.42 g (51%) of product, mp 161–163°. Recrystallization from 2-propanol afforded analytical material, mp 162–165° [dried at 140° (0.1 mm) for 5 hr].

Anal. Calcd for $C_{20}H_{31}NO_2 \cdot HClO_4$: C, 57.48; H, 7.72; N, 3.35; Cl, 8.48. Found: C, 57.24; H, 7.88; N, 3.61; Cl, 8.60.

1,2,5,6,7,8-Hexahydro-14,15-dimethoxy-9-methyl-3-benzazacyclotetradecine-4,10(3H,9H)-dione (IX).—A solution of 5 g of I in 125 ml ethanol was treated with 6.5 ml of a 0.17 *N* solution of sodium in ethanol and was refluxed for 1.5 hr with exclusion of moisture. The solvent was removed *in vacuo*, and the residue was dissolved in 125 ml of $CHCl_3$ and washed twice with H_2O. Drying and concentration of the solution yielded crude IX. Crystallization from 95% ethanol and recrystallization from ethyl acetate afforded 0.56 g (11.2%) of analytical material: mp 188–189°; λ_{max} 222 mμ (ϵ 11,700) plateau, 246 (11,200), 305 (11,700) shoulder, and 339 (16,000); ν_{max} 3330 (m), 1660 (s), 1640 (s), 1600 (s), 1535 (m), and 1525 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.77; H, 8.02; N, 4.13.

5,6,10,11,12,13,15,15a-Octahydro-2,3-dimethoxy-13-methyl-9H-azecino[2,1-*a*]isoquinoline-8,14-dione 14-Oxime (X).—A solution of 10 g of I in 750 ml of 95% ethanol was combined with a solution of 25 g of $NH_2OH \cdot HCl$ in 150 ml of H_2O, treated with 100 ml of 10% NaOH, and refluxed for 15 hr. After evaporation of the ethanol *in vacuo*, the residue was treated with 500 ml of H_2O, made acid with concentrated HCl, and extracted three times with 300-ml portions of chloroform. The chloroform solution was dried and concentrated to dryness *in vacuo*. Crystallization of the crude oxime from methanol afforded 9.1 g (87%) of product. Recrystallization from methanol gave the analytical material: mp 217–220°; λ_{max} 282 mμ (ϵ 4500) and 286 (4500); ν_{max} 3200 (m), 1615 (s), 1590 (s), and 1520 cm^{-1} (ms).

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.60; H, 7.80; N, 7.51.

5,6,9,10,11,12,13,14,16,16a-Decahydro-2,3-dimethoxy-13-methylisoquino[2,1-*a*][1,5]diazacycloundecine-8,15-dione (XI).—Powdered X (5 g) was added to polyphosphoric acid (100 g) and heated on a steam bath (95–100°) with occasional stirring for 0.5 hr. After cooling and dilution with 1 l. of ice water with vigorous stirring, the mixture was extracted with $CHCl_3$. Evaporation of combined and dried extracts yielded the crude product, which was crystallized from 100 ml of ethyl acetate to give 4.05 g (81%) of chromatographically pure material. Recrystallization from acetonitrile gave analytical material: mp 252–255°; λ_{max} 282 mμ (ϵ 4550) and 286 (4590); ν_{max} 3450 (w), 3350 (ms) 3300 (w), 1660 (s), 1630 (s), 1545 (s), and 1515 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.73; H, 7.69; N, 7.63.

Hydrolysis of XI.—A mixture of 0.5 g of XI and 25 ml of 4 *N* HCl was refluxed for 17 hr, cooled, washed with chloroform, and evaporated to dryness. The residue was dissolved in pyridine, treated with 2 ml of acetic anhydride, and heated on a steam bath for 15 min. Ice–water was added; the mixture was made strongly basic with NaOH solution and was washed with chloroform and ethyl acetate. Acidification gave 0.2 g of product which was identified as N-acetyl-1,2,3,4-tetrahydroisoquinoline-1-acetic acid by comparison with the authentic sample: ν_{max} 1710 (-COOH) and 1620 cm^{-1} ($NCOCH_3$).

5,6,8,9,10,11,12,13,14,15,16,16a-Dodecahydro-2,3-dimethoxy-13-methylisoquino[2,1-*a*][1,5]diazacycloundecin-15-one (XII). A. $LiAlH_4$ Reduction of XI.—A solution of 3.68 g of XI in 500 ml of tetrahydrofuran was chilled, treated with 3.6 g of $LiAlH_4$, and stirred at room temperature for 3 hr. Excess $LiAlH_4$ was destroyed with water with external cooling. The reaction mixture was filtered and the cake was washed several times with tetrahydrofuan. The combined filtrate and washings were dried and evaporated under reduced pressure. The residue was crystallized from aqueous ethanol to give 2.5 g (71%) of analytically pure material: mp 173–175°; λ_{max} 282 mμ (ϵ 4400) and 286 (4400); ν_{max} 3300 (m), 1630 (s), 1540 (m), and 1515 cm^{-1} (ms).

Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.12; H, 9.03; N, 7.99.

B. Beckmann Rearrangement of XIII.—A mixture of 0.5 g of XIII and 18 g of polyphosphoirc acid was heated on the steam bath for 40 min with frequent stirring. The reaction mixture was cooled and dissolved in 100 ml of ice–water. The solution was made basic with 40% KOH and extracted with $CHCl_3$. Drying and evaporation of the chloroform solution and crystallization of the residue from ethyl acetate yielded 0.11 g of XII: mp 172–174.5°; with XII prepared by reduction of XI, mmp 173–175°.

5,6,9,10,11,12,13,14,15,15a-Decahydro-2,3-dimethoxy-13-methyl-8H-azecino[2,1-*a*]isoquinolin-14-one Oxime (XIII).—A solution of 10 g of X in 1 l. of tetrahydrofuran was cooled, treated with 5 g of $LiAlH_4$, and stirred at room temperature for 3.5 hr. Excess $LiAlH_4$ was destroyed with water; the inorganic material was filtered off and washed with hot tetrahydrofuran. Combined and dried filtrate and washings were evaporated to dryness. The oily residue (10 g) was dissolved in ethyl acetate and adsorbed on a 250-g Florisil column. Elution with ethyl acetate then chloroform gave 7.7 g (80%). When this was dissolved in hot "Skelly B" and the solution allowed to cool, a glassy product was obtained which liquified at 65–90°: δ 1.05 (d, CH_3–CH), 3.84 (CH_3O), 3.8-4.2 (m, H-15a, equatorial H-6), and 6.60, 7.07 (aromtic H); λ_{max} 281 mμ (ϵ 4160); ν_{max} 3200 (m), 1605 (w), and 1510 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.25; H, 8.65; N, 8.19.

5,6,8,9,10,11,12,13,14,15a-Decahydro-2,3-dimethoxy-13-methyl-14H-azecino[2,1-*a*]isoquinolin-14-one O-Acetyl Oxime (XIIIa).—A solution of 2 g of oxime XIII in 50 ml of pyridine was treated with 5 ml of acetic anhydride and allowed to stand at room temperature overnight. The reaction was concentrated on a rotary evaporator below 60°. The solution of the residue in 50 ml of ethyl acetate was washed with 5% NaOH then with water and was evaporated under reduced pressure. Trituration of the residue with petroleum ether (bp 37–47°) yielded 1.86 g (83%) of crude XIII. A twofold crystallization from anhydrous ether afforded analytical material: mp 131–133°; ν_{max} 1750 cm^{-1}; δ 1.12 (d, CH_3–CH), 2.23 (CH_3CO), 3.85 (CH_3O), 3.8–4.2 (m, H-15a, equatorial H-6), and 6.58, 6.85 (aromatic H).

Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.27. Found: C, 68.07; H, 8.39; N, 7.51.

1,2,3,4,5,6,7,8-Octahydo-14,15-dimethoxy-9-methyl-3-benzazacyclotetradecin-10(9H)-one Oxime (XIV).—A solution of XIII (3.6 g) in 50 ml of 3 *N* HCl was stirred at room temperature for 1 hr. The acidic suspension was made basic with 10% NaOH and extracted with $CHCl_3$. The dried chloroform solution was evaporated *in vacuo*. The residue was crystallied from 50 ml of ethyl acetate to give 1 g (28%) of product. Evaporation of the ethyl acetate mother liquor and treatment of the residue with 20 ml of 6 *N* HCl for 2 hr at room temperature afforded an additional 0.9 g (25%) of XIV. An analytical sample was prepared by a single crystallization from methanol: mp 199–202° dec; δ 1.15 (d, CH_3–CH), 3.82 (CH_3O), and 6.88, 7.20 7.29 (*ca.* 1:1:2, H-11, H-12, H-13, H-16); λ_{max} 221 mμ (ϵ 13,500), 238 (12,400), 295 (15,800), 325 (16,800); ν_{max} 3300 (m), 2650 (m), 1600 (m), 1510 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.28; H, 8.85; N, 8.32.

3-Acetyl-1,2,3,4,5,6,7,8-octahydro-14,15-dimethoxy-9-methyl-3-benzazecyclotetradecin-10 (9H)-one O-Acetyl Oxime (XIVa).—A solution of 1.8 g of XIV in 50 ml of pyridine was treated with 5 ml of acetic anhydride and allowed to stand overnight. Concentration under reduced pressure yielded an oily residue which was triturated with cold H_2O and dissolved in chloroform. The solution was washed with water, dried, and concentrated *in vacuo* to yield 1.16 g (52%) of XIVa. Twofold crystallization from ethyl acetate gave analytical material: mp 59–62°; λ_{max} 224 mμ (ϵ 14,500) shoulder, 242 (14,900), 303 (13,800) plateau, and 336 (17,700); ν_{max} 1750 (s) and 1635 cm^{-1} (s); δ 1.32 (d, CH_3–CH), 2.12 (CH_3CON), 2.23 (CH_3COO), 3.93 (CH_3O), and 6.75, 6.87, 7.15, 7.28 (4 H, AB quartet superimposed on two singlets, H-11, H-12, H-13, H-16).

Anal. Calcd for $C_{24}H_{34}N_2O_5$: C, 66.95; H, 7.96; N, 6.51. Found: C, 67.22; H, 7.96; N, 6.65.

Registry No.—IIb, 17628-55-6; IV, 17628-56-7; V, 17628-67-0; VI, 17628-57-8; VIIa, 17628-58-9; VIIb, 17628-59-0; VIII, 17628-60-3; IX, 17658-47-8; X, 17628-61-4; XI, 17628-62-5; XII, 17658-46-7; XIII, 17628-63-6; XIIIa, 17628-64-7; XIV, 17628-65-8; XIVa, 17628-66-9.

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Rearrangement of Azidoquinones. Reaction of Thymoquinone and 2,5-Dimethyl-1,4-benzoquinone with Sodium Azide in Trichloroacetic Acid

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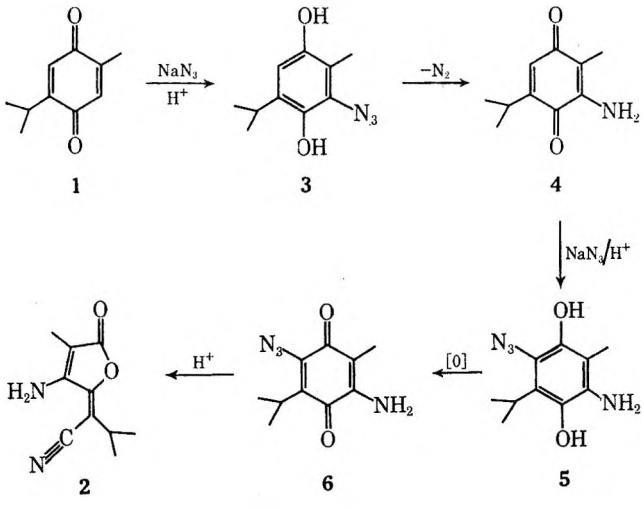
The rearrangements of thymoquinone (1) and 2,5-dimethyl-1,4-benzoquinone (18) to the γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides (2) and (19), respectively, upon reaction with sodium azide in trichloroacetic acid has been studied. In the case of thymoquinone a mechanism for this rearrangement is presented based upon the synthesis of the proposed intermediates **3**, **4**, and **6** and their subsequent conversion into **2** under the reaction conditions. By analogy, the rearrangement of **18** is also explained. Two new rearrangements of azidoquinones to ring-contracted compounds are also described: an acid-catalyzed rearrangement to γ-lactones and a thermal rearrangement to 5-cyanocyclopentene-1,4-diones.

The rearrangement of thymoquinone (1) to the γ-lactone, **2**, was recently reported by Rees[1,2] who observed this transformation when the quinone was treated with excess sodium azide in trichloroacetic acid at 65°. Described here is an investigation which indicates that this reaction proceeds as shown in Scheme I. The intermediates **3**, **4**, and **6** have been synthesized and found to give the lactone, **2**, when subjected to the reported reaction conditions.[1,2] In addition to the mechanistic implications concerning the rearrangement of **1** to **2** this study includes the following results of particular interest: (i) demonstration that azidohydroquinones undergo an intramolecular oxidation–reduction reaction to yield aminoquinones, and (ii) establishment of two interesting rearrangements of azidoquinones, an acid-catalyzed rearrangement to γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides and a thermal rearrangement to 5-cyano-cyclopentene-1,4-diones.

The azidohydroquinone, **3**, proposed as an intermediate in Scheme I, was prepared in 92% yield by dithionite reduction of an aqueous ethanolic solution of the corresponding azidoquinone, **7**. The quinone, **7**, was prepared by displacement of chloride by azide from 3-chloro-2-methyl-5-isopropyl-1,4-benzoquinone[3] according to the method reported by Fieser and Hartwell.[4] The spectral data for the new compounds, **3** and **7**, are reported in Table I.

SCHEME I



(1) A. H. Rees, *Chem. Ind.* (London), 931 (1964).
(2) A. H. Rees, *ibid.*, 1298 (1965).
(3) Kehrmann and Kruger, *Ann. Chem.*, **310**, 99 (1919).
(4) L. F. Fieser and J. L. Hartwell, *J. Amer. Chem. Soc.*, **57**, 1482 (1935).

TABLE I
SPECTRAL PROPERTIES

Compound	MP °C	IR (cm^{-1})*	NMR (ppm from TMS)**	Mass Spec.
2	175-177	3550, 3400, 2220, 1775, 1675, 1640	1.20 d (6) J = 7 cps; 1.78 s (3); 3.13 h (1) J = 7 cps; 5.25 b (2).	see ref. 2
3	91-93	3430, 3320, 2105, 1580	1.18 d (6) J = 7 cps; 2.21 s (3); 3.25 h (1) J = 7 cps; 5.02 b (2); 6.47 s (1)	M^+, 207 (27%); 179 (100%); 164 (35%); 151 (46%); 136 (85%) 108 (45%); 81 (50%); 68 (45%); 53 (100%)
4	oil	3500, 3310, 1650, 1610, 1575	1.12 d (6) J = 6.2 cps; 1.78 s (3); 2.98 h (1) J = 6.2 cps; 4.75 b (2); 6.31 (d) (1) J = 1.3 cps	M^+, 179 (100%); 164 (33%); 136 (45%); 108 (26%)
6	97-98	3500, 3410, 2120, 1650, 1600	1.19 d (6) J = 7 cps; 1.85 s (3); 3.18 h (1) J = 7cps; 5.00 b (2)	M^+, 220 (4%); 192 (17%); 177 (55%); 150 (100%); 106 (72%) 94 (35%); 68 (25%); 55 (66%); 54 (56%)
7	65-67	2125, 1665, 1610	1.17 d (6) J = 6.9 cps; 1.92 s (3); 3.03 h (1) J = 6.9 cps; 6.46 d (1) J = 1.2 cps	M^+, 205 (3%); 177 (50%); 162 (34%); 149 (18%); 134 (51%); 96 (50%); 81 (58%); 53 (100%).
9	70-71	3550, 3440, 2120	1.37 d (6) J = 7 cps; 2.27 s (3); 3.39 h (1) J = 7 cps; 5.30 b (2)	M^+ 248 (2%); 192 (17%); 177 (100%); 150 (85%); 149 (21%); 109 (32%); 94 (58%)
10	86-88	3460, 3320, 2120, 1665, 1600	1.21 d (6) J = 7.1 cps; 1.86 s (3); 2.94 h (1) J = 7.1 cps; 5.23 b (2)	M^+, 220 (4%); 192 (16%); 177 (100%); 150 (8%); 122 (13%); 106 (11%); 94 (24%); 68 (50%)
11	oil	2100, 1675, 1590	1.25 d (6) J = 7 cps; 1.93 s (3); 3.19 h (1) J = 7 cps	M^+, 246 (2%); 109 (24%); 94 (100%); 81 (61%); 66 (49%); 53 (78%); 43 (57%)
13	214-216	3400, 3320, 1660, 1640, 1525	1.07 d (6) J = 7 cps; 1.60 s (3); 2.77 h (1) J = 7cps; 6.68 b (4)	M^+, 194 (100%); 179 (53%); 162 (50%); 151 (39%); 119 (18%) 68 (14%)
14	38-40	2110, 1780, 1645	1.26 d (6) J = 7 cps; 2.12 s (3); 2.80 h (1) J = 7 cps; 7.30 d (1) J = 1.7 cps	M^+, 177 (100%); 162 (48%); 134 (52%); 162 (31%); 118 (30%); 96 (46%); 81 (40%); 53 (51%)
15	139-140	3500, 3340, 2210, 1750, 1660, 1630	1.27 d (6) J = 7 cps; 2.05 s (3); 2.60 h (1) J = 7 cps; 5.18 b (2)	M^+, 192 (39%); 177 (100%); 149 (21%); 163 (21%); 150 (13%); 68 (61%)
17	158-159	3420, 3310, 2275, 1750, 1700, 1630	1.30 d (6) J = 7 cps; 1.60 s (3); 2.90 h (1) J = 7 cps; 5.18 b (2)	M^+, 192 (25%); 177 (100%); 163 (8%); 149 (10%); 82 (8%); 68 (20%)
19	207-208	3500, 3380, 2215, 1775, 1640	1.78 s (3); 2.05 s (3)	M^+, 164 (100%); 149 (3%); 136 (16%); 108 (11%); 93 (27%); 82 (20%); 54 (43%)

* mujol

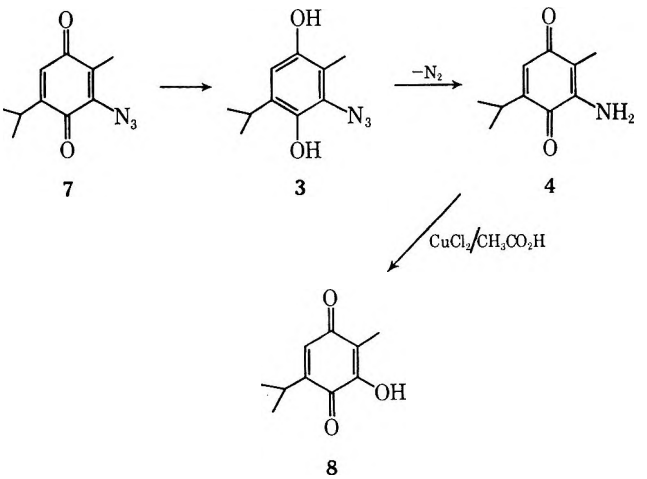
** solvent = $CDCl_3$; b = broad; d = doublet; s = singlet; h = heptet

Azidohydroquinones were proposed by Fieser and Hartwell[4] as intermediates in the preparation of aminoquinones from quinones upon treatment with sodium azide under acidic conditions. It proved possible to realize such a reaction for compound **3**. After refluxing a chloroform solution of **3** under an argon atmosphere for 3 hr, a 95% isolated yield of 3-aminothymoquinone (**4**) was obtained.[5] In addition, when the azidohydroquinone, **3**, was subjected to the reaction conditions reported by Rees,[1] it was first converted into the aminoquinone, **4**, which subsequently reacted to give the γ-lactone, 2.[6]

In addition to the preparation of 3-aminothymoquinone (**4**) as described above, the same compound was detected[4] and isolated by preparative thin layer chromatography on silica gel from the reaction of thymoquinone with sodium azide in trichloroacetic acid.[1] Gas chromatographic analysis of the reaction solution showed the gradual buildup of **4** and its subsequent disappearance as the γ-lactone, 2, formed. The aminoquinone isolated from this reaction was identical in all respects with 3-aminothymoquinone (**4**), which had previously been prepared from 3-azidothymohydroquinone (**3**). Confirmation of the position of the amino group in **4** was obtained by its hydrolysis to 3-hydroxy-2-methyl-5-isopropyl-1,4-benzoquinone (**8**), a compound of known constitution (Scheme II).[7]

The observed conversion of 3-azidothymohydroquinone (**3**) into 3-aminothymoquinone (**4**) suggested

SCHEME II



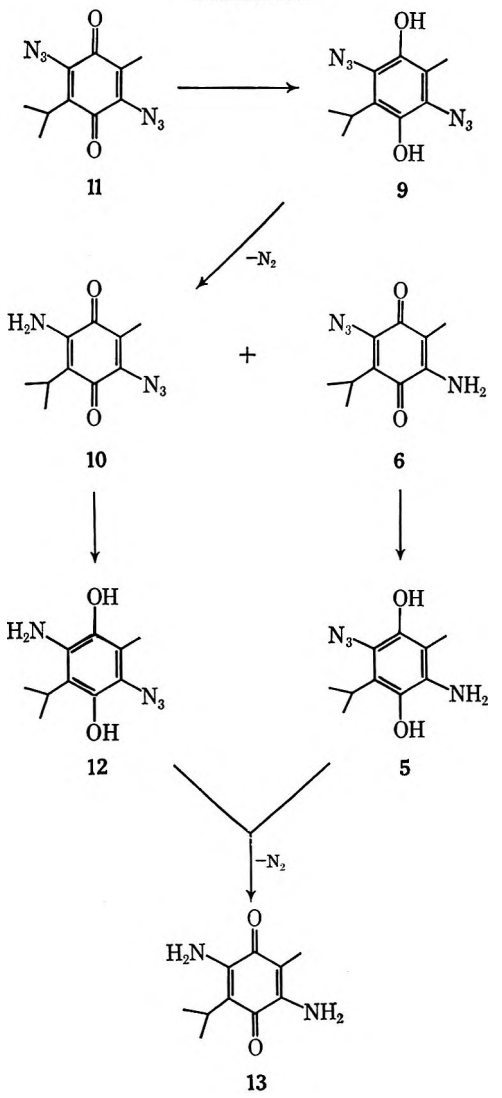
a convenient synthesis of the proposed intermediate 3-amino-6-azido-2-methyl-5-isopropyl-1,4-benzoquinone (**6**) (Scheme I). It was anticipated that 3,6-diazido-2-methyl-5-isopropyl-1,4-benzohydroquinone (**9**) would undergo an internal oxidation–reduction reaction to give a mixture of the two azidoaminothymoquinone isomers, **6** and **10**. Indeed, such a reaction was observed. The required 3,6-diazidothymoquinone (**11**) was obtained in 87% yield from the reaction of dichlorothymoquinone with sodium azide in aqueous ethanol. Reduction of **11** with sodium dithionite gave the corresponding hydroquinone, **9**, which rapidly decomposed to give a 2:1 mixture of **6** and **10**, respectively. The isomeric relationship of compounds **6** and **10** was demonstrated chemically by reduction of the quinones to the corresponding hydroquinones, **5** and **12**, followed by their thermal disproportionation to the *same* com-

(5) The oxidation–reduction reaction of **3** appears to be an intramolecular reaction. The kinetics of this reaction in chloroform at 25° follows first-order kinetics ($k = 1.2 \times 10^{-7}$ sec^{-1}) with a half-life of 6.8 days.

(6) This reaction was followed by gas chromatographic analysis of the reaction solution on 8 × 0.25 in. silicon gum rubber columns run isothermally at 195°.

(7) H. W. Moore, *J. Org. Chem.*, **32**, 1996 (1967).

SCHEME III



pound, 3,6-diamino-2-methyl-5-isopropyl-1,4-benzoquinone (13) (Scheme III).[8]

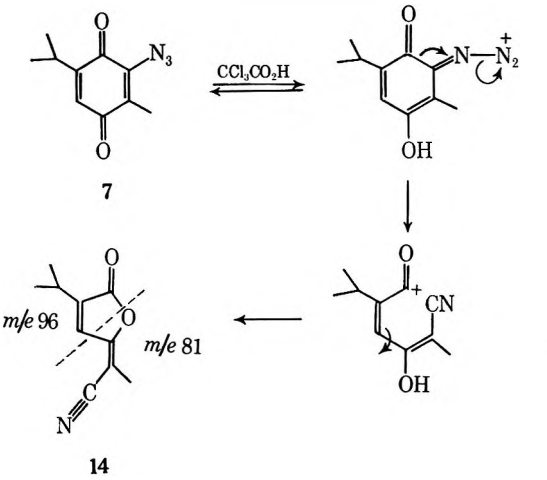
The two isomeric aminoazidothymoquinones, 6 and 10, are not readily distinguishable by their spectral data alone (Table I). They both show characteristic ir absorptions for amino, azido, and quinoid carbonyl groups. The nmr spectra of these two compounds are very similar, except for small differences in chemical shifts. They both show small molecular ion peaks in their mass spectra at 220. However, the remaining fragments correspond almost exactly to those observed for γ-lactones 2 and 15, indicating a rearrangement to these compounds upon electron impact.

To establish the orientation of the amino and azido groups in isomers 6 and 10, a model experiment was performed. 3-Azidothymoquinone (7) was treated with trichloroacetic acid at 65° and found to rearrange in 87% yield to γ-lactone 14. The structure of this γ-lactone was readily assigned on the basis of the spectral data presented in Table I. For example, it shows coupling in the nmr between the vinyl proton and the isopropyl methine proton of 1.7 cps. Also, the mass spectrum of 14 shows characteristic[9] peaks at *m/e* 96 and 81 corresponding to the fragments indicated by the dotted lines in the structure below (Scheme IV).

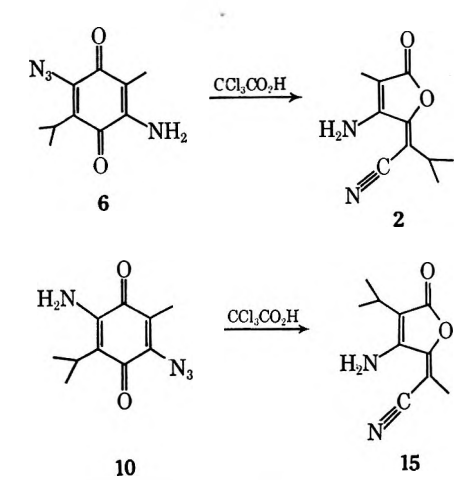
(8) R. Anschutz and J. W. Leather, *Ann.*, **237**, 90 (1887).
(9) S. H. Eggers and R. M. Letcher, *Tetrahedron Lett.*, 3541 (1967).

Therefore, the substituent adjacent to the azide group in the starting azidoquinone occupies a position on the γ-alkylidene double bond in the rearranged product. This is consistent with the mechanism presented below (Scheme IV).[10]

SCHEME IV



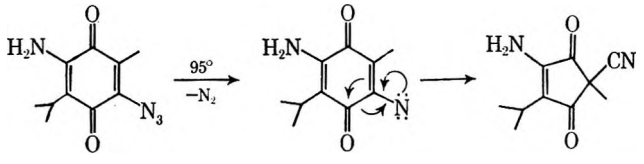
The structures of the two isomeric aminoazidothymoquinones, 6 and 10, could now be readily assigned on the basis of the structures of products 2 and 15, obtained in the acid-catalyzed rearrangement of the corresponding quinone. 3-Amino-6-azido-2-methyl-5-isopropyl-1,4-benzoquinone (6) is suggested as an intermediate in the over-all conversion of thymoquinone into the γ-lactone, 2 (Scheme I), and when 6 was treated with trichloroacetic acid at 65° it was converted into the γ-lactone, 2, in 95% yield. This same type of rearrangement was observed for compound 10. Reaction of 10 under the same conditions gave the γ-lactone, 15, in 94% yield. The structure of 15 is based upon a comparison of its spectral properties with those obtained and reported[1] for the isomeric γ-lactone, 2 (Table I).



These acid-catalyzed rearrangements of azidoquinones (7 → 14, 6 → 2, and 10 → 15) differ in detail

(10) Such a mechanism implies a stereoselective rearrangement; *i.e.* the nitrile group in the product should be *trans* to the lactone oxygen. No direct evidence concerning the stereochemistry of 14 was obtained to substantiate this point. However, the authors find this rearrangement to be very general for azidoquinones, and in simpler examples where the product lends itself to direct stereochemical investigation by nmr spectroscopy, such a *trans* relationship is observed.

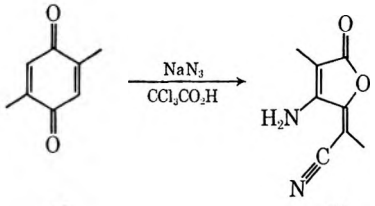
(Scheme III) from the proposed mechanism reported by Rees,[1] who suggested that the rearrangement of thymoquinone to the γ-lactone, **2**, involved the nitrene intermediate, **16**. Although this specific point was not critically investigated, an experiment was performed which indicates that the nitrene is not involved. If a nitrene intermediate was involved in the formation of either of the γ-lactone isomers, **2** or **15**, then one would expect pyrolysis[11] of either of the isomeric aminoazidothymoquinones, **6** or **10**, to give the corresponding γ-lactone. Contrary to this expectation, it was found that thermal decomposition of 3-amino-6-azido-2-methyl-5-isopropyl-1,4-benzoquinone (**10**), at 95° did *not* give the γ-lactone, **15**. Instead, the reaction resulted in the formation of the cyclopentene-1,4-dione, **17**, presumably through the nitrene intermediate, **16**. The γ-lactone, **15**, was found to be stable at 130°, thus ruling out the possibility that it was the initial product in the decomposition of the azide, **10**. Also, **17** did not react with trichloroacetic acid at 65°, eliminating it as an intermediate to **10**.



10 **16** **17**

No direct evidence was obtained which could establish compound **5** (Scheme I) as an intermediate in the over-all conversion of thymoquinone into the γ-lactone, **2**. However, in view of the results presented above the intermediacy of **5** seems very likely The most reasonable pathway for the conversion of the *observed* intermediate 3-aminothymoquinone (**3**) into the *assumed* intermediate, **6**, would be by oxidation of the hydroquinone, **5**. This transformation could be accomplished by several potential oxidizing agents which are present in the reaction media[12]—hydrazoic acid (ϵ^0 = 1.96 V),[13] thymoquinone (ϵ^0 = 0.5875 V),[14] and 3-aminothymoquinone (ϵ^0 < 0.5875 V).[14] In addition to oxidation of **5** by one of the above reagents, an intramolecular oxidation–reduction to give 3,6-diaminothymoquinone (**13**) would be expected. When the reaction of thymoquinone with sodium azide was carried out according to the reported conditions,[1] **13** was detected in small amounts by thin layer chromatography. This compound, **13**, was found to be unreactive to sodium azide in trichloroacetic acid, thus eliminating it as a possible precursor to the γ-lactone ring system.

The results reported here suggest that other 2,5-disubstituted quinones should react with sodium azide in trichloroacetic acid to give products analogous to the lactone, **2**. This was, in fact, found to be true for the only other quinone investigated, 2,5-dimethyl-1,4-benzoquinone (**18**).[15] Treatment of this quinone with a threefold excess of sodium azide in trichloroacetic acid at 65° gave the γ-lactone, **19**, in 32% yield. The assigned structure of **19** is in complete agreement with its spectral data presented in Table I.



18 **19**

The transformations reported in this paper aid in the understanding of several reactions which have appeared concerning the interactions of quinones with hydrazoic acid. These reactions appear to fall into two general classifications: (i) 1,4 addition of hydrazoic acid to the quinone nucleus, and (ii) 1,2 addition of hydrazoic acid to one of the quinone carbonyl groups. The former gives azidohydroquinones which can disproportionate to aminoquinones[4] or the hydroquinone can be oxidized to azidoquinones which can undergo an acid-catalyzed ring contraction to γ-lactones.[1,16] The latter, 1,2 addition, results in typical Schmidt reaction products giving ring expansion to azipenediones.[17–20] These two pathways (1,4 addition *vs.* 1,2 addition) depend to a great extent on the solvent and acid used. This difference can be graphically illustrated with thymoquinone (**1**) and 2,5-dimethyl-1,4-benzoquinone (**18**). In trichloroacetic acid at 65° these quinones react with sodium azide to give the γ-lactones, **2** and **19**, respectively. However, when the reactions are carried out in concentrated sulfuric acid at 0–5°, ring expansion takes place, thymoquinone giving 2,5-1H-4-isopropyl-7-methylazepinedione and 2,5-dimethyl-1,4-benzoquinone giving 2,5-1H-4,7-dimethylbenzoazepinedione.[17]

Experimental Section[21]

Reaction of Thymoquinone with Sodium Azide in Trichloroacetic Acid.—Thymoquinone (5 g, 0.032 mol) was dissolved in 100 ml of trichloroacetic acid at 65°. To this solution was added 6.5 g (0.1 mol) of sodium azide in one portion. The resulting mixture gradually became red, and nitrogen evolution was observed. This reaction mixture was kept between 60 and 70° for 4 hr while a stream of nitrogen was passed through the solution. The reaction was monitored periodically by gas chromatography, and it was observed that 3-aminothymoquinone (**4**) formed during the early stages of the reaction and subsequently disappeared as the γ-lactone **2** formed. After 4 hr the red solution was poured into 300 ml of ice–water, resulting in the precipitation of the γ-lactone **2**. Filtration and recrystallization of the product from ethanol gave 3.5 g (57% yield) of

(11) It is generally accepted that the primary step in the thermal decomposition of organic azides is loss of molecular nitrogen to give nitrenes. See, for example, P. A. S. Smith, "Open-Chain Nitrogen Compounds" Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, p 215.

(12) Atmospheric oxygen is not involved in this reaction since it was found that the conversion of **1** into **2** also takes place when the reaction is run under an atmosphere of nitrogen.

(13) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1961, p 102. The potential reported here is that obtained for the reduction of hydrazoic acid to ammonium ion and nitrogen in acidic media.

(14) W. M. Clark, "Oxidation–Reduction Potentials of Organic Systems," Williams and Wilkins Co., Baltimore, Md., 1960.

(15) It was previously reported[1] that the quinone **18** did not give ring contraction to the γ-lactone ring system upon reaction with sodium azide in trichloroacetic acid.

(16) H. W. Moore and H. R. Shelden, *J. Org. Chem.*, **32**, 3603 (1967).

(17) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Lett.*, 1071 (1965).

(18) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron*, **22**, 1201 (1965).

(19) R. W. Richards and R. M. Smith, *Tetrahedron Lett.*, 2361 (1966).

(20) G. R. Bedford, G. Jones, and B. R. Webster, *ibid.*, 2367 (1966).

(21) Melting points are uncorrected. Nmr spectra were obtained using a Varian Associates A-56/60A spectrometer. Ir spectra were obtained using a Perkin-Elmer Model 137 spectrometer. Mass spectra were obtained from West Coast Technical Service, San Gabriel, Calif., using a Hitachi-Perkin-Elmer RMU-6D mass spectrometer.

the lactone 2, mp 175–177°.[1] See Table I and ref 1 and 2 for the spectral properties of this compound.

The mother liquor from the above reaction was extracted three times with chloroform. The organic extracts were then combined, and the solvent was removed *in vacuo*. The residue was examined by thin layer chromatography on silica gel G plates in chloroform solvent. This method indicated the presence of unreacted thymoquinone, 3-aminothymoquinone (**4**), and a small amount of 3,6-diaminothymoquinone (**13**). In addition to these three compounds several unidentified spots were detected.

3-Aminothymoquinone (**4**) was isolated from the reaction of thymoquinone with sodium azide in trichloroacetic acid which was carried out in a manner analogous to the above procedure, except the reaction time was 2 hr instead of 4 hr. The quinone was isolated by preparative thin layer chromatography on silica gel G plates using chloroform as the solvent. The spectral properties of **4** are recorded in Table I. The mass spectrum exhibited a molecular ion at *m/e* 179 in accord with the molecular fomulation $C_{10}H_{13}NO_2$. The coupling of 1.3 cps between the vinyl proton and the isopropyl methine proton in the nmr spectrum shows the amino group in **4** to be at the 3 position.

Reaction of 2,5-Dimethyl-1,4-benzoquinone (18) with Sodium Azide in Trichloroacetic Acid.—A 5-g sample (0.037 mol) of 2,5-dimethyl-1,4-benzoquinone was treated with a threefold excess of sodium azide in trichloroacetic acid at 65° in a manner analogous to the above procedure with thymoquinone. However, the product (**19**) did not precipitate when the reaction solution was poured into water. Instead, the aqueous mixture was extracted several times with chloroform, and the combined organic extracts were concentrated *in vacuo*. The residue was recrystallized from 95% ethanol to give 1.9 g (32% yield) of the γ-lactone **19**, mp 207–208°. The spectral data (Table I) are in agreement with structure **19**. The ir spectrum shows the presence of a nitrile group (2215 cm^{-1}), a primary amino group (3500 and 3380 cm^{-1}), and a γ-lactone carbonyl (1775 cm^{-1}). The nmr spectrum shows characteristic absorptions for the two amino and six methyl protons. The mass spectrum exhibits a molecular ion at *m/e* 164 in accord with the molecular formulation $C_8H_8N_2O_2$.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.87. Found: C, 58.42; H, 4.81.

2-Methyl-3-azido-5-isopropyl-1,4-benzoquinone (7).—A 5-g sample (0.025 mol) of 2-methyl-3-chloro-5-isopropyl-1,4-benzoquinone[3] was dissolved in 50 ml of 95% ethanol in a 250-ml erlenmeyer flask. A solution of 1.9 g (0.03 mol) of sodium azide in 10 ml of water was then added to the above yellow solution. Upon addition of the azide the solution became deep red. The reaction solution was allowed to stand at room temperature for 30 min and then poured into 200 ml of water. The precipitate which formed was recrystallized from warm 80% ethanol to give 4.7 g (92% yield) of 3-azidothymoquinone (**7**), mp 65–67°. The spectral properties for **7** are recorded in Table I. The ir spectrum shows absorptions for azide (2125 cm^{-1}) and quinone carbonyl groups (1665 and 1610 cm^{-1}). The nmr spectrum shows characteristic peaks for the isopropyl and methyl protons, and the position of the azide group is fixed by the presence of the doublet (J = 1.2 cps) for the C-6 vinyl proton. The mass spectrum exhibits a molecular ion at *m/e* 205 in accord with the molecular formulation $C_{10}H_{11}N_3O_2$.

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.36. Found: C, 58.57; H, 5.19.

2-Methyl-3-azido-5-isopropyl-1,4-benzohydroquinone (3).—A 1-g sample (0.005 mol) of 2-methyl-3-azido-5-isopropyl-1,4-benzoquinone was dissolved in 50 ml of 95% ethanol in a 250-ml erlenmeyer flask. A rapid stream of nitrogen was bubbled through the above solution while a solution of 40% aqueous sodium dithionite was added dropwise. The dithionite solution was added until the reaction solution changed from orange to colorless. The reaction solution was then poured into water, and the resulting mixture was extracted three times with chloroform. The combined organic extract was dried over anhydrous magnesium sulfate, and then the solvent was removed *in vacuo* at room temperature. It is necessary *not* to allow the temperature to rise much above 25°, since at higher temperatures the rate of disproportionation of the azidohydroquinone to the aminoquinone rapidly increases. Removal of the solvent gave 0.93 g (92% yield) of the white crystalline 2-methyl-3-azido-5-isopropyl-1,4-benzohydroquinone (**3**), mp 91–93° dec. The spectral properties of **3** are reported in Table I. The ir spectrum showed characteristic absorptions for azide (2105 cm^{-1}) and phenolic hydroxyl groups (3430 and 3320 cm^{-1}). The nmr spectrum showed absorptions for the methyl and isopropyl protons and for the single aromatic proton. The mass spectrum exhibited a molecular ion at *m/e* 207 in accord with the formulation $C_{10}H_{13}N_3O_2$.

2-Methyl-3-amino-5-isopropyl-1,4-benzoquinone (4).—A solution of 235 mg (1.14 mmol) of 2-methyl-3-azido-5-isopropyl-1,4-benzohydroquinone in 30 ml of Spectrograde chloroform was refluxed under argon for 2 hr. During this time nitrogen evolution was observed, and the initial colorless solution became deep red. The solvent was then removed *in vacuo* to give 220 mg of 3-aminothymoquinone (**4**). This compound failed to crystallize; however, all of the spectral data (Table I) showed it to be a pure compound.

2-Methyl-3-hydroxy-5-isopropyl-1,4-benzoquinone (8).—A solution of 50 mg of the aminoquinone **4** in 10 ml of glacial acetic acid was treated with 20 mg of $CuCl_2$.[22] The resulting mixture was heated on the steam bath for 20 min and then poured into water. The aqueous solution was extracted with ether. The ether was removed *in vacuo*, and the residue was recrystallized from ethanol to give 30 mg of the known 3-hydroxythymoquinone (**8**), mp 167–168° (lit.[6] mp 167°).

3,6-Diazido-2-methyl-5-isopropyl-1,4-benzoquinone (11).—To a solution of 10 g (0.043 mol) of 3,6-dichlorothymoquinone[7] in 100 ml of 95% ethanol was added a solution of 6.4 g (0.10 mol) of sodium azide in 20 ml of water. The reaction solution immediately became deep red and was allowed to stand at room temperature for 30 min. It was then poured into 300 ml of water, and the resulting solution was extracted three times with chloroform. The combined organic extract was dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo* leaving 9.2 g (87% yield) of a viscous orange oil, 3,6-diazidothymoquinone (**11**). All attempts to crystallize this compound failed. However, the spectral data (Table I) for **11** show it to be pure. The ir spectrum shows azide (2100 cm^{-1}) and quinone carbonyl groups (1675 and 1590 cm^{-1}). The nmr spectrum shows absorptions for only the methyl and isopropyl groups. The mass spectrum exhibits a molecular ion at *m/e* 246 in accord with the formulation $C_{10}H_{10}N_6O_2$.

3,6-Diazido-2-methyl-5-isopropyl-1,4-benzohydroquinone (9).—A 1-g sample (0.0041 mol) of 3,6-diazido-2-methyl-5-isopropyl-1,4-benzoquinone (**11**) was dissolved in 50 ml of 95% ethanol in a 250-ml erlenmeyer flask. A rapid stream of nitrogen was bubbled through the above solution while a solution of 40% aqueous sodium dithionite was added dropwise. The dithionite solution was added until the reaction solution changed from orange to colorless. The reaction solution was then poured into water, and the resulting mixture was extracted with chloroform. The combined organic extract was dried over anhydrous magnesium sulfate, and then the solvent was removed *in vacuo* at room temperature to leave a light brown solid. This solid was taken up in the minimum amount of carbon tetrachloride at 25° and then kept at 0° for 2 days. During this time crystallization took place to give a white crystalline precipitate of 0.75 g (75% yield) of 3,6-diazido-2-methyl-5-isopropyl-1,4-benzohydroquinone (**9**), mp 70–71° dec. The spectral data for **9** are reported in Table I. The ir spectrum show phenolic hydroxyl (3550 and 3440 cm^{-1}) and azide absorption (2120 cm^{-1}). The nmr spectrum shows only the absorptions for the methyl and isopropyl protons. The mass spectrum exhibits a molecular ion at *m/e* 248 in accord with the formulation $C_{10}H_{12}N_6O_2$.

3-Amino-6-azido- and 3-Azido-6-amino-2-methyl-5-isopropyl-1,4-benzoquinone (6 and 10).—A chloroform solution of 8 g (0.032 mol) of 3,6-diazido-2-methyl-5-isopropyl-1,4-benzohydroquinone (**9**) was prepared by the dithionite reduction of the corresponding quinone (see above procedure). The hydroquinone **9** was not isolated but used immediately after its preparation. This solution was refluxed under an argon atmosphere for 4 hr. During this time the solution became deep purple, and nitrogen evolution was observed. After 4 hr nitrogen evolution ceased, and the solvent was removed *in vacuo*. Thin layer chromatographic analysis of the resulting oily residue showed primarily two purple spots. Analysis of the residue by nmr showed it to be primarily a mixture of the two isomers **6** and **10** in a ratio of 2:1, respectively. This mixture was separated by column

(22) These reaction conditions had previously been reported as a method of conversion of aminoquinones into hydroxyquinones: H. W. Moore and K. Folkers, *J. Amer. Chem. Soc.*, **88**, 567 (1966).

chromatography on 600 g of silicic acid using chloroform as the eluting solvent. The isomer **10** was eluted first followed closely by **6**. The central portions of these two bands were collected, and the solvent was removed *in vacuo* giving 1.2 g of **6**, mp 97–98° dec, and 0.8 g of **10**, mp 86–87° dec. The spectral data (Table I) for these two isomers are consistent with their structures. For compound **6** the ir spectrum showed characteristic absorptions for azide (2120 cm^{-1}), primary amino (3500 and 3410 cm^{-1}), and quinone carbonyl (1650 and 1610 cm^{-1}) groups. The nmr spectrum of **6** showed absorptions for the methyl, isopropylmethyl, and amino protons at 1.85, 1.19, and 5.00 ppm, respectively. The ir spectrum of **10** showed absorptions for azide (2120 cm^{-1}), primary amino (3460 and 3320 cm^{-1}), and quinone carbonyl (1665 and 1600 cm^{-1}) groups. Its nmr spectrum varied only slightly from that of **6**, showing absorptions at 1.86, 1.21, and 5.23 ppm, respectively, for the methyl, isopropylmethyl, and amino protons. The mass spectra of both isomers exhibited a molecular ion at *m/e* 220 in accord with their formulation $C_{10}H_{12}N_4O_2$.

Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.45. Found: C, 54.73, 54.49; H, 5.42, 5.53.

3,6-Diamino-2-methyl-5-isopropyl-1,4-benzoquinone (13).—The diaminothymoquinone **13** was prepared from each of the isomers **6** and **10** by the following method. A solution of 0.2 g (0.009 mol) of the corresponding azidoaminothymoquinone were reduced to the respective hydroquinone with sodium dithionite according to the procedures outlined above. The hydroquinones were extracted into chloroform, and the dried solutions were refluxed under argon for 3 hr. During this time the solutions became purple, and nitrogen was evolved. The solvent was then removed *in vacuo* to give the purple crystalline 3,6-diaminothymoquinone (**13**). Recrystallization from methanol gave the pure product, mp 214–216°. 3-Amino-6-azido-2-methyl-5-isopropyl-1,4-benzoquinone (**6**) gave 134 mg of **13** and the corresponding 3-azido-6-amino isomer **10** gave 125 mg of **13**.

The spectral data (Table I) for the diaminoquinone **13** is in agreement with its proposed structure. The ir spectrum shows absorptions for the primary amino (3400 and 3320 cm^{-1}) and quinone carbonyl (1525 cm^{-1}) groups. The nmr spectrum shows absorptions for the four amino protons and for the methyl and isopropyl protons. The mass spectrum of **13** exhibits a molecular ion at *m/e* 194 in accord with the formulation $C_{10}H_{14}N_2O_2$.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.21. Found: C, 61.59; H, 7.32.

Reaction of 3-Azidothymoquinone (7) with Trichloroacetic Acid.—A 1-g sample (0.0049 mol) of 3-azidothymoquinone (**7**) was dissolved in 20 ml of trichloroacetic acid at 65°. There was an immediate evolution of nitrogen, and the solution gradually became light orange. After 15 min the reaction solution was poured into 50 ml of water, and the resulting precipitate was collected and recrystallized from 95% ethanol to give 0.82 g (87% yield) of the γ-lactone **14**, mp 38–40°. Table I lists the spectral data for compound **14**. The ir spectrum of **14** shows nitrile (2110 cm^{-1}) and γ-lactone carbonyl (1780 cm^{-1}) absorptions. Vinyl, methyl, and isopropyl protons are shown by the nmr spectrum. The mass spectrum of **14** shows a molecular ion at *m/e* 177 in accord with the formulation $C_{10}H_{11}NO_2$.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21. Found: C, 67.82; H, 6.30.

Reaction of 3-Amino-6-azido-2-methyl-5-isopropyl-1,4-benzoquinone (6) with Trichloroacetic Acid.—A 0.5-g sample (0.0023 mol) of 3-amino-6-azido-2-methyl-5-isopropyl-1,4-benzoquinone (**6**) was dissolved in 20 ml of trichloroacetic acid at 65°. An immediate evolution of nitrogen was observed, and the reaction solution became light yellow. After 15 min the reaction solution was poured into 50 ml of water, and the resulting precipitate was collected giving 0.42 g (95% yield) of the γ-lactone **2**, mp 175–177° (lit.[1,2] mp 177°). This compound was identical with the product obtained from the reaction of thymoquinone with sodium azide in trichloroacetic acid.[1,2] See Table I for the spectral properties of **2**.

Reaction of 3-Azido-6-amino-2-methyl-5-isopropyl-1,4-benzoquinone (10) with Trichloroacetic Acid.—A 0.5-g sample (0.0023 mol) of 3-azido-6-amino-2-methyl-5-isopropyl-1,4-benzoquinzone (**10**) was dissolved in 20 ml of trichloroacetic acid at 65°. An immediate evolution of nitrogen was observed, and the reaction solution became light yellow. After 15 min the reaction solution was poured into 50 ml of water, and the resulting precipitate was collected to give 0.41 g (94% yield) of the γ-lactone **15**, mp 139–140°. The spectral data for this compound (Table I) are consistent for the proposed structure **15**. The ir spectrum shows nitrile (2210 cm^{-1}), primary amino (3500 and 3340 cm^{-1}), and γ-lactone carbonyl (1750 cm^{-1}) absorptions. The nmr spectrum shows absorptions for the amino, methyl, and isopropyl groups. The mass spectrum of **15** exhibits a molecular ion at *m/e* 192 in accord with the formulation $C_{10}H_{12}N_2O_2$.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25. Found: C, 62.72; H, 6.34.

Pyrolysis of 3-Azido-6-amino-2-methyl-5-isopropyl-1,4-benzoquinone (10).—A 50-mg sample (0.23 mmol) of 3-azido-6-amino-2-methyl-5-isopropyl-1,4-benzoquinone (**10**) was placed in a test tube and heated slowly to 95° under an atmosphere of nitrogen. This decomposition should be performed with caution since in one experiment the azide violently decomposed. Nitrogen evolution began as the azide melted, and the melt slowly changed from red to colorless. After the color change was complete, the new compound solidified. Recrystallization of this new solid from ethanol gave 39 mg (89% yield) of the cyclopentene-1,4-dione (**17**), mp 158–159°. The spectral data reported in Table I for **17** are consistent with its proposed structure. Nitrile (2275 cm^{-1}), amino (3420 and 3310 cm^{-1}), and cyclopentenedione carbonyl (1750 and 1700 cm^{-1}) absorptions are evidenced by its ir spectrum. The nmr spectrum of **17** show the two amino protons and the methyl and isopropyl protons. The mass spectrum of **17** exhibits a molecular ion at *m/e* 192 in accord with the formulation $C_{10}H_{12}N_2O_2$.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25. Found: C, 62.43; H, 6.17.

Registry No.—Sodium azide, 12136-89-9; trichloroacetic acid, 76-03-9; **1**, 490-91-5; **2**, 2689-09-0; **3**, 17414-17-4; **4**, 17414-18-5; **6**, 17414-19-6; **7**, 17414-20-9; **9**, 17448-04-3; **10**, 17414-21-0; **11**, 17448-05-4; **13**, 17414-22-1; **14**, 17414-26-5; **15**, 17414-23-2; **17**, 17414-24-3; **18**, 137-18-8; **19**, 17414-25-4.

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The Chemistry of Some Sterically Hindered Mono- and Diketones

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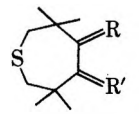
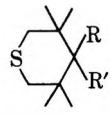
Received March 8, 1968

The reaction of 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione (I), under the conditions of the benzilic acid rearrangement, and the reaction of 5-diazo-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (VII), under the conditions of the Wolff rearrangement, were studied. The results are compared with those of dipivaloyl and its α-diazo derivative in these reactions to show the influence of the cyclic nature of I and VII. The reactivity of diketone I in addition reactions was investigated to study the shielding effect of the two *gem*-dimethyl functions. The same effect was also investigated in the 3,3,5,5-tetramethyl-1-thiacyclohexane system (III–V). The reaction of 4-carboxy-4-hydroxy-3,3,5,5-tetramethyl-1-thiacyclohexane (III) with thionyl chloride to yield 3,3,5,5-tetramethyl-1-thiacyclohexanone (V) appeared interesting.

In connection with studies in this laboratory on highly sterically hindered aromatic[1] and aliphatic compounds[2] we explored the chemistry of the cyclic compounds (I–V).



I, R = R′ = O
II, R = O; R′ = N–NH$_2$



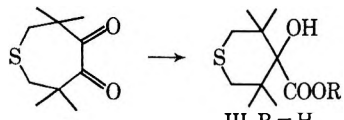
III, R = OH; R′ = COOH
IV, R = OH; R′ = COOCH$_3$
V, R = R′ = O

The factors governing the chemistry of the substituted thiacycloheptane (I and II) and thiacyclohexane derivatives (III–V) are connected with (i) the cyclic nature of these molecules,[1] (ii) the shielding effect due to the two *gem*-dimethyl functions,[3] (iii) the presence of the sulfur atom in the ring,[4] and (iv) the size of the ring.

In this paper several interesting aspects of the rearrangement and addition reactions of diketone I are discussed. A comparison with the chemical behavior of the acyclic analog dipivaloyl draws attention to the influence of the cyclic nature of diketone I,[1] especially in rearrangement reactions. Steric effects due to the *gem*-dimethyl functions appear to play an important part in the addition reactions of I and in the chemistry of the thiacyclohexane derivatives III–V. The influence of the sulfur atom in the ring is currently being investigated.[4]

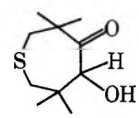
Benzilic Acid Rearrangement.—Dipivaloyl does not give a benzilic acid rearrangement;[5] diketone I gave the hydroxy acid III in 82% yield when it was refluxed with potassium hydroxide in a mixture of *t*-butyl alcohol and water. When a mixture of 1-propanol and water was used as solvent, the yield of III was 52%, and as a by-product the hydroxy ketone VI was isolated in 22% yield. When diketone I was refluxed with sodium methoxide in methanol the hydroxy ester IV was isolated in 82% yield.[6]

Wolff Rearrangement.—A second difference in behavior between dipivaloyl and diketone I is the decomposition of the corresponding α-diazo ketones VII and XII. Oxidation of the ketohydrazone II with manganese dioxide probably gave the α-diazo ketone VII which spontaneously decomposed at room temperature. This α-diazo ketone VII is not stabilized by resonance; the conformation of the seven-membered ring in VII is such that the diazo function and the carbonyl function are orthogonal to one another (skew). This can be seen from the conformation of diketone I and 4,5-dimethylene-3,3,6,6-tetramethyl-1-thiacycloheptane (XVI). Ultraviolet spectra indicate that there is no double-bond resonance in compounds I and XVI.[2] During the decomposition, a Wolff rearrangement takes place and ketene VIII (stable as monomer) and the acid IX are formed in a combined yield of 49%. A third product, isolated in 30% yield, had uv absorption at 246 mμ (ε 4400) and a medium-intensity ir absorption at 1645 cm^{-1}. No decision can be made between structure X or XI for this α,β-unsaturated ketone on the basis of these spectra.[7]

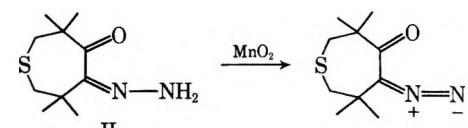


I

III, R = H
IV, R = CH$_3$

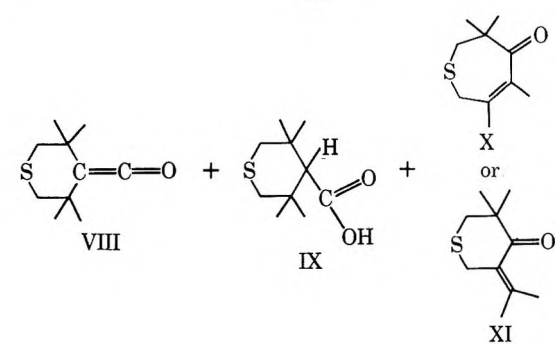


VI



II

VII



VIII

IX

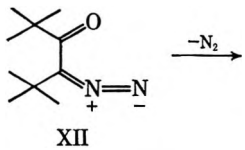
X

or

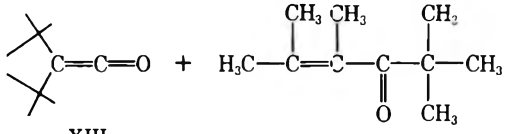
XI

(1) Ae. de Groot and H. Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).
(2) Ae. de Groot, B. Evenhuis, and H. Wynberg, *ibid.*, **33**, 2214 (1968).
(3) Ae. de Groot, J. A. Boerma, and H. Wynberg, *Chem. Commun.*, 347 (1968).
(4) Ae. de Groot, J. A. Boerma, and H. Wynberg, *Tetrahedron Lett.*, 2365 (1968).
(5) F. G. Roberts and P. C. Teague, *J. Amer. Chem. Soc.*, **77**, 6258 (1955).
(6) W. von E. Doering and R. S. Urban, *ibid.*, **78**, 5938 (1956).
(7) Care need be exercised to apply Woodward's rules in this case. Not only a seven-membered ring is involved, and few if any correlations are known for α,β-unsaturated seven-membered ketones, but in addition steric factors can cause appreciable lowering of the ultraviolet maximum in the six-membered α,β-unsaturated ketone XI as well as in the seven-membered ketone X.

Newman[8] isolated in very low yield (0–3%) di-*t*-butyl ketene XIII as the decomposition product of the much more stable diazo ketone XII. The α,β-unsaturated ketone XIV was formed in 80–92% yield in this case. The much higher yield of ketene VIII



XII

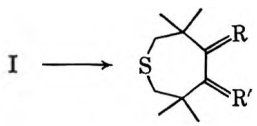


XIII XIV

and acid IX in our case supports the suggestion of Kaplan, *et al.*,[9] that a *cis* position is necessary for the Wolff rearrangement. Our cyclic diazo ketone VII meets this condition better than Newman's diazo ketone XII; the large *t*-butyl groups prevent the *cis* position in XII.[10]

The stable ketene VIII was hydrolyzed to the corresponding acid IX by water and a trace of mineral acid. Reduction of VIII with lithium aluminum hydride gave 4-formyl-3,3,5,5-tetramethyl-1-thiacyclohexane (XV).

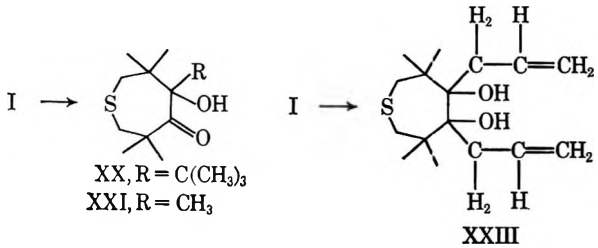
Addition Reactions.—Both diketone I and dipivaloyl react similarly to form mainly monoaddition–elimination products.[1,8,11] Several types of Wittig reactions gave monoaddition products except in the formation of diene XVI.[2] Reactions of compounds XVIII[12]



XVI, R = R′ = CH_2
XVII, R = O; R′ = CH_2
XVIII, R = O; R′ = $CHOCH_3$
XIX, R = O; R′ = $CHCOOC_2H_5$

and XIX with the corresponding ylides did not give diaddition products; methylene ketone XVII could be converted into diene XVI.

Reaction of diketone I with *t*-butyllithium or with methylmagnesium iodide gave the monoaddition products XX and XXI, respectively; only XXI could be reduced with lithium aluminum hydride to the corresponding diol XXII. Addition of allyllithium to diketone I gave the diaddition product XXIII in 81% yield.



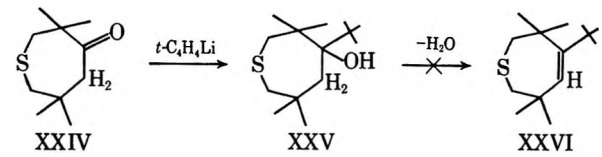
XX, R = $C(CH_3)_3$
XXI, R = CH_3

XXIII

Dipivaloyl also gives monoaddition products with organometallic reagents,[13,14] except when treated under forcing conditions.[13] These results indicate that, in general, addition of two molecules of a reagent to diketone I or dipivaloyl does not take place, except when small and reactive reagents are used (see compounds XVI and XXIII).

The steric hindrance due to the *gem*-dimethyl groups is the main reason for this behavior, but some minor points need consideration. For instance, small variations in the size of the ring cause subtle changes in the reactivity of the functional groups. Thus no enediol sulfite was isolated in the reaction of 2-hydroxy-3,3,5,5-tetramethylcyclohexanone with thionyl chloride.[15] In the reaction of the seven-membered hydroxy ketone VI with thionyl chloride, a stable enediol sulfite was isolated.[3] Under normal reaction conditions, 2,2,5,5-tetramethylcyclohexanone gives a hydrazone,[15,16] but from monoketone XXVII no hydrazone was obtained. Inductive effects (one carbonyl group upon the other) probably play a role, for no hydrazone was obtained in the reaction of monoketone XXIV, hydroxy ketone VI, or methylene ketone XXVII with hydrazine, although the steric hindrance in these compounds is comparable with the hindrance in diketone I.

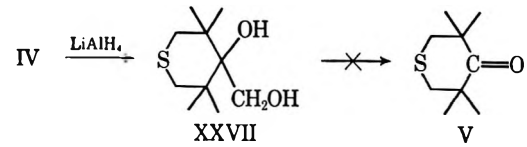
Monoketone XXIV does react with the more reactive *t*-butyllithium to give the adduct XXV in 82% yield.



XXIV XXV XXVI

Attempts to convert the alcohol XXV into alkene XXVI *via* a modified Chugaev reaction[2] were unsuccessful.

Reactions of the Thiacyclohexane Derivatives.—The steric effect of the two *gem*-dimethyl functions is evident in the chemistry of the thiacyclohexane derivatives III–V. The hydroxy ester IV could not be converted into its hydrazide. Reduction of ester IV gave the diol XXVII in 85% yield, but fission of this diol was not possible.



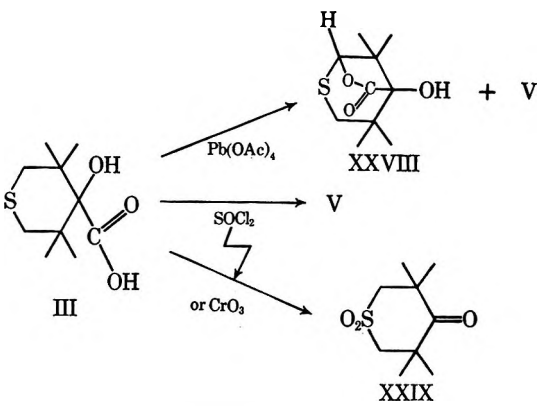
XXVII V

Oxidation of hydroxy acid III with CrO_3 or with lead tetraacetate gave small yields of the ketones XXIX and V, respectively. The bicyclic lactone XXVIII was isolated in 27% yield in the reaction of III with lead tetraacetate.[17] Electrolysis of acid III gave ketone XXIX in 30% yield.

Interestingly, the hydroxy acid III gave the ketone V directly in 76% yield upon treatment with thionyl chloride. Other less hindered hydroxy acids yield

(8) M. S. Newman and A. Arkell, *J. Org. Chem.*, **24**, 385 (1959).
(9) F. Kaplan and G. K. Meloy, *J. Amer. Chem. Soc.*, **88**, 950 (1966).
(10) N. J. Leonard and P. M. Mader, *ibid.*, **72**, 5388 (1950).
(11) L. Bouveault and R. Loquin, *Bull. Soc. Chim. Fr.*, (3) **35**, 655 (1906).
(12) Ae. de Groot and H. Wynberg, *J. Org. Chem.*, **33**, 3337 (1968).
(13) M. S. Newman and G. R. Kahle, *ibid.*, **23**, 666 (1958).
(14) H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **57**, 967 (1938).
(15) D. E. Gwynn, Ph.D. Thesis, University of Illinois, 1962.
(16) H. A. Bruson, F. W. Grant, and E. Bobko, *J. Amer. Chem. Soc.*, **80**, 3633 (1958).
(17) Analogous reactions of sulfide acids with lead tetraacetate are not known in the literature as far as we know.

stable mixed anhydrides under these conditions.[18,19] These anhydrides decompose to form polyesters instead of ketones.[18] It is evident that steric crowding around the reaction center has once again altered the reaction path.



The cyclic ketones V and XXIX could not be converted into their oximes under normal reaction conditions. Here too the influence of the size of the ring is noticeable. 2,2,5,5-Tetramethylcyclopentanone does not give a 2,4-dinitrophenylhydrazone,[20] but 2,2,4,4-tetramethylcyclobutanone gives an oxime, a semicarbazone, and a 2,4-dinitrophenylhydrazone.[21]

Experimental Section

Infrared spectra were determined in carbon tetrachloride, in potassium bromide discs or neat on a Perkin-Elmer Infracord Model 137 or on a Unicam SP 200. Ultraviolet spectra were recorded on a Zeiss spectrophotometer, Model PMQ II; the solvents are indicated. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as the internal standard and are reported in τ values (parts per million). The solvents used are indicated. Melting points and boiling points are uncorrected. Microanalyses were performed by the analytical department of this laboratory under the supervision of Mr. W. M. Hazenberg.

4-Carboxy-4-hydroxy-3,3,5,5-tetramethyl-1-thiacyclohexane (III).—A solution of 5.0 g (0.025 mol) of diketone I and 30 g of KOH in a mixture of 25 ml of water and 250 ml of 1-propanol was refluxed and stirred for 20 hr. The reaction mixture was concentrated, and water and ether were added. The water solution was extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and concentrated, giving 1.1 g (22%) of the hydroxy ketone VI. The water layer was acidified with concentrated hydrochloric acid, and the hydroxy acid was filtered and washed with water. Recrystallization from CCl_4 gave 2.7 g (52%) of the hydroxy acid III: mp 174–175°; ir (Nujol) 3600 (OH) and 1690 cm^{-1} (C=C); nmr ($DCCl_3$) τ 6.75, 6.97, 7.60, and 7.83 (d, methylene protons) and 8.72 and 9.92 (s, methyl protons).

Anal. Calcd for $C_{10}H_{18}O_3S$ (218.31): C, 55.01; H, 8.31; S, 14.69. Found: C, 55.4, 55.1; H, 8.3, 8.3; S, 14.2, 14.2.

When a mixture of 25 ml of water and 250 ml of *t*-butyl alcohol was used as a solvent a yield of 82% of the hydroxy acid VI was obtained. No hydroxy ketone was isolated.

4-Carbomethoxy-4-hydroxy-3,3,5,5-tetramethyl-1-thiacyclohexane (IV).—A solution of 10.0 g (0.05 mol) of diketone I and 6.7 g of Na in 200 ml of absolute methanol was refluxed for 20 hr. The reaction mixture was concentrated, and water was added. The water solution was extracted with ether. The ethereal extract was washed with water, dried ($CaCl_2$), and concentrated. The residue was recrystallized from ethanol giving 9.5 g (82%) of the hydroxy ester IV: mp 67–68°; ir (Nujol) 3500 (OH) and 1720 cm^{-1} (C=O); nmr ($DCCl_3$) τ 9.05 and 8.78 (s, methyl protons), 7.89, 7.65 and 7.10, 6.87 (d, methylene protons), 6.30 (s, OH proton), and 6.17 (s, ester methyl protons).

Anal. Calcd for $C_{11}H_{20}O_3S$ (232.34): C, 56.86; H, 8.68; S, 13.80. Found: C, 56.7, 56.8; H, 8.6, 8.6; S, 13.4, 13.5.

Rearrangement of 4-Diazo-3,3,6,6-tetramethyl-1-thiacycloheptan-5-one (VII).—A solution of 4.3 g (0.02 mol) of monohydrazone II in 50 ml of benzene was added to a stirred suspension of 6.0 g of active MnO_2 and 10 g of anhydrous $MgSO_4$ in 50 ml of dry benzene over a period of 30 min. The solution became yellow, and gas evolution started at once. After 48 hr at room temperature no gas evolution was observed, and the reaction mixture was filtered and concentrated. A small portion (500 mg) of the residue was refluxed with dilute hydrochloric acid for 30 min. After cooling to room temperature dilute NaOH solution was added, and the water solution was extracted with ether. The water solution was acidified, and filtration gave 195 mg of the carboxylic acid IX, mp 149–152°. From this amount of acid IX it was concluded that the Wolff rearrangement of diazo ketone VII occurred in 48% yield. Recrystallization of acid IX from absolute ethanol gave an analytical sample: mp 152–153.5°; ir (Nujol) 1700 cm^{-1} (C=O); nmr ($DCCl_3$) τ 7.35, 7.57 7.63, and 7.87 (d, methylene protons), 7.79 (s, α proton), and 8.75 and 8.88 (s, methyl protons).

Anal. Calcd for $C_{10}H_{18}O_2S$ (202.31): C, 59.36; H, 8.97; S, 15.86. Found: C, 59.4, 59.3; H, 9.0, 9.0; S, 15.8, 15.6.

The rest of the residue was chromatographed over silica gel. After elution with dry benzene, 0.55 g (16.5%) of ketene VIII was obtained. Distillation, bp 103–104° (12 mm), gave an analytical sample of X: ir (neat) 2200 cm^{-1} (ketene absorption); nmr (CCl_4) τ 7.65 (s, methylene protons) and 8.73 (s, methyl protons).

Anal. Calcd for $C_{10}H_{16}OS$ (184.29): C, 65.17; H, 8.75; S, 17.40. Found: C, 65.0, 65.0; H, 8.8, 8.9; S, 17.2, 17.4.

After elution with H_2CCl_2, 0.82 g (25%) of ketone X or XI was obtained. Distillation, bp 118–119° (13 mm), gave an analytical sample: uv max (95% EtOH) 246 mμ (ϵ 4400) and 308 (280); ir (neat) 1645 (C=C), 1690 cm^{-1} (C=O); nmr (CCl_4) τ 6.58 and 7.32 (s, methylene protons), 8.22 and 8.30 (s, methyl protons), and 8.83 (s, methyl protons).

Anal. Calcd for $C_{10}H_{16}OS$ (184.29): C, 65.17; H, 8.75; S, 17.40. Found: C, 65.1, 65.3; H, 8.9, 8.8; S, 17.6, 17.5.

After elution with methanol, 0.95 g (26%) of the carboxylic acid IX was isolated.

4-Formyl-3,3,5,5-tetramethyl-1-thiacyclohexane (XV).—A solution of 0.45 g (12 mmol) of ketene VIII in 10 ml of dry ether was added to a stirred suspension of 0.10 g of $LiAlH_4$ in 30 ml of ether. The reaction mixture was refluxed for 1.5 hr, and, after cooling, the excess of the $LiAlH_4$ was destroyed by addition of 2 ml of ethyl acetate. Dilute hydrochloric acid was added and the water solution was extracted with ether. The ethereal extract was washed with Na_2CO_3 solution, dried (Na_2SO_4), and concentrated. Distillation of the residue gave 0.30 g (67%) of the aldehyde XV, bp 120° (13 mm). An analytical sample of XV, mp 71.5–73°, was obtained after three crystallizations from pentane at low temperature: ir (Nujol) 1710 cm^{-1} (C=O); nmr (CCl_4) τ 0.03, 0.10 (d, aldehyde proton), 8.30, 8.38 (d, α proton), 7.43, 7.65 and 7.75, 7.97 (d, methylene protons), and 8.65 and 9.00 (s, methyl protons).

Anal. Calcd for $C_{10}H_{18}OS$ (186.31): C, 64.46; H, 9.74. Found: C, 64.3, 64.3; H, 9.8, 9.9.

4-Carboethoxymethylene-3,3,6,6-tetramethyl-1-thiacycloheptan-5-one (XIX).—A solution of 9.5 g (0.045 mol) of triethyl phosphonoacetate in 10 ml of dry dimethoxyethane was added to a suspension of 2.2 g (0.045 mol) of NaH in 75 ml of dimethoxyethane. This mixture was stirred until no gas evolution was observed (45 min). A solution of 8.0 g (0.04 mol) of diketone I in 10 ml of dimethoxyethane was added, and the reaction mixture was stirred for 2 hr and refluxed for 1 hr. The reaction mixture was poured into 500 ml of water, and the water solution was extracted with pentane. The pentane extract was dried ($MgSO_4$) and concentrated. The residue was distilled, bp 98–128° (0.1 mm), giving 8.4 g (78%) of the keto ester XIX: ir (neat) 1720 (C=O), 1700 (C=O), 1640 (C=C), 1095 cm^{-1} (C—O—C); nmr (CCl_4) τ 8.85, 8.73, 8.62 (t, ester methyl protons), 8.68 (s, ring methyl protons), 7.5 (m, ring methylene protons), 6.07, 5.95, 5.83, 5.70 (q, ester methylene protons), and 4.20 (s, vinyl proton).

Saponification of the ester XIX gave in 60% yield the corresponding carboxylic acid. Crystallization from ethanol gave

(18) E. E. Blaise and A. Montagne, *Compt. Rend.*, **174**, 1553 (1922).
(19) N. J. Turro, S. S. Edelson, J. R. Williams, and T. R. Darling, *J. Amer. Chem. Soc.*, **90**, 1926 (1968).
(20) L. Eberson, *Tetrahedron Lett.*, 23 (1966).
(21) H. L. Herzog and E. R. Buchman, *J. Org. Chem.*, **16**, 99 (1951).

an analytical sample: mp 184–186°; ir (KBr) 3450 (OH), 1740 (C=O), 1625 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{18}O_3S$ (242.32): C, 59.47; H, 7.44; S, 13.22. Found: C, 59.3, 59.2; H, 7.5, 7.6; S, 13.0, 13.2.

5-*t*-Butyl-5-hydroxy-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (XX).—A solution of 15.5 g (0.17 mol) of *t*-butyl chloride in 20 ml of ether was added over a period of 4 hr to a dispersion of 2.8 g (0.4 g-atom) of Li in 60 ml of ether. The temperature of the reaction mixture was kept below −40°. After the addition of the *t*-butyl chloride, the mixture was stirred for 30 min and then cooled to −70°. At this temperature a solution of 5.0 g (0.02 mol) of diketone I in 40 ml of ether was added, and the reaction mixture was stirred for 2 hr at −70°. The reaction mixture was allowed to come to room temperature, and pieces of unreacted Li were removed. Water was added, and the ether layer was separated, dried (Na_2SO_4), and concentrated. The residue was recrystallized from ethanol giving 3.2 g (59%) of the hydroxy ketone XX: mp 155–156°; ir (Nujol) 3540 (OH), 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 8.87 and 8.73 (s, methyl and *t*-butyl protons), 8.37, 8.12 and 7.93, 7.68 (d, methylene protons), 8.90 (s, OH proton), and 6.75, 6.52 and 6.52, 6.30 (d, methylene protons).

Attempted Reduction of Hydroxy Ketone XX.—A solution of 1.0 g of hydroxy ketone XX was refluxed for 4 hr with a suspension of $LiAlH_4$ in ether. Excess $LiAlH_4$ was destroyed, and the reaction mixture was treated as described for aldehyde XV. The ir spectrum and melting point of the residue were identical with those of an original sample of XX.

5-Hydroxy-3,3,5,6,6-pentamethyl-1-thiacycloheptan-4-one (XXI).—A solution of 6.0 g (0.03 mol) of diketone I in 20 ml of ether was added to a solution of 0.035 mol of methylmagnesium iodide in 40 ml of ether. The reaction mixture was refluxed for 1 hr, and then dilute H_2SO_4 solution was added. The ether layer was separated, washed with water and with dilute $NaHCO_3$ solution, dried (K_2CO_3), and concentrated. The residue was recrystallized from petroleum ether (bp 40–60°) giving 5.3 g (82%) of the hydroxy ketone XXI: mp 80–81°; ir (KBr) 3410 (OH), 1700 cm^{-1} (C=O); nmr ($DCCl_3$) τ 9.07, 8.98, 8.79, 8.67, and 8.58 (s, methyl protons), 7.63, 7.38; 7.05, 6.80 and 7.47, 7.25; 7.22, 7.00 (d, methylene protons), and 6.57 (s, OH proton).

Anal. Calcd for $C_{11}H_{20}O_2S$ (216.33): C, 61.08; H, 9.32; S, 14.83. Found: C, 61.1, 61.2; H, 9.2, 9.2; S, 14.9, 14.7.

A reaction of diketone I with a twofold excess methylmagnesium iodide in boiling toluene gave the same hydroxy ketone XXI.

3,3,4,6,6-Pentamethyl-1-thiacycloheptane-4,5-diol (XXII).—A solution of 3.8 g (0.018 mol) of hydroxy ketone XXI in 50 ml of ether was added to a suspension of 0.9 g (0.024 mol) of $LiAlH_4$ in 100 ml of ether over a period of 30 min. The reaction mixture was refluxed for 4 hr and worked up as described for compound XV. The yield of diol XXII, mp 157–158°, was 3.1 g (81%): ir (Nujol) 3470 and 3400 cm^{-1} (OH).

Anal. Calcd for $C_{11}H_{22}O_2S$ (218.36): C, 60.50; H, 10.16. Found: C, 61.1, 60.8; H, 10.5, 10.4.

4,5-Diallyl-3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-diol (XXIII).—A suspension of 64 g (9.1 g-atoms) of Li in 750 ml of ether was cooled to −15°. A solution of 107 g (0.8 mol) of allyl phenyl ether in 375 ml of ether was added over a period of 1 hr, and the reaction mixture was stirred for 15 min at room temperature. The solution was filtered through glass wool in a nitrogen atmosphere to remove the excess Li. A solution of 20 g (0.1 mol) of diketone I in 50 ml of ether was added, and the reaction mixture was stirred for a period of 40 hr at room temperature. The reaction products were hydrolyzed with water; the ether layer was separated; and the water layer was extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was recrystallized from ethanol–water (1:1) giving 23.6 g (83%) of the diol XXIII: mp 82.5–83°; ir (Nujol) 3400 (OH) and 1620 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{28}O_2S$ (284.47): C, 67.54; H, 9.92; S, 11.29. Found: C, 67.4, 67.7; H, 9.8, 10.0; S, 11.3, 11.1.

4-*t*-Butyl-3,3,6,6-tetramethyl-1-thiacycloheptan-4-ol (XXV).—A solution of 0.15 mol of *t*-butyllithium in 200 ml of ether was prepared and cooled to −80° (see compound XX). A solution of 12.0 g (0.065 mol) of ketone XXIV in 75 ml of ether was added, and the reaction mixture was stirred for 1 hr at −80°, and then allowed to come to room temperature. Dilute hydrochloric acid was added, and the layers were separated. The ether solution was washed with $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The residue was distilled, bp 164–166° (14 mm), giving 13.0 g (82%) of the alcohol XXV: ir (neat) 3500 cm^{-1} (OH); nmr ($DCCl_3$) τ 6.86 (s, OH proton), 7.10, 7.35; 7.63, 7.89; 7.22, 7.45; 7.53, 7.89 (d, methylene protons), 8.79, 8.83, and 9.00 (s, methyl protons), and 8.92 (s, *t*-butyl protons).

Anal. Calcd for $C_{14}H_{28}OS$ (244.43): C, 68.79; H, 11.55. Found: C, 69.1, 69.0; H, 11.4, 11.5.

Attempted Preparation of the Xanthate of XXV.—A suspension of 0.28 g (0.006 mol) of NaH in mineral oil was washed with pentane under nitrogen. After evaporation of the pentane 50 ml of dimethyl sulfoxide was added, and the mixture was heated at 60–70° for 1 hr. After cooling to room temperature 1.2 g (0.005 mol) of alcohol XXV in 10 ml of dimethyl sulfoxide was added. After 30 min, 2 ml of CS_2 was added, and, after another 30 min, 2 ml of CH_3I was added. The reaction mixture was stirred for 1 hr and poured into 150 ml of water. The water solution was extracted with pentane. The pentane extract was dried ($CaCl_2$) and concentrated. A tlc of the residue showed that starting material and one other compound were isolated. After chromatography over silica gel this second compound was isolated, and the ir spectrum suggested that the dithio ester, $CH_3S{=}OCH_2C{=}SSCH_3$, was obtained.

4-Hydroxy-4-hydroxymethylene-3,3,5,5-tetramethyl-1-thiacyclohexane (XXVII).—A solution of 7.0 g (0.03 mol) of hydroxy ester IV in 50 ml of ether was added to a suspension of 1.1 g (0.03 mol) of $LiAlH_4$ in 100 ml of ether. The reaction mixture was refluxed for 4 hr and then worked up as described for compound XV. Recrystallization of the diol XXVII from ethanol gave 5.2 g (82%): mp 180.5–181.5°; ir (Nujol) 3550 cm^{-1} (OH); nmr (CD_3OD) τ 6.35 (s, CH_2OH), 7.01, 7.25, and 7.72, 7.97(d, methylene protons), and 8.95 (s, methyl protons).

Anal. Calcd for $C_{10}H_{20}O_2S$ (204.32): C, 58.78; H, 9.87; S, 15.56. Found: C, 58.9, 58.7; H, 9.9, 9.9; S, 15.6, 15.7.

Oxidation of Hydroxycarboxylic Acid III with $Pb(OAc)_4$.—A solution of 7.0 g (0.032 mol) of acid III and 18.5 g (0.046 mol) of $Pb(OAc)_4$ in 150 ml of acetic acid was stirred for 15 hr at 60–70°. The reaction mixture was concentrated, and water and ether were added. The water solution was extracted with ether, and the ethereal extract was washed with dilute NaOH solution and with water. The ethereal extract was dried (Na_2SO_4) and concentrated. The residue was recrystallized from petroleum ether (bp 40–60°) giving 1.9 g (27.5%) of the lactone XXVIII: mp 95–96°; ir (Nujol) 3480 (OH), 1762 (C=O), and 1100 cm^{-1} (C—O—C); nmr ($DCCl_3$) τ 4.87 (s, S—CH—O), 6.98, 7.22 and 7.55, 7.79 (d, methylene protons), 7.55 (s, OH proton), and 8.53 8.73, 8.83, and 8.93 (s, methyl protons).

Anal. Calcd for $C_{10}H_{16}O_3S$ (216.30): C, 55.52; H, 7.46; S, 14.83. Found: C, 55.6, 55.7; H, 7.5, 7.5; S, 14.7, 14.5; mol wt, 227, 224.

Concentration of the petroleum ether mother liquor gave a liquid residue. Chromatography of this oil over silica gel gave, upon elution with CH_2Cl_2, a small amount (200 mg) of impure ketone V. The ir and nmr spectra were identical with those of an original sample of V.

4-Keto-3,3,6,6-tetramethyl-1-thiacyclohexane 1,1-Dioxide (XXIX).—A solution of 7.0 g (0.032 mol) of hydroxy acid III and 0.1 g of Na in 200 ml of methanol was electrolyzed until the mixture grew dark. The temperature was kept below 35°. The reaction mixture was concentrated, and water and ether were added. The water layer was extracted with ether, and the ethereal extract was dried (Na_2SO_4) and concentrated. The solid residue was recrystallized from hexane giving 2.1 g (31%) of the ketone XXIX: mp 127.5–129°; ir (KBr) 1707, 1692 (C=O), and 1120, 1322 cm^{-1} (SO_2); nmr ($DCCl_3$) τ 6.62 (s, methylene protons) and 8.63 (s, methyl protons).

Anal. Calcd for $C_9H_{16}O_3S$ (204.28): C, 59.90; H, 7.98; S, 15.68. Found: C, 52.9, 52.8; H, 7.9, 7.9; S, 15.5, 15.5.

Ketone XXIX (Second Method).—A solution of 4.0 g (0.018 mol) of hydroxy acid III and 8.0 g of CrO_3 in a mixture of 25 ml of acetic acid and 75 ml of water was stirred for 15 hr at room temperature. Water and ether were added, and the water layer was extracted with ether. The ethereal extract was dried (K_2CO_3) and concentrated, giving 0.60 g (16%) of the ketone XXIX, mp 119–123°. The ir spectrum was identical with that of an original sample of XXIX.

Attempted Reactions with Ketone XXIX.—An attempt to prepare the oxime of ketone XXIX using standard procedures only gave the starting material back. An attempt to prepare the thio ketone of XXIX by heating a mixture of 0.5 g of ketone XXIX and 2.0 g of P_2S_5 in 50 ml of sulfolane at 140° for 30 hr

was also unsuccessful. A small amount of ketone XXIX was the only product that was isolated.

3,3,5,5-Tetramethyl-1-thiacyclohexan-4-one (V).—A solution of 5 g (0.023 mol) of hydroxycarboxylic acid III and 2.8 g (0.023 mol) of $SOCl_2$ in 40 ml of benzene was refluxed for 2 hr. The reaction mixture was concentrated, and the residue was chromatographed over silica gel. Upon elution with CH_2Cl_2, 3.0 g (76%) of the ketone V was obtained. Distillation, bp 88 (12 mm), gave an analytical sample: ir (neat) 1690 cm^{-1} (C=O); nmr (CCl_4) τ 7.37 (s, methylene protons) and 8.82 (s, methyl protons).

Anal. Calcd for $C_9H_{16}OS$ (172.30): C, 62.72; H, 9.36; S, 18.61. Found: C, 62.9, 62.8; H, 9.4, 9.4; S, 18.6, 18.5.

Attempts to prepare an oxime of ketone V using standard procedures were unsuccessful. Starting material was recovered almost quantitatively.

Registry No.—III, 17539-59-2; IV, 17539-60-5; V, 17539-61-6; IX, 17539-62-7; X, 17539-63-8; XI, 17539-64-9; XV, 17539-65-0; XIX, 17539-66-1; XIX (free acid), 17539-67-2; XX, 17539-68-3; XXI, 17539-69-4; XXII, 17539-70-7; XXIII, 17605-19-5; XXV, 17539-71-8; XXVII, 17539-72-9; XXVIII, 17539-73-0; XXIX, 17539-74-1.

Synthesis and Nuclear Magnetic Resonance Spectra of 2-Oxazolidones

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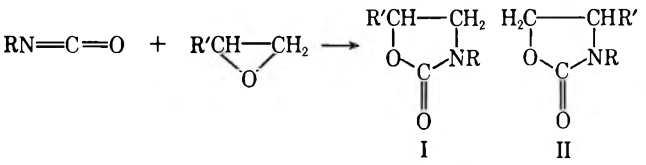
N-substituted 2-oxazolidones have been prepared from isocyanates and epoxides in refluxing DMF with lithium chloride as catalyst. Although the major products are 5-substituted 2-oxazolidones, 4-substituted isomers were also isolated in several cases. The nmr spectra of the 2-oxazolidones were determined, and chemical shift–structure relationships are reported.

The reaction of organic isocyanates with 1,2-epoxides has been reported to yield 2-oxazolidones.[3] A number of catalysts and solvents have been used with varying degrees of success. Most workers reported the formation of only the 5-substituted 2-oxazolidone (I) from the reaction of an isocyanate with an unsymmetrically substituted epoxide. In one case,[3b] however, the



I II

product from the reaction of phenyl isocyanate with phenyl glycidyl ether was assigned the structure of the isomeric 4-substituted 2-oxazolidone (II, R′ = $PhOCH_2$; R = Ph). Previous workers had reported the structure I (R′ = $PhOCH_2$; R = Ph) for this reaction product.

Of interest to us were the literature reports that only one isomeric 2-oxazolidone is obtained from the reaction of isocyanates with unsymmetrical 1,2-epoxides despite the relatively vigorous conditions employed (reaction temperatures *ca.* 150° or greater) and possible effects (steric, conjugative, and polar) of substituent groups in the epoxide on the reaction course. We have examined the reaction in more detail and have shown that, although the 5 isomer predominates, some 4 isomer is also formed.

We have also examined the nmr spectra of a variety of N-substituted (I and II) (Table I) and unsubstituted (III and IV) (Table II) 2-oxazolidones, and have made structural assignments on the basis of the results obtained. In one case, that involving **1** (Table I), independent confirmation of the nmr assignments was made by synthesis and hydrolysis studies. The rationale and discussion of the nmr assignments will be given presently. The preparation of the N-unsubstituted 2-oxazolidones and the N-phenyl-5-decyl- and -dodecyl-2-oxazolidones (**8** and **9**) has been described elsewhere.[4] The remaining N-substituted 2-oxazolidones based on *p*-tolyl and *n*-butyl isocyanates were prepared by adding the requisite isocyanate to a solution of the epoxide and lithium chloride catalyst in refluxing N,N-dimethylformamide (DMF). After completing the addition of isocyanate, the reaction mixtures were refluxed for 6 hr and then worked up to give the 2-oxazolidones in good yields (70% or better). These general reaction conditions were arrived at by briefly examining the effect of solvent, catalyst, and mode of addition of reactants on the yield of the 2-oxazolidone prepared from *p*-tolyl isocyanate and styrene oxide.

Weiner[5] has shown that aryl isocyanates react with DMF at elevated temperatures to give formamidines (**11**). To suppress this reaction, we added the isocyanate to a refluxing DMF solution containing the epoxide and catalyst. Initially, using this mode of addition and tetramethyl ammonium iodide as the catalyst, N′-tolyl-N,N-dimethylformamidine (**11**, R = *p*-tolyl), was the only reaction product identified; it accounted for 35% of the starting isocyanate. When the reaction was repeated with lithium chloride as the catalyst, formamidine formation was negligible, and the superiority of lithium chloride as a catalyst for 2-oxazolidone formation was confirmed.

$$RN{=}C{=}O + HC(O)N(Me)_2 \longrightarrow \underset{\mathbf{11}}{RN{=}CHN(Me)_2} + CO_2$$

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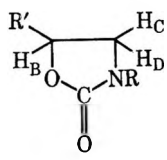
(3) (a) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967), and references therein; (b) S. Sandler, *J. Polym. Sci.*, **A1-5**, 1481 (1967); (c) R. DiLeone, *Polymer Preprints*, **9**, 1 (1968).

(4) M. E. Dyen and D. Swern, *J. Org. Chem.*, **33**, 379 (1968); *J. Amer. Oil Chem. Soc.*, **45**, 325 (1968).

(5) M. L. Weiner, *J. Org. Chem.*, **25**, 2245 (1960).

TABLE I

NMR DATA AND ASSIGNMENTS FOR N-SUBSTITUTED 2-OXAZOLIDONES



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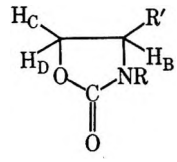


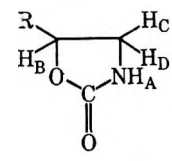
II

Compound	R	R′	Mp or bp (mm), °C	Isomer	Chemical shifts, ppm (δ) (TMS = 0) H_B	H_C, H_D	H_E	H_F
1	*p*-Tolyl	Phenyl	95–97	I	5.58 (d, d, J_{BC} = 7.5, J_{BD} = 8.5 cps)	3.87 (d, d, J_{CB} = 7.5, J_{CD} = 8.5 cps) 4.33 (t, J_{DB}, J_{DC} = 8.5 cps)		
2	*p*-Tolyl	Phenyl	107–109	II	5.34 (d, d, J_{BC} = 6.0, J_{BD} = 8.5 cps)	4.14 (d, d, J_{CB} = 6.0, J_{CD} = 8.5 cps) 4.72 (t, J_{DB}, J_{DC} = 8.5 cps)		
3	$CH_3(CH_2)_2CH_2E$	Phenyl	142.5–144.5 (0.13)	I	5.63 (d, d, J_{BC} = 7.5, J_{BD} = 9.0 cps)	3.49 (d, d, J_{CB} = 7.5, J_{CD} = 9.0 cps) 4.03 (t, J_{DB}, J_{DC} = 9.0 cps)	3.4 (t, J = 7.0 cps)	
4	$CH_3(CH_2)_2CH_2E$	Phenyl	142.5–144.5 (0.13)	II[a]	5.55 (t, J = 8.0 cps)	4.75 (m) 4.1 (m)	3.4 (m)	
5	$CH_3(CH_2)_2CH_2E$	$PhOCH_2F$	41.5–43.5	I	5.06 (m)[b]	3.64 (d, d, J_{CB} = 7.0, J_{CD} = 9.0 cps) 3.86 (t, J_{DB}, J_{DC} = 9.0 cps)	3.42 (t, J = 7.5 cps)	4.31 (d, J = 5.0 cps)
6	$CH_3(CH_2)_2CH_2E$	$CH_3(CH_2)_2CH_2FOCH_2F$	132–139 (0.25)	I	4.6 (m)[b]	3.45 (m)[c]	3.45 (m)	3.45 (m)
7	*p*-Tolyl	$PhOCH_2F$	153.5–155.5	I	5.12 (m)[b]	4.27 (m)[c]		4.34 (d, J = 5.0 cps)
8	*p*-Tolyl	$CH_3(CH_2)_2CH_2FOCH_2F$	185.5–188 (0.2)	I[d]	4.55 (m)[b]	3.68 (m)[c]		3.68 (m)
9[e]	Phenyl	Decyl	68.5–69	I	4.55 (m)[b]	3.59 (d, d, J_{CB} = 7.5, J_{CD} = 8.5 cps) 4.04 (t, J_{DB}, J_{DC} = 8.5 cps)		
10[e]	Phenyl	Dodecyl	74–75	I	4.62 (m)[b]	3.64 (d, d, J_{CB} = 7.5, J_{CD} = 8.5 cps) 4.09 (t, J_{DB}, J_{DC} = 8.5 cps)		

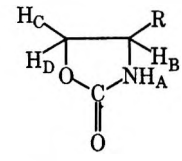
[a] Compound 4 was contaminated with its isomer, 3. H_B proton appears as a triplet (broad center peak) but should be a double doublet. The multiplicity of H_C, H_D, and H_E is also not readily discernible owing to the presence of 3. [b] The methine proton H_B appears as a multiplet owing to interaction with H_F, H_C, and H_D. [c] The multiplicity of H_C and H_D could not be determined owing to the overlap of the signal with H_F. [d] Determined in carbon tetrachloride solution. [e] See ref 4.

TABLE II

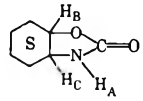
NMR DATA AND ASSIGNMENTS FOR UNSUBSTITUTED 2-OXAZOLIDONES



III (5 isomer)



IV (4 isomer)

Compound	R	Mp, °C	Isomer	Chemical shifts, ppm (δ) (TMS = 0) H_A	H_B	H_C, H_D
13[a]	Decyl	86.5–87.5	III	6.47 (s, broad)	4.57 (m)	3.22 (t, J_{CD}, J_{CB} = 8.5 cps) 3.68 (t, J_{DB}, J_{DC} = 8.5 cps)
14[a]	Decyl	31.5–32.5	IV		4.48 (m)	3.93 (m)
15[a]	Dodecyl	88–89	III	6.39 (s, broad)	4.62 (m)	3.23 (t, J_{CD}, J_{CB} = 8.5 cps) 3.70 (t, J_{DB}, J_{DC} = 8.5 cps)
16[a]	Dodecyl	46–47	IV	6.71 (s, broad)	4.45 (m)	3.87 (m)
17[b]	Phenyl	87–88	III[c]	6.83 (s, broad)	5.54 (d, d, J_{BC} = 8.0, J_{BD} = 8.5 cps)	3.42 (d, d, J_{CB} = 8.0, J_{CD} = 8.5 cps) 3.87 (t, J_{DB}, J_{DC} = 8.5 cps)
18[b]		54–55		6.73 (s, broad)	4.65 (sextet, axial)	3.8 (H_C, q, broad, equatorial)
19[d]	—CN—	94.5–95.5	III[e]	*ca.* 7.0 (broad)	5.65 (d, d, J_{BC} = 5.0, J_{BD} = 8.5 cps)	3.9 (d, d, J_{CB} = 5.0, J_{CD} = ~10.0 cps) 4.16 (t, J_{DB}, J_{DC} = ~9.0 cps)
20[d]	$CH_3OC(O)$	66–67	III[f]	6.48 (broad)	5.06 (d, d, J_{BC} = 6.0, J_{BD} = 9.0 cps)	3.7 (d, d, J_{CD} = 9.0, J_{CB} = 6.0 cps) 3.93 (t, J_{DB}, J_{DC} = 9.0 cps)

[a] See ref 4. [b] See ref 7. [c] Exchange of H by D on nitrogen sharpens the signals of H_A, H_B, and H_C and permits accurate determination of multiplicity and J values. [d] T. A. Foglia and D. Swern, *J. Org. Chem.*, **33**, 766 (1968). [e] Determined in hexadeuterioacetone. [f] Methyl protons, δ 3.85 (s).

A number of other highly polar solvents were used as reaction media (Table III) and all, except triethyl

TABLE III

PREPARATION OF N-*p*-TOLYL-4- AND -5-PHENYL-2-OXAZOLIDONES (1 AND 2) FROM *p*-TOLYL ISOCYANATE (0.1 MOL) AND STYRENE OXIDE (0.1 MOL) IN DIFFERENT SOLVENTS

Reaction solvent	Catalyst	Reaction products, % yield 1	2
DMF[a]	$Me_4\overset{+}{N}\overset{-}{I}$		
DMF[b]	LiCl	76.5	14.6
N-Methyl-2-pyrrolidone	LiCl	73	3.0
DMSO	LiCl	66.5	6.7
Triethyl phosphate[c,d]	LiCl	10.7	0.8
Tetramethylene sulfone (sulfolane)[e]	LiCl	74	

[a] N'-tolyl-N,N-dimethylformamidine (**11**, R = *p*-tolyl) [bp 92–94° (0.15 mm), $n^{20}D$ 1.5844 (accounting for 35% of the isocyanate)] was the only reaction product identified. *Anal.* Calcd for $C_{10}H_{14}N_2$ (**11**, R = *p*-tolyl): C, 74.03; H, 8.70; N, 17.27; mol wt, 162. Found: C, 74.34; H, 8.82; N, 17.07; mol wt, 155 (cryoscopically in benzene). [b] Details in Experimental Section. [c] A mixture of styrene oxide and DMF was recovered from the reaction mixture by distillation. Separation was effected by glpc using a 6 ft × 0.25 in. column containing 5% free fatty acid phase on Chromosorb G (60–80 mesh). The results showed that 84% of the styrene oxide had not reacted. [d] The dimer and trimer of *p*-tolyl isocyanate, mp 174–177° and 269–273°, respectively, were isolated and identified by mixture melting point with authentic samples. They accounted for 1.3 and 14% respectively, of the isocyanate. In addition, *p*-tolylurea (5 mmol) was also isolated. [e] The reaction mixture was poured into cold water to precipitate **1**.

phosphate, gave satisfactory results. With triethyl phosphate, 84% of the styrene oxide was recovered; a considerable amount (46%) of the isocyanate was converted into its corresponding trimer and dimer; and only a small amount of the desired 2-oxazolidone was isolated. Since the use of solvents such as sulfolane, DMSO, and N-methyl-2-pyrrolidone did not appear to offer any advantage over DMF, the latter was used in all subsequent reactions.

The ability of a highly polar, basic solvent such as DMF to enhance the formation of 2-oxazolidone was further demonstrated when an equimolar mixture of *p*-tolyl isocyanate and styrene oxide at room temperature and in the presence of a catalytic amount of lithium chloride (solvent absent) was heated to 156° for 7 hr; only a 25% yield of crude 2-oxazolidones (**1** and **2**) was realized. The remaining *p*-tolyl isocyanate was accounted for as its trimer. Repetition of the reaction in DMF increased the yield of crude 2-oxazolidones (**1** and **2**) to 54%. The amount of isocyanate trimer present upon work-up of the reaction mixture accounted for only 19% of the starting isocyanate. In contrast, addition of the isocyanate to a refluxing DMF solution of the epoxide and catalyst gave optimum yields of the 2-oxazolidones (**1** and **2**), and trimer formation was not observed. Another procedure that gave equally satisfactory results was the addition of an equimolar mixture of isocyanate and epoxide to a refluxing solution of DMF containing catalyst (LiCl).

The reaction of styrene oxide and *p*-tolyl isocyanate carried out in DMF using lithium chloride as a catalyst gave two reaction products of differing melting points but possessing elemental analyses and molecular weights corresponding to the isomeric 2-oxazolidones **1** and **2** (Table I). The two products were shown to be the 5 and 4 isomers of the 2-oxazolidone (**1**-I and **2**-II). In every case, the low melting product (**1**-I), mp 95–97°, was obtained in much larger amounts than the higher melting material (**2**-II), mp 107–109° (>4:1 by weight).

Confirmation of the low melting product as the 5 isomer (**1**) was obtained by hydrolyzing it with alcoholic potassium hydroxide to 2-*p*-tolylamino-1-phenyl-1-ethanol (**12**), determined by elemental analysis, nmr, and synthesis *via* an alternate route[6] (see Experimental Section).

Reaction of *n*-butyl isocyanate with styrene oxide also gave a mixture of isomeric oxazolidones (**3**-I and **4**-II). The liquid isomers were separated by preparative glpc. The 5 isomer (**3**-I) was again the major component of the isomeric mixture (>4:1 by weight). Reaction of *n*-butyl and *p*-tolyl isocyanates with epoxides of the glycidyl ether type, *e.g.*, *n*-butyl and phenyl glycidyl ethers, also gave predominantly 5-substituted 2-oxazolidones (**5**–**8**).

Tables I and II give the chemical shifts and multiplicity of the pertinent protons in the 5- and 4-substituted 2-oxazolidones prepared. The isomeric pair **1**-I and **2**-II are clearly distinguished and identified by nmr. In the 5 isomer (**1**-I), H_B is an anticipated double doublet farther downfield than the corresponding proton H_B in **2**-II which is on a carbon atom attached to nitrogen, a less electronegative atom. Conversely, H_C and H_D in **1**-I are farther upfield than H_C and H_D in **2**-II. The same first order analysis has been used to identify **3**-I and **4**-II, **13**-III and **14**-IV, and **15**-III and **16**-IV. Thus, in 5-substituted 2-oxazolidones the chemical-shift difference between H_B and $H_{C,D}$ is greater than that in isomeric 4-substituted 2-oxazolidones. These results have been confirmed by unequivocal chemical synthesis in several related cases,[7] and by hydrolysis of **1** and identification of the resulting amino alcohol (**12**) (see above and Experimental Section for synthesis of **12**).

Compounds **9** and **10**, Table I, are assigned the 5-substituted 2-oxazolidone structure on the basis of the similarity of their nmr spectra with those of analogs unsubstituted on nitrogen (**13** and **15**, Table II). Compounds **5**, **6**, and **7** are assigned the 5 structure because they are the predominant products of the epoxide ring-opening reaction, now known to yield the 5 isomer as the major reaction product. The nmr spectra are consistent with the structural assignment.

Compounds **17**, **19**, and **20** were prepared by independent, unequivocal synthesis from styrene, acrylonitrile, and methyl acrylate, respectively, by addition of N,N-dichlorourethan (DCU) followed by washing the adduct with aqueous sodium bisulfite and then pyrolysis.[7]

Compound **18** was prepared from cyclohexene by a similar sequence and also by the method of Hassner

(6) 2-*p*-Tolylamino-1-phenyl-1-ethanol (**12**) was prepared by a two-step synthesis. 2-Bromoacetophenone was condensed with *p*-toluidine to give 2-*p*-tolylaminoacetophenone, mp 127.5–131°, which was reduced by sodium borohydride in monoglyme to give an 82% yield of **12**. A mixture melting point of the reduction product with **12** obtained from the hydrolysis of **1** showed no depression.

(7) T. A. Foglia and D. Swern, *J. Org. Chem.*, **32**, 75 (1967).

and Heathcock.[8] The downfield signal at 4.65 ppm is assigned to H_B, the proton attached to the ring carbon linked to oxygen, and the upfield signal at 3.8 ppm is assigned to H_C. Since H_B is a sextet and H_C a quartet, the protons must be axial and equatorial, respectively.

From these results and those obtained from a study of the nmr spectra of simple 2-oxazolidones of known structure and stereochemistry,[9] J_{cis} and J_{gem} are approximately 8–10 cps and J_{trans} is 5–7.5 cps. Thus 2-oxazolidones are another heterocyclic ring system in which *cis* coupling is larger than *trans*, a result previously noted.[10]

Experimental Section

General.—Isocyanates and epoxides were freshly distilled prior to use. Solvents used as reaction media were dried and purified by distillation.

Melting points are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville 21, Tenn. Infrared absorption spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. The pmr spectra were determined on a Varian A-60 spectrometer using TMS as an internal standard and, except where noted, deuteriochloroform as a solvent. An F & M Model 500 chromatograph and an Aerograph Autoprep (Model A-700) were used for glpc. Tables I and II list the 2-oxazolidones studied. Only those previously unreported are described here.

N-*p*-Tolyl-5-phenyl-2-oxazolidone (1).—*p*-Tolyl isocyanate (13.3 g, 0.1 mol) and styrene oxide (12.0 g, 0.1 mol) were heated in several different solvents in the presence of catalysts (Table III). The reactions were carried out by adding the isocyanate and solvent (10 ml) in 30 min to a stirred solution of the epoxide and catalyst in solvent (40 ml) heated at *ca.* 155° under a nitrogen atmosphere. Upon completing the addition of isocyanate, the reaction mixtures were heated at *ca.* 160° for 6 hr.

After *ca.* 16 hr at ambient temperatures, unreacted starting materials and solvent were removed by vacuum distillation with still temperature below 150°. The still residues were treated with hot carbon tetrachloride or hexane and then worked up to yield the isomeric 2-oxazolidones and various other products (Table III).

In the reaction utilizing DMF and lithium chloride as solvent and catalyst (Table III), respectively, the still residue (25.1 g), a cream-colored solid, was dissolved in 50 ml of boiling carbon tetrachloride and filtered. The filtrate on cooling afforded 18.6 g of a cream-colored solid, mp 89–91°. Recrystallization of the crude product from hexane gave **1** as glistening plates (16 g, 63 mmol): mp 95–97°; ir (KBr) 1733 (vs, C=O), 1515 (s), 1480 (s), 1420 (s), 1405 (s), 1315 (s), 1233 (s), 1129 (s), 1118 (s), 1025 (s), 804 (s), 748 (s), and 690 (s) cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_2$ (**1**): C, 75.87; H, 5.97; N, 5.53; mol wt, 253. Found: C, 76.00; H, 5.98; N, 5.56; mol wt, 245 (cryoscopically in benzene).

The carbon tetrachloride filtrate was chromatographed over alumina to yield 0.75 g (3.0 mmol) of **1** identified by melting point and mixture melting point. In addition, 3.7 g (14.6 mmol) of the crude 4-substituted 2-oxazolidone **2** was eluted using carbon tetrachloride and chloroform and mixtures thereof. Analytically pure **2**, mp 107–109°, was obtained after three recrystallizations from hexane: ir (KBr) 1740 (vs, C=O), 1515 (s), 1405 (s), 1226 (m), 1130 (w), 1043 (m), 810 (s), and 693 (w) cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_2$ (**2**): C, 75.87; H, 5.97; N, 5.53; mol wt, 253. Found: C, 76.27 and 76.09; H, 6.10 and 6.02; N, 5.32 and 5.28; mol wt, 254 (cryoscopically in benzene).

Hydrolysis of N-*p*-Tolyl-5-phenyl-2-oxazolidone (1).—A mixture of **1** (5.06 g, 20 mmol) and alcoholic potassium hydroxide (1.6 g, 29 mmol in 50 ml of 95% alcohol) was refluxed for 6.5 hr. After 12 hr at ambient temperatures, the reaction mixture, consisting of a pale yellow solid and clear, colorless liquid phase, was distilled at reduced pressure (water aspirator, pot temperature <96°). The pale yellow solid residue was extracted twice with 25-ml portions of warm ether. On cooling of the combined ether extracts, a white solid (1.3 g, 5.1 mmol) precipitated and was identified as **1** by melting point and mixture melting point. The ethereal filtrate was extracted four times with 5-ml portions of 3 *N* hydrochloric acid; evaporation of ether yielded additional **1** (0.7 g, 2.8 mmol).

The combined aqueous acidic extracts were made alkaline with aqueous 10% sodium hydroxide. The aqueous alkaline mixture was extracted with ether, and the combined ether extracts were concentrated to dryness. The dried solid residue (2.7 g, 11.9 mmol) melted at 78–82°. Three recrystallizations from carbon tetrachloride gave analytically pure **12**: mp 80.5–81.5°;[6] ir (KBr) 3340 (vs, NH), 3200 (s, OH), 2920 (m), 2845 (m), 1620 (m), 1525 (vs), 1450 (s), 1302 (m), 1245 (m), 1090 (m), 1060 (s), 1043 (m), 898 (m), 815 (vs), 742 (s), and 692 (s) cm^{-1}; nmr ($CDCl_3$) δ 2.24 (s, 3, CH_3), 3.20 (d, 2, J = 3.5 cps, —CH_2—), 3.30 (s, 1, NH), 3.41[11] (s, 1, OH), 4.80 (d d, 1, —CH—), 6.53 (d, 2, H_A), 6.99 (d, 2, H_B $J_{A'B}$ = $J_{AB'}$ = 8.5 cps, *p*-tolyl), and 7.34 (s, 5, phenyl).

Anal. Calcd for $C_{15}H_{17}NO$ (**12**): C, 79.26; H, 7.54; N, 6.16; mol wt, 227. Found: C, 79.43; H, 7.68; N, 6.17; mol wt, 251 (cryoscopically in benzene).

Reaction of Butyl Isocyanate with Styrene Oxide.—*n*-Butyl isocyanate (9.9 g, 0.1 mol) and styrene oxide (12.6 g, 0.105 mol) were heated in DMF with lithium chloride as catalyst, as described for **1**. Removal of solvent by distillation *in vacuo* left 21.2 g of a clear pale yellow oil. The residual oil was distilled twice *in vacuo* to give 15.7 g (72% yield) of a pale yellow liquid, bp 142.5–144.5° (0.13 mm). The liquid distillate analyzed correctly for **3** and **4**: ir (neat) 2965 (s), 2935 (s), 2875 (m), 1755 (vs), 1498 (m), 1460 (m), 1430 (m), 1255 (s, broad), 1138, (m, broad), 1065 (m, broad), 1040 (m, broad), 1027 (m, broad), 998 (m), 756 (s), and 695 (s) cm^{-1}.

Anal. Calcd for $C_{13}H_{17}NO_2$ (**3** and **4**): C, 71.20; H, 7.82; N, 6.39; mol wt, 219. Found: C, 71.41; H, 7.83; N, 6.51; mol wt, 226 (determined in benzene by vapor pressure osmometry).

A portion of the distillate was analyzed by glpc on columns 2.5 ft × 0.25 in. containing 10% Carbowax 20M and terephthalic acid on Chromosorb WAW (60–80 mesh). The column temperature was programmed from 100–240° at the rate of 11°/min. Three peaks were observed.

Integration indicated that the three components were present in the following amounts by weight (given in order of elution): A, 0.7%; B, 18.9%; and C, 80.4%. The initial peak A accounting for 0.7% of the material had a retention time similar to that of butyl isocyanate trimer chromatographed under comparable conditions.[12]

Still another sample of the distillate was fractionated by preparative glpc at 225° using a 10 ft × 3/8 in. column packed with 10% Apiezon L on Chromosorb WAW (60–80 mesh); the two major components (B and C), the isomeric oxazolidones (**4** and **3**), were collected after 13 and 14 min, respectively.

N-Butyl-5-butoxymethylene-2-oxazolidone (6).—*n*-Butyl isocyanate (9.9 g, 0.1 mol) and *n*-butyl glycidyl ether (13.65 g, 0.105 mol) were allowed to react in DMF using lithium chloride catalyst as described. After removal of solvent, the pale amber residual oil (20.7 g) was distilled twice to give 16.3 g of a colorless liquid, bp 132–139° (0.25 mm). The distillate was fractionated by preparative glpc at 225° using a 10 ft × 3/8 in. column packed with 10% Apiezon L on Chromosorb WAS (60–80 mesh). Two components were collected. The initially eluted component (13.2% by weight) was identified as *n*-butyl isocyanate trimer by ir (neat): 2965 (s), 2935 (s), 2870 (m), 1685 (vs), 1465 (vs), 1420 (s), 1375 (m), 1330 (m), and 760 (s) cm^{-1}. The major component (86% by weight, 78% yield) gave ir (neat) 2965 (s), 2940 (m), 2870 (m), 1750 (vs, C=O), 1490 (m), 1450 (m, broad), 1265 (m, broad), 1135 (m, broad), 1060 (m, broad), and 757 (w) cm^{-1}.

(8) A. Hassner and C. Heathcock, *Angew. Chem. Intern. Ed. Engl.*, **2**, 213 (1963).

(9) T. A. Foglia and D. Swern, unpublished results.

(10) (a) I. Fleming and D. H. Williams, "Spectroscopic Methods in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 109; (b) S. L. Manatt, D. D. Elleman, and S. J. Brois, *J. Amer. Chem. Soc.*, **87**, 2220 (1965); (c) S. J. Brois and G. P. Beardsley, *Tetrahedron Lett.*, 5113 (1966).

(11) Shifted to δ 3.88 on adding trifluoroacetic acid. The position of other signals was essentially unchanged.

(12) The nmr spectrum of pure *n*-butyl isocyanate trimer in $CDCl_3$ showed multiplets at δ 0.97 (CH_3—, 9 H) and 1.51 (—CH_2CH_2—, 12 H) and a triplet at 3.91 (methylene protons adjacent to ring nitrogens, 6 H).

Anal. Calcd for $C_{12}H_{23}NO_3$ (6): C, 62.85; H, 10.11; N, 6.11; mol wt, 229. Found: C, 62.82; H, 10.08; N, 6.22; mol wt, 237 (determined in benzene by vapor phase osmometry).

N-*p*-Tolyl-5-*n*-butoxymethylene-2-oxazolidone (8).—After reaction of *p*-tolyl isocyanate (26.6 g, 0.2 mol) with butyl glycidyl ether (27.3 g, 0.21 mol) and removal of the solvent as described earlier, an amber oil (54 g) remained. The oil was distilled twice to yield 38 g of **8**: bp 185.5–188° (0.2 mm); $n^{20}D$ 1.5255; ir (neat) 2965 (s), 2935 (s), 2870 (m), 1753 (vs), 1523 (s), 1425 (s), 1410 (s), 1320 (s), 1228 (s), 1135 (s), 983 (m), 810 (m), and 750 (w) cm^{-1}.

Anal. Calcd for $C_{15}H_{21}NO_3$ (8): C, 68.41; H, 8.04; N, 5.32; mol wt, 263. Found: 68.32; H, 7.99; N, 5.52; mol wt, 264 (determined in benzene by vapor phase osmometry).

Glpc of analytically pure **8** at 250° using an 8 ft × 1/8 in. column packed with 3% SE-52 on Chromosorb W indicated the presence of two components: a minor component A, thought to be the 4 isomer, (*ca.* 4% by weight), and a major component B, **8** (*ca.* 96% by weight, 70% yield).

The reaction was repeated using 0.98 mol of *p*-tolyl isocyanate and 1.03 mol of *n*-butyl glycidyl ether to provide a 78% yield of analytically pure **8**.

N-*p*-Tolyl-5-phenoxymethylene-2-oxazolidone (7).—Reaction of *p*-tolyl isocyanate (26.6 g, 0.2 mol) with phenyl glycidyl ether (31.5 g, 0.21 mol) in the presence of a catalytic amount of lithium chloride (0.08 g) gave 48.2 g (0.17 mol, 85% yield) of crude **7**, mp 153–155°, after removing the solvent (DMF) and subsequent treatment with ice-cold carbon tetrachloride. Recrystallization from boiling 95% ethyl alcohol gave analytically pure **7**: mp 153.5–155.5°; ir (KBr) 1735 (vs), 1595 (m), 1520 (s), 1500 (m), 1445 (m), 1420 (m), 1405 (s), 1340 (s), 1253 (s), 1226 (m), 1146 (s), 1095 (m), 1085 (m), 1043 (m), 988 (m), 803 (m), 753 (s), and 687 (m) cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_3$ (7): C, 72.06; H, 6.05; N, 4.94; mol wt, 283. Found: C, 71.84; H, 5.88; N, 5.01; mol wt, 280 (determined in benzene by vapor phase osmometry).

N-*n*-Butyl-5-phenoxymethylene-2-oxazolidone (5).—The preceding reaction was repeated using 19.8 g (0.2 mol) of *n*-butyl isocyanate. Removal of solvent (DMF) *in vacuo* left 51.6 g of an oily amber solid. One recrystallization from carbon tetrachloride (35 ml)–hexane (70 ml) provided 41.7 g (168 mmol, 84% yield) of **5**, mp 35–39°. Analytically pure **5**, mp 41.5–43.5°, was obtained after recrystallization from 50% aqueous alcohol and then from cyclohexane: ir (KBr) 2950 (m), 2920 (m), 2860 (w), 1740 (s), 1580 (m), 1480 (m), 1445 (m), 1240 (m), 1055 (m, broad), 750 (w), and 685 (w) cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$ (5): C, 67.45; H, 7.68; N, 5.62; mol wt, 249. Found: C, 67.70; H, 7.68; N, 5.51; mol wt, 243 (determined in benzene by vapor phase osmometry).

Registry No.—**1**, 17539-79-6; **2**, 17539-80-9; **3**, 17539-81-0; **4**, 17539-82-1; **5**, 17539-83-2; **6**, 17539-84-3; **7**, 5255-84-5; **8**, 17539-86-5; **9**, 17539-87-6; **10**, 17539-88-7; **11** (R = *p*-tolyl), 7549-96-4; **12**, 17539-90-1; **13**, 7693-76-7; **14**, 7693-82-5; **15**, 14627-60-2; **16**, 17539-94-5; **17**, 7693-77-8; **18**, 17539-96-7; **19**, 15042-67-8; **20**, 15042-69-0.

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The Thermal Rearrangement of Some Optically Active Pyrroles[1]

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At 575° (+)-N-(1-phenylethyl)pyrrole isomerizes to the corresponding 2- (42 ± 3%) and 3-(1-phenylethyl)-pyrrole (11 ± 1%), each isomer being formed with 77 ± 3% retention of configuration. Under the same conditions (+)-2-(1-phenylethyl)pyrrole is converted into the 3 isomer in 18% yield, the 2 isomer being recovered with 73 ± 3% retention of configuration. Likewise at 600° the *sec*-butyl group in N-(*sec*-butyl)pyrrole migrates to both the 2 and 3 positions with 85 ± 1 and 75 ± 2% retention of configuration, respectively. (+)-N-(1-Phenylethyl)- or N-(*sec*-butyl)-2,5-dimethylpyrrole on pyrolysis give mixtures of 2-alkyl-3,5-dimethylpyrrole and 3-alkyl-2,5-dimethylpyrrole. When the migrating group is 1-phenylethyl, migration produces both isomers with 40% retention of configuration; when the migrating group is *sec*-butyl, the 2 and 3 isomers are produced with 77 and 75% retention of configuration, respectively. The results are consistent with the formation of a 2H-pyrrole intermediate arising through a closely associated transition state.

Alkyl[2] and benzyl[3] substituents in N-substituted pyrroles migrate at high temperatures to the 2 and 3 positions in the pyrrole ring by a homogeneous unimolecular process. The large negative entropies of activation observed imply a cyclic transition state. In addition, the facts that activation energies were about 90% as large as the estimated bond dissociation energies and that all substituents (in substituted benzyl substituents) increased the reaction rate led Pine[3] to suggest that homolytic bond breaking had occurred to the extent of 90% in the transition state.

To investigate further the nature of a migration involving a radicallike species, thermal isomerizations were carried out with pyrroles in which the migrating group was asymmetric. The results of experiments in which (+)-N-(1-phenylethyl)-, (+)-2-(1-phenylethyl)-, (+)-N-(*sec*-butyl)-, and (+)-2-(*sec*-butyl)-pyrrole were pyrolyzed are reported in Table I. The precision of the data is indicated by the average deviations obtained from duplicate and triplicate experiments.

While the extent of the isomerization (and decomposition) was dependent on temperature and heat exchanger (catalysis by Berl saddles) in the N-phenylethylpyrrole pyrolyses, the amount of retention of configuration was not influenced appreciably by these variables. In the N-*sec*-butylpyrrole experiments, catalysis by the Berl saddles was nil. The expected increase in product formation with higher temperatures was observed. Also the 2 isomer was formed with a greater degree of stereospecificity than the 3 isomer in the migration of the *sec*-butyl group.

The estimate of the extent of retention of configuration for the formation of 3 isomer previously reported (10%)[1] was based upon the rotation of an impure sample (3-*sec*-butylpyrrole) and upon the erroneous

(1) (a) Supported by the U. S. Army Research Office, Durham. (b) A portion of these results were communicated previously: J. M. Patterson and L. T. Burka, *J. Amer. Chem. Soc.*, **88**, 3671 (1966).

(2) (a) I. A. Jacobson, Jr., H. H. Heady, and G. V. Dinneen, *J. Phys. Chem.*, **62**, 1563 (1958); (b) I. A. Jacobson, Jr., and H. B. Jensen, *ibid.*, **66**, 1245 (1962); (c) I. A. Jacobson, Jr., and H. B. Jensen, *ibid.*, **68**, 3068 (1964).

(3) L. A. Pine, *Dissertation Abstr.*, **24**, 522 (1963).

TABLE I

YIELD AND PER CENT RETENTION OF CONFIGURATION OF PYROLYSIS PRODUCTS FROM THE N-SUBSTITUTED PYRROLES[a]

Substituent	Pyrolysis temp, °C	Yield[b] of isomer, % N	2	3	Decompn, %	Retention of isomer, % 2	3
(+)-N-Ph(Me)CH[c]	575	36 ± 8[d]	42 + 3	11 + 1	11 ± 5	77 ± 3	77 + 3
(+)-2-Ph(Me)CH[e]	575		74	18	8	73 ± 3	
(+)-N-Ph(Me)CH	550	69	24	4	3	80	
(+)-N-Ph(Me)CH[f]	550[g]	41 ± 7	40 ± 2	8 ± 1	11 ± 5	77 ± 5	80 ± 2
(+)-N-*sec*-Bu	575[g]	69	23	4	4	79	
(+)-N-*sec*-Bu	600[g]	49 ± 1[e]	34 ± 1[e]	8 ± 1[e]	9 ± 1[e]	86	78
(+)-N-*sec*-Bu[e]	600	59 ± 4[h]	30 ± 1	6 ± 2	5 ± 2	84 ± 1	74 ± 1
(+)-N-*sec*-Bu	625	36[i]	41	13	10	77	71
(+)-2-*sec*-Bu	600		64	23	11	100	56 ± 10[j]

[a] Pyrolysis over Vycor beads. [b] Reported as glpc area per cent. [c] Average of three experiments. [d] Retention of optical activity, 99.5 ± 0.2%. [e] Average of two experiments. [f] Average of four experiments. [g] Pyrolysis over Berl saddles. [h] Retention of optical activity, 99.1 ± 0.1%. [i] Retention of optical activity, 96.2%. [j] Based on average deviation of observed rotation.

TABLE II

YIELD AND PER CENT RETENTION OF CONFIGURATION OF PYROLYSIS PRODUCTS FROM THE SUBSTITUTED DIMETHYLPYRROLES[a]

Substituent	Pyrolysis temp, °C	Yield[b] of isomer, % N	2[c]	3[d]	Decompn, %	Retention of isomer, % 2[c]	3[d]
(+)-N-Ph(Me)CH[e]	525	25 ± 5[f]	15 ± 2	46 ± 9	15 ± 5	40 ± 1	39 ± 1
(+)-N-Ph(Me)CH	500	37	10	43	10	...	49
(+)-N-*sec*-Bu[e]	575	16 ± 4[g]	31 ± 5	40 ± 1	13 ± 2	77 ± 3	75 ± 1
(+)-N-*sec*-Bu	525	59	14	23	4	77	75

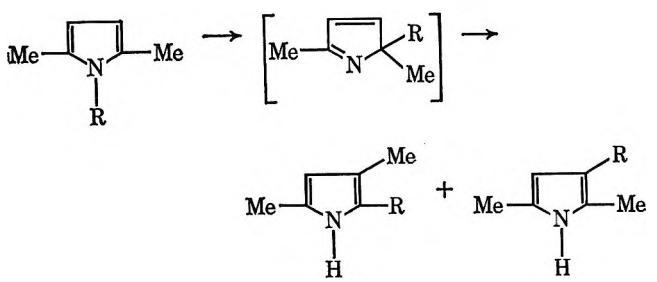
[a] Pyrolysis over Vycor beads. [b] Reported as glpc area per cent. [c] 2-Substituted 3,5-dimethylpyrrole. [d] 3-Substituted 2,5-dimethylpyrrole. [e] Average of two experiments. [f] Retention of optical activity, 97 ± 2%. [g] Retention of optical activity, 99.6 ± 0.2%.

assumption (phenylethylpyrroles) that the rotations of the 2 and 3 isomers were approximately the same.

In all experiments except those carried out at 625°, the N isomer was recovered with 99+% of its original optical activity. At the higher temperature some racemization of the N isomer was found. These results are consistent with the mechanism proposed by Jacobson and coworkers[2] in which the 2 isomer is irreversibly formed from the N isomer, while the 3 isomer is reversibly formed from the 2 isomer.

In some preliminary experiments in which the 2 isomer was pyrolyzed under the same conditions as the N isomer, the recovered starting material was obtained in 73 + 3% retention when the migrating group was 1-phenylethyl and in 100% retention when the migrating group was *sec*-butyl. The 3-(*sec*-butyl)pyrrole was obtained with 56 ± 10% retention in this experiment.

As the pyrolysis of trisubstituted pyrroles leads to rearrangement products probably arising through a 2H-pyrrole intermediate,[4] the stereochemistry of the thermal isomerization of optically active N-substituted 2,5-dimethylpyrroles was also investigated. The results of these pyrolysis studies are reported in Table II.



Both the ease of isomerization and the extent of racemization appear to be a function of the stability of the radicals or partially developed radicals making up the closely associated transition state involved in the migration. Thus the phenylethyl substituent migrates more readily and is racemized to a greater extent than the *sec*-butyl substituent. Similarly, the methyl substituents enhance the stability of the partially developed pyrryl radical, and the result is a more facile isomerization and a larger amount of racemization than that observed with the N-substituted pyrroles. Steric crowding at the migration terminus (by the methyl substituents) may also contribute to the higher degree of racemization observed with the dimethylpyrroles and to increased radical dissociation. The isolation of *meso*-2,3-diphenylbutane as a minor product from the N-(1-phenylethyl)-2,5-dimethylpyrrole pyrolysate and of 2,4- and 2,5-dimethylpyrrole from the N-(*sec*-butyl)-2,5-dimethylpyrrole pyrolysate is evidence for the radical dissociation. No special effort was made to detect the presence of *dl*-2,3-diphenylbutane in the pyrolysate.

The N-substituted pyrroles were synthesized from the appropriate amine and 2,5-dimethoxytetrahydrofuran[5] or from the appropriate amine and 2,5-hexanedione.[4] The (+)-N-substituted pyrroles were obtained from the (+)-amine in all synthesis experiments except for (+)-N-(1-phenylethyl)pyrrole which was obtained from (−)-amine.

The ir and nmr spectra of the (+)-2-*sec*-butyl- and (+)-3-*sec*-butylpyrroles (obtained from the pyrolyses) were consistent with the structures assigned, and the properties of these isomeric pyrroles corresponded to

(4) J. M. Patterson and S. Soedigdo, *J. Org. Chem.*, **33**, 2057 (1968).

(5) Procedure adapted from N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **5**, 867 (1952).

those previously reported.[6] The relationship of rotation to optical purity as well as the relationship of the configurations of (+)-2-*sec*-butyl- and (+)-3-*sec*-butylpyrroles to (+)-*sec*-butyl bromide has been established previously.[6] Since (+)-*sec*-butyl bromide has the same configuration as (+)-*sec*-butylamine,[7] migration of the substituent occurred with retention of configuration.

The structures assigned to the pyrolysis products of N-(1-phenylethyl)pyrrole were verified by synthesis from pyrrylmagnesium bromide and 1-phenylethyl bromide. The ir and nmr spectra of each of the isomers were consistent with the assigned structures.

The configuration and optical purity of the (+)-2 and (+)-3 isomers, obtained from the pyrolysis of (+)-N isomer and in turn synthesized from (−)-phenylethylamine, were established by permanganate oxidation[6] to (+)-hydratropic acid. The acid was converted into methyl hydrotropate for purification by glpc. The two isomers had the same configuration and exhibited very similar optical rotatory dispersion curves. As it has been shown by Bernstein and Whitmore[8] that (+)-hydratropic acid and (−)-phenylethylamine have the same configuration, the 1-(phenylethyl) group migrates to both the 2 and 3 positions with retention of configuration.

The ir and nmr spectra obtained from the (+)-N-(*sec*-butyl)-2,5-dimethylpyrrole pyrolysis products were identical with those obtained from the reaction products of 2,5-dimethylpyrrylmagnesium bromide and of 2,4-dimethylpyrrylmagnesium bromide with *sec*-butyl bromide. The configuration and optical purity of the isomeric pyrroles were established by permanganate oxidation;[6] both the (+)-2-(*sec*-butyl)- and (+)-3-(*sec*-butyl)dimethylpyrroles were converted into (+)-2-methylbutyric acid. The isomerization occurs with retention of configuration.

Likewise the structures of the pyrolysis products of (+)-N-(1-phenylethyl-2,5-dimethylpyrrole were verified by synthesis from 2,5-dimethylpyrryl- and 2,4-dimethylpyrrylmagnesium bromides and 1-phenylethyl bromide.

Pyrolysis of (+)-N-(1-phenylethyl)-2,5-dimethylpyrrole, synthesized from (+)-1-phenylethylamine produced (+)-2-(1-phenylethyl)- and (−)-3-(1-phenylethyl)dimethylpyrroles. Since oxidation of each isomer followed by esterification produced methyl (−)-hydratropate, the N substituent migrates to the 2 and 3 position with retention of configuration.

Experimental Section

Boiling points are uncorrected. Gas chromatographic analyses and separations were made on an F & M Model 810-R-12 gas chromatograph using the columns and temperatures specified. Infrared spectra were measured on a Beckman IR-8 spectrophotometer; ultraviolet spectra were measured on a Perkin-Elmer Model 202 spectrophotometer; and nmr spectra (δ) were measured on a Varian HA-60 IL spectrometer in carbon tetrachloride solutions (*ca.* 10%) using tetramethylsilane (TMS) as an internal standard (δ 0). Optical rotatory dispersion curves were measured on a Jasco recording spectropolarimeter. Rotations were obtained on neat liquids in 1-dm tubes, unless otherwise specified, using a Rudolph Model 63 polarimeter. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

N-(1-Phenylethyl)pyrrole.[5]—To a solution of 60.6 g (0.5 mol) of 1-phenylethylamine in 100 ml of glacial acetic acid (exothermic reaction) was added 66.0 g (0.5 mol) of 2,5-dimethoxytetrahydrofuran, and the mixture was refluxed 1.5 hr. After removal of the acetic acid by distillation, the reaction mixture was cooled and dissolved in 150 ml of ether. The ether solution was washed with two 100-ml portions of water, two 100-ml portions of 0.1 *N* sodium hydroxide, and two 100-ml portions of 0.05 *N* hydrochloric acid and then dried over magnesium sulfate. After removal of the drying agent by filtration and the ether by distillation, the residue was distilled at reduced pressure. There was obtained 58 g (68%) of colorless liquid: bp 116–117° (7 mm); n^{25}D 1.5581; λ_{max}^{MeOH} 206 mμ (ϵ 17,000), 258 (280), 262 (250), 268 (170); nmr spectrum, 1.71 (doublet, 3 H), 5.08 (quartet, 1 H), 5.97 (triplet, 2 H), 6.51 (triplet, 2 H), and 7.05 ppm (multiplet, 5 H).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.31; H, 7.86; N, 7.96.

(+)-N-(1-Phenylethyl)pyrrole.—1-Phenylethylamine was resolved by the method of Theilacker and Winkler[9] using (+)-tartaric acid: bp 69.5–70.5° (12 mm); n^{25}D 1.5244; $[\alpha]^{25}$D −37.97 ± 0.02°. Rotations reported are $[\alpha]^{22}$D −40.3°,[9] $[\alpha]^{15}$D +40.7°,[10] $[\alpha]^{23}$D +39.9°.[11] Using the rotation of Leithe,[10] the optical purity was 93.3%. Reaction of the amine with 2,5-dimethoxytetrahydrofuran produced 73.7 g (67%) of colorless liquid: bp 112–112.5° (6 mm); n^{25}D 1.5588; d^{25} 1.018 g/ml; $[\alpha]^{25}$D +47.65 ± 0.02° (neat). The nmr and ir spectra were identical with those obtained with the racemic N-(1-phenylethyl)pyrrole. Gas chromatographic analysis on a 6 ft × 0.125 in. 10% SE-30 column at 150° showed one peak.

N-(*sec*-Butyl)pyrrole.[5]—2,5-Dimethoxytetrahydrofuran (40.8 g, 0.31 mol) was added to a solution of 23.0 g (0.32 mol) of *sec*-butylamine in 75 ml of glacial acetic acid, and the mixture was refluxed 3.5 hr. The reaction mixture was cooled, poured into 900 ml of water, and extracted with four 500-ml portions of ether. The ether extract was washed four times with water and once with saturated sodium bicarbonate solution and dried over magnesium sulfate. After removal of the drying agent by filtration and the ether by distillation, the residue was distilled at atmospheric pressure yielding 17 g (45%) of colorless liquid: bp 156–157.5°; n^{25}D 1.4687; λ_{max}^{MeOH} 215 mμ (ϵ 7030); nmr spectrum, 0.74 (triplet, 3 H), 1.34 (doublet, 3 H), 1.63 (triplet, 2 H), 3.77 (quartet, 1 H), 5.90 (triplet, 2 H), and 6.45 ppm (triplet, 2 H).

Anal. Calcd for $C_8H_{13}N$: C, 77.99; H, 10.63; N, 11.37. Found: C, 78.34; H, 10.57; N, 11.30.

(+)-N-(*sec*-Butyl)pyrrole.—*sec*-Butylamine was resolved by the method of Leithe[12] using (+)-tartaric acid: bp 62.5–63°; n^{25}D 1.3912; $[\alpha]^{25}$D +8.12 ± 0.04° (neat). Based upon the reported rotation of $[\alpha]^{25}$D +8.1° (neat),[11] optical purity was 100%. Treatment of 36.5 g (0.50 mol) of the amine with 66.0 g (0.50 mol) of 2,5-dimethoxytetrahydrofuran in 100 ml of glacial acetic acid yielded 31.3 g (51%) of colorless liquid: bp 156.5–157.5°; n^{25}D 1.4683; d^{25} 0.871 g/ml; $[\alpha]^{25}$D +34.8 ± 0.1°. The ir spectrum was identical with the one obtained from the racemic N-(*sec*-butyl)pyrrole. Gas chromatographic analysis using a 6 ft × 0.125 in. 10% SE-30 column showed only one peak.

In another experiment, N-(*sec*-butyl)pyrrole of 30.8% optical purity, $[\alpha]^{25}$D +10.2° (neat), was prepared from *sec*-butylamine, $[\alpha]^{25}$D +2.5° (neat).

(+)-N-(1-Phenylethyl)-2,5-dimethylpyrrole.—(+)-1-Phenylethylamine was recovered from the mother liquor of the resolution of 1-phenylethylamine with (+)-tartaric acid by the procedure described by Ault:[13] bp 71–71.5° (12 mm); n^{25}D 1.5245; $[\alpha]^{25}$D +39.72 ± 0.02°; 97.6% optical purity.[10] The procedure reported for the synthesis of N-benzyl-2,5-dimethylpyrrole was employed.[4] From 85.9 g (0.75 mol) of 2,5-hexanedione, 90.8 g (0.75 mol) of (+)-1-phenylethylamine, and 15 ml of acetic acid in benzene, there was obtained 125.8 g (86%) of colorless liquid

(6) P. S. Skell and G. P. Bean, *J. Amer. Chem. Soc.*, **84**, 4660 (1962).
(7) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 179 (1950).
(8) H. I. Bernstein and F. C. Whitmore, *J. Amer. Chem. Soc.*, **61**, 1324 (1939).
(9) W. Theilacker and H. Winkler, *Ber.*, **87**, 690 (1954).
(10) W. Leithe, *Monatsh. Chem.*, **51**, 381 (1929).
(11) H. E. Smith, S. L. Cook, and M. E. Warren, Jr., *J. Org. Chem.*, **29**, 2263 (1964).
(12) W. Leithe, *Ber.*, **63**, 800 (1930).
(13) A. Ault, *J. Chem. Educ.*, **42**, 269 (1965).

boiling at 133–134° (7 mm): $n^{25}D$ 1.5554; d^{25} 1.006 g/ml; $[\alpha]^{25}D$ +26.97 ± 0.02° (neat), +35.6 ± 0.4° (c 6.29, CCl_4); λ_{max}^{MeOH} 213 mμ (ε 4880); nmr spectrum, 1.72 (doublet, 3 H), 1.96 (singlet, 6 H), 5.30 (quartet, 1 H), 5.57 (singlet, 2 H), and 7.07 ppm (multiplet, 5 H).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.36; H, 8.60; N, 7.03. Found: C, 84.58; H, 8.86; N, 7.15.

(+)-N-(*sec*-Butyl)-2,5-dimethylpyrrole.—A solution of 59.4 g (0.81 mol) of (+)-*sec*-butylamine {$[\alpha]^{25}D$ +7.91 ± 0.02° (neat); 97.6% optical purity[11]} and 92.5 g (0.81 mol) of 2,5-hexanedione was refluxed for 4 hr during which time the water formed in the reaction was removed by azeotropic distillation. After removal of the benzene, the residue was distilled through a 10-cm Vigreux column to give 98.5 g (81%) of colorless liquid: bp 199°; $n^{25}D$ 1.4834; d^{25} 0.8952 g/ml; $[\alpha]^{25}D$ +25.40 ± 0.01° (neat), 27.0 ± 0.1 (c 8.12, CCl_4); λ_{max}^{MeOH} 214 mμ (ε 7564); nmr spectrum, 0.76 (triplet, 3 H), 1.39 (doublet, 3 H), 1.75 (multiplet, 2 H), 2.16 (singlet, 6 H), 4.0 (multiplet, 1 H), 5.47 ppm (singlet, 2 H).

Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.06; H, 11.10; N, 9.10.

Pyrolysis of the Substituted Pyrroles—The following procedures are representative of the pyrolysis experiments. The pyrolyses were carried out in a vertically arranged 95 × 2.5 cm Vycor reactor tube which contained 50 ml of Vycor beads or Berl saddles used as a heat exchanger. The tube was heated in a Lindberg Hevi-Duty three-zone tube furnace; the temperature was regulated to ±5° of the indicated value over the volume containing the heat exchanger. The sample was introduced at a constant rate from a syringe mounted on a syringe drive (driven by a Troemner monodrum unit) and swept through the reactor by a stream of dry nitrogen at a flow of 100 ml/min. The liquid products were collected in a trap cooled by an ice–water mixture, weighed, and analyzed by gas chromatography. A 6 ft × 0.125 in. 10% SE-30 column was used for the analysis of the phenylethylpyrroles (150°), the *sec*-butylpyrroles (80°), and the phenylethyldimethylpyrroles (160°); a 6 ft × 0.125 in. 10% UC-W98 column was used for the analysis of the *sec*-butyldimethylpyrroles (130°).

Pyrolysis of (+)-N-(1-Phenylethyl)pyrrole.—The pyrrole (28.8 g) was added at a constant rate over 6.5 hr to the reactor tube, containing Vycor beads, at 575°. The crude pyrolysate weighed 27.3 g (94% recovery) and contained (glpc analysis) 28.5% N isomer, 41.3% 2-(1-phenylethyl)pyrrole, 12.0% 3-(1-phenylethyl)pyrrole, and 18.2% decomposition products. Unrearranged N isomer was removed from the pyrolysate by distillation through a 30 × 1 cm column packed with glass helices. The fraction boiling at 110–113° (7 mm) was 100% pure (glpc analysis) and had a rotation of $[\alpha]^{25}D$ +47.37 ± 0.05° (neat), which corresponds to 99.4% retention of its optical activity.

The residue was distilled through a short-path distillation apparatus, and the distillate was separated into the 2 and 3 isomers by preparative glpc using a 12 ft × 0.375 in. 20% Carbowax 20M column at 225°.

(+)-2-(1-Phenylethyl)pyrrole was further purified by glpc using a 12 ft × 0.375 in. 20% SE-30 column at 225° (99.9% pure, glpc analysis): bp 138–140° (10 mm); $n^{25}D$ 1.5708; d^{25} 1.043 g/ml; $[\alpha]^{25}D$ +60.19 ± 0.03°, +66.2 ± 0.7° (c 10.07, CCl_4), $[\alpha]_{546}^{25}$ +71.84 ± 0.03° (neat); $\nu_{max}^{CCl_4}$ 3490 cm^{-1} (N–H); λ_{max}^{MeOH} 209 mμ (ε 13,800), 262 (610), 269 (343); nmr spectrum, 1.48 (doublet, 3 H), 3.83 (quartet, 1 H), 5.84 (multiplet, 2 H), 6.23 (multiplet, 1 H), and 7.03 ppm (multiplet, 5 H).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.82; H, 7.41; N, 8.10.

(+)-3-(1-Phenylethyl)pyrrole was further purified by glpc using an 8 ft × 0.375 in. 24% Apiezon L column at 175° (99.1% pure, glpc analysis): bp 153° (10 mm); $n^{25}D$ 1.5728; d^{25} 1.047 g/ml; $[\alpha]^{25}D$ +8.58 ± 0.04° (neat), +24.0 ± 0.7° (c 4.62, CCl_4), $[\alpha]_{546}^{25}$ +10.10 ± 0.04°; $\nu_{max}^{CCl_4}$ 3490 cm^{-1} (N–H); λ_{max}^{MeOH} 210.5 mμ (ε 12,800), 262.5 (383), 269 (290); nmr spectrum, 1.48 (doublet, 3 H), 3.88 (quartet, 1 H), 5.85 (multiplet, 1 H), 6.10 (multiplet, 1 H), 6.30 (multiplet, 1 H), and 7.10 ppm (multiplet, 5 H).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.29; H, 7.67; N, 8.06.

Synthesis of 2- and 3-(1-Phenylethyl)pyrrole.—To pyrrylmagnesium bromide, prepared from ethylmagnesium bromide (0.5 mol, 12 g of magnesium and 54 g of ethyl bromide) and 33.5 g (0.5 mol) of pyrrole was added slowly 92.5 g (0.5 mol) of 1-phenylethyl bromide. The mixture was heated on a steam bath for 30 min and allowed to stand overnight. After the complex was decomposed with 200 ml of 15% ammonium chloride solution, the ether layer was separated, washed with water, and dried over magnesium sulfate. After removal of the drying agent and the ether, the residue was distilled under reduced pressure, bp 137–142° (9 mm). The 2 and 3 isomers were separated on an 8 ft × 0.375 in. Carbowax 20M column at 250° giving refractive indices of $n^{25}D$ 1.5709 and 1.5724, respectively. The gas chromatography retention times, the ir spectra, and the nmr spectra were identical with those obtained from the 2 and 3 isomers produced on pyrolysis.

Oxidation of (+)-2-(Phenylethyl)pyrrole.—The method of Skell and Bean[6] was adapted. To a solution of 44 g (0.28 mol) of potassium permanganate in 500 ml of water cooled to 10°, 4.0 g (0.023 mol) of (+)-2-(1-phenylethyl)pyrrole ($[\alpha]^{25}D$ +60.19°) was added portionwise while maintaining the temperature at 10°. After stirring at 5–10° for an additional 2 hr, the manganese dioxide and excess permanganate were decomposed with sulfur dioxide. The reaction mixture was made acidic to congo red with concentrated hydrochloric acid. The acidic material, obtained by extraction of the reaction mixture with five 50-ml portions of ether, was extracted into 125 ml of 25% sodium hydroxide solution which, in turn, was extracted twice with 50 ml of ether. The acid was recovered from the alkaline solution by acidification with 50% sulfuric acid and by extraction with three 100-ml portions of ether. After drying over anhydrous magnesium sulfate, the drying agent was removed by filtration, and the ether was removed by distillation. The crude acid residue was converted into the acid chloride by the method of Smejkal and Farkas[14] in which the acid was refluxed for 30 min with a mixture of 3 ml of thionyl chloride and 10 ml of hexane. After removal of the hexane and thionyl chloride on a rotary evaporator, the crude acid halide was treated with an excess of anhydrous methanol (*ca.* 5 ml). The unreacted methanol was removed by distillation; the residue was dissolved in ether; and the ether solution was washed twice with 25 ml of saturated sodium bicarbonate solution. After drying (magnesium sulfate), the ether was distilled and the crude methyl hydratropate purified by preparative glpc using an 8 ft × 0.375 in. 24% Apiezon L column at 125°: $n^{25}D$ 1.4933; $[\alpha]^{25}D$ +79.4° (c 3.59, ethanol) (authentic sample, $n^{25}D$ 1.5000). The ester showed only one peak on glpc analysis (retention time identical with that obtained on an authentic sample), and the ir spectrum was identical with one obtained from authentic material. Based upon the reported[15] rotation of $[\alpha]^{23}D$ + 108.7° (c 5.5 ethanol) for ester prepared from 96% optically pure hydratropic acid, the methyl hydratropate obtained from the oxidation of the 2 isomer is 70% optically pure. The isomerization of the substituent from the N to the 2 position occurred with 75% retention of configuration.

Oxidation of (+)-3-(Phenylethyl)pyrrole.—Using the procedure described for the oxidation of the 2 isomer, there was obtained insufficient methyl hydratropate for an accurate rotation. Oxidation of a larger sample of the 3 isomer (obtained in another experiment from the isomerization of the N isomer of 83.7% optical purity), $[\alpha]^{25}D$ +7.55 ± 0.03° (neat), +20.4 ± 0.1° (c 3.77, CCl_4), gave methyl hydratropate (99.3% pure, glpc analysis) with a rotation of $[\alpha]^{25}D$ +73 ± 1° (c 3.91, ethanol) and optical purity of 65%. Using these values, the optical purity of the 3 isomer initially oxidized was 74%. The ir spectrum and the glpc retention time of the ester were identical with those obtained from an authentic sample. The isomerization to the 3 position occurred with 79% retention of configuration.

Pyrolysis of (+)-2-(1-Phenylethyl)pyrrole.—When 5 g of the 2-substituted pyrrole {bp 136–138° (10 mm); $n^{25}D$ 1.5723; 99.9% pure, glpc analysis; $[\alpha]^{25}D$ +63.11 ± 0.03° (neat); 70.7% optical purity} was pyrolyzed under the conditions used for the N isomer, there was obtained 4.7 g (94% recovery) of of pyrolysate which contained (by glpc analysis) 74.1% 2 isomer, 18.6% 3 isomer, and 6.6% decomposition products. In addition, there was produced material (0.7%) which had the same glpc retention as the N isomer but which was not characterized further. Separation and purification of the pyrolysate by the procedures previously described for the N-(1-phenylethyl)pyrrole pyrolysis gave recovered 2-(1-phenylethyl)-

(14) J. Smejkal and J. Farkas, *Coll. Czech. Chem. Commun.*, **28**, 481 (1963).
(15) W. A. Bonner and J. A. Zderic, *J. Amer. Chem. Soc.*, **78**, 3218 (1956).

pyrrole (99.5% pure, glpc analysis; $n^{25}D$ 1.5716; $[\alpha]^{25}D$ +48.09 ± 0.04°) with 76% retention of optical activity.

In another experiment, the 2 isomer was obtained in 74.3% yield (70% retention of optical activity), and the 3 isomer was obtained in 18.1% yield.

The ir spectra of all the isomers were identical with those obtained from authentic samples.

Pyrolysis of (+)-N-(*sec*-Butyl)pyrrole.—The pyrrole (24.6 g, $[\alpha]^{25}D$ +34.8 ± 0.1°, optical purity 100%) was added at a constant rate over 6 hr to the reactor tube (containing Vycor beads) at 600°. The pyrolysate (21.7 g, 88% recovery) contained (glpc analysis) 54.9% N isomer, 31.1% 2-(*sec*-butyl)-pyrrole, 7.5% 3-(*sec*-butyl)pyrrole, and 6.5% decomposition products. Most of the unreacted N isomer was removed from the pyrolysate by distillation through a 30 × 1 cm column packed with glass helices. The fraction boiling at 65–69° (40 mm) was collected and further purified by preparative glpc using an 8 ft × 0.375 in. 30% SE-30 column at 70°: 99.7% pure (glpc analysis); $n^{25}D$ 1.4685; $[\alpha]^{25}D$ +34.5 ± 0.1° (neat), 99.1% optical purity. This represents 99.1% retention of the optical activity. The residue, consisting of 2 and 3 isomers, was separated by preparative glpc using an 8 ft × 0.375 in. 30% Carbowax 20M column at 150°.

The (+)-2-(*sec*-butyl)pyrrole after further purification using glpc (8 ft × 0.375 in. 30% SE-30 column at 85°) was 99.7% pure: $n^{25}D$ 1.4910; d^{25} 0.904 g/ml; $[\alpha]^{25}D$ +22.00 ± 0.05°, 84% optical purity; ν_{CCl_4} 3390, 3480 cm^{-1} (N–H); nmr spectrum, 0.90 (multiplet, 3 H), 1.22 (multiplet, 3 H), 1.50 (multiplet 2 H), 2.57 (multiplet, 1 H), 5.79 (multiplet, 1 H), 5.97 (multiplet, 1 H), 6.43 (multiplet, 1 H), and 7.55 ppm (broad) {lit.[6] $n^{25}D$ 1.4900; $[\alpha]^{25}D$ +11.24 (43% optical purity)}. The isomerization to the 2 isomer occurred with 84% retention of configuration.

The (+)-3-(*sec*-butyl)pyrrole was purified by preparative glpc using an 8 ft × 0.375 in. 30% SE-30 column at 100°: 99.9% pure, glpc analysis; $n^{25}D$ 1.4873; d^{25} 0.910 g/ml; $[\alpha]^{25}D$ +20.4 ± 0.1° (neat, 0.5 dm), +22.0 ±0.8° (*c* 2.50, ethanol), 22.3 ± 0.4° (*c* 5.16, ethanol); ν_{CCl_4} 3390, 3490 cm^{-1} (N–H); nmr spectrum, 0.80 (triplet, 3 H), 1.12 (doublet, 3 H), 1.40 (multiplet, 2 H), 2.43 (multiplet, 1 H), 5.90 (multiplet, 1 H), 6.30 (multiplet, 1 H), and 6.40 ppm (multiplet, 1 H) {lit.[6] $n^{25}D$ 1.4878; $[\alpha]^{25}D$ +11.98° (43% optical purity)}. The isomerization to the 3 isomer occurred with 73% retention of configuration.

In another experiment in which pyrrole (9.73 g) of 30.8% optical purity {$[\alpha]^{25}D$ 10.2° (neat)} was pyrolyzed in a tube containing Berl saddles at 575°, there was obtained 8.68 g (90% recovery) of pyrolysate containing (glpc analysis) 69% N isomer, 23% 2 isomer, and 4% 3 isomer. The (+)-2-(*sec*-butyl)pyrrole obtained on isolation was 24% optically pure ($[\alpha]^{25}D$ +26.1°). The 2 isomer was obtained with 79% retention of configuration during the isomerization.

Pyrolysis of (+)-2-(*sec*-Butyl)pyrrole.—Pyrolysis of 1.35 g of the pyrrole {$[\alpha]^{25}D$ +23.4 ± 0.4° (*c* 5.26, CCl_4); 99.9% pure, glpc analysis} at 600° in a tube containing Vycor beads produced 63.5% 2 isomer, 23.0% 3 isomer, and 10.5% decomposition products. The 2 and 3 isomers were separated by preparative glpc using a 12 ft × 0.375 in. 20% Apiezon L column at 120°. The 2 isomer, thus recovered (100% pure, glpc analysis), had the same optical purity {$[\alpha]^{25}D$ +24.3 ± 1.5° (*c* 2.63, CCl_4)} as starting material. The 3 isomer (99.7% pure, glpc analysis was formed with 56 ± 10% retention of configuration during the pyrolysis.

Pyrolysis of (+)-N-(1-Phenylethyl)-2,5-dimethylpyrrole.—The pyrrole (38.5 g) was added at a constant rate over 9.75 hr to the reactor tube at 525°. The crude pyrolysate weighed 34.5 g (90% recovery) and contained (glpc analysis) 30% N isomer, 13% 2-(1-phenylethyl)-3,5-dimethylpyrrole, 37% 3-(1-phenylethyl)-2,5-dimethylpyrrole, and 20% decomposition products. The pyrolysate was separated by preparative glpc using a 10 ft × 0.375 in. 30% Carbowax 20M column at 200–250°.

Meso-2,3-Diphenylbutane was obtained from the decomposition products, mp 128° after two recrystallizations from hexane (lit. mp 128°,[16] 125.5°[17]). Calculations of the molecular weight and empirical formula from the mass spectrum gave 210 and $C_{16}H_{18}$, respectively.

The N isomer recovered from the pyrolysate was further purified by glpc using a 12 ft × 0.375 in. 20% Apiezon L column at 225°: 100% pure (glpc analysis); $[\alpha]^{25}D$ +34.6 ± 0.4° (*c* 6.74, CCl_4). This corresponds to 97 ± 2% retention of its optical activity.

(+)-2-(1-Phenylethyl)-3,5-dimethylpyrrole was further purified by glpc using a 12 ft × 0.375 in. 20% Apiezon L column at 190°: 99.5% pure (glpc analysis); $n^{25}D$ 1.5623; bp 226–228°; $[\alpha]^{25}D$ +12.5 ± 0.4 (*c* 4.57, CCl_4); $\nu_{max}^{CCl_4}$ 3460 cm^{-1} (N–H); λ_{max}^{MeOH} 211 mμ (ε 5800); nmr spectrum, 1.50 (doublet, 3 H), 1.89 (singlet, 3 H), 2.08 (singlet, 3 H), 4.07 (quartet, 1 H), 5.39 (singlet, 1 H), and 7.10 ppm (singlet 5 H).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.36; H, 8.60; N, 7.03. Found: C, 84.43; H, 8.72; N, 7.02.

Oxidation of the 2 isomer followed by esterification of the acid produced gave methyl hydratropate: 100% pure (glpc analysis); $[\alpha]^{25}D$ −45.2 ± 0.5° (*c* 4.20, ethanol); optical purity, 39.9 ± 0.4%. The ir spectrum was identical with that obtained from an authentic sample. The isomerization from the N to the 2 position occurred with 40.9 ± 0.4% retention of configuration.

The structure of the 2 isomer was verified by synthesis from 3,5-dimethylpyrrylmagnesium bromide and 1-phenylethyl bromide. The ir and nmr spectra obtained from the Grignard reaction product were identical with those obtained from the pyrolysis product.

(−)-3-(1-Phenylethyl)-2,5-dimethylpyrrole was further purified by glpc using a 12 ft × 0.375 in. 20% Apiezon L column at 225°: 100% pure (glpc analysis); mp 73–75°; $[\alpha]^{25}D$ −6.6 ± 0.7° (*c* 4.57, CCl_4); $\nu_{max}^{CCl_4}$ 3465, 3420 cm^{-1} (N–H); λ_{max}^{MeOH} 210.7 mμ (ε 4480); nmr spectrum, 1.40 (doublet, 3 H), 1.85 (singlet, 3 H), 2.03 (singlet, 3 H), 3.78 (quartet, 1 H), 5.54 (singlet, 1 H), and 7.03 ppm (singlet, 5 H).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.36; H, 8.60; N, 7.03. Found: C, 84.21; H, 8.74; N, 7.12.

Oxidation of the 3 isomer followed by esterification gave methyl hydratropate: $[\alpha]^{25}D$ −43.4 ± 0.5° (*c* 2.07, ethanol); 100% pure (glpc analysis); optical purity 38.3%. The ir spectrum and glpc retention time of the ester were identical with those obtained from an authentic sample. The isomerization to the 3 position occurred with 39.2 ± 0.5% retention of configuration.

The structure of the 3 isomer was verified by synthesis from 2,5-dimethylpyrrylmagnesium bromide and 1-phenylethyl bromide. The ir and nmr spectra obtained from the Grignard reaction product were identical with those obtained from the pyrolysis product.

Pyrolysis of (+)-N-(*sec*-Butyl)-2,5-dimethylpyrrole.—The pyrolysis temperature producing the maximum isomerization was determined by pyrolyzing samples of the pyrrole at various temperatures. From 50 g (0.33 mol) of the pyrrole added to the reactor tube (575°) at a rate of 3.9 g/hr, there was obtained 41 g (82% recovery) of pyrolysate, which contained (glpc analysis) 12% N isomer, 36% 2-(*sec*-butyl)-3,5-dimethylpyrrole, 41% 3-(*sec*-butyl)-2,5-dimethylpyrrole, and 11% decomposition products. Distillation of the crude pyrolysate through a 30 × 1 cm column packed with glass helices gave the following fractions: decomposition product, bp 60–63° (14 mm); N isomer, bp 63–75° (12 mm); 2 isomer, bp 75–78° (10 mm); and residue (3 isomer).

The first fraction, bp 60–63° (14 mm), was purified by preparative glpc using a 12 ft × 0.375 in. 20% Apiezon L column at 160°. The fraction, a mixture of 2,4-dimethylpyrrole and 2,5-dimethylpyrrole, showed a glpc retention time and ir and nmr spectra which were identical with those obtained from a mixture of authentic samples of the two pyrroles.

Purification of the recovered N isomer was accomplished by glpc using a 12 ft × 0.375 in. 20% Apiezon L column at 130°: purity 99.9%; $[\alpha]^{25}D$ +25.37 ± 0.01° (neat); 99.8% retention of optical activity.

(+)-2-(*sec*-Butyl)-3,5-dimethylpyrrole was purified further (glpc) using a 10 ft × 0.375 in. 30% Carbowax 20M column at 200°: purity, 98.7%; bp 210°; $n^{25}D$ 1.4915; d^{25} 0.8968 g/ml; $[\alpha]^{25}D$ +36.9 ± 0.1° (*c* 8.02, CCl_4); $\nu_{max}^{CCl_4}$ 3480 cm^{-1} (N–H); λ_{max}^{MeOH} 222 mμ (ε 8284); nmr spectrum, 0.80 (triplet, 3 H), 1.12 (doublet, 3 H), 1.37 (multiplet, 2 H), 1.88 (singlet, 3 H), 2.10 (singlet, 3 H), 2.63 (multiplet, 1 H), 5.39 (doublet, 1 H), 7.04 ppm (singlet, 1 H).

Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.40; H, 11.46; N, 9.30.

(16) F. Wesseley and H. Welleba, *Ber.*, **74**, 777 (1941).

(17) H. H. Richmond, E. J. Underhill, A. G. Brook, and G. F. Wright, *J. Amer. Chem. Soc.*, **69**, 937 (1947).

Oxidation of the 2-*sec*-butyl isomer by the procedure used for the oxidation of 2-(1-phenylethyl)pyrrole gave on distillation 2-methylbutyric acid: bp 165–175°; $n^{25}D$ 1.4048; $[\alpha]^{25}D$ +15.31 ± 0.01° (neat) (lit.[18] bp 176–177.5°; $n^{25}D$ 1.4042). The ir spectrum of the acid was identical with that obtained from an authentic sample. Assuming that the value of $[\alpha]^{25}D$ +20.5° [6,17] represents the rotation of 100% optically pure acid, the 2-methylbutyric acid obtained on oxidation was 75% optically pure. The isomerization from the N to the 2 position occurred with 77% retention of configuration.

The structure of the 2-(*sec*-butyl)-3,5-dimethylpyrrole was confirmed by synthesis from 2,4-dimethylpyrrylmagnesium bromide and *sec*-butyl bromide. The glpc retention times and nmr and ir spectra were identical with those of authentic samples.

(+)-3-(*sec*-Butyl)-2,5-dimethylpyrrole was purified by glpc (12 ft × 0.375 in. 20% Apiezon L column at 170°): purity, 99.4%; mp 28°; d^{28} 0.8859 g/ml; $[\alpha]^{25}D$ +30.1 ± 0.2° (c 8.46, CCl_4); $\nu_{max}^{CCl_4}$ 3840 cm^{-1} (N–H); λ_{max}^{MeOH} 211 mμ (ε 6900); nmr spectrum, 0.75 (triplet, 3 H), 1.05 (doublet, 3 H), 1.34 (multiplet, 2 H), 2.00 (singlet, 3 H), 2.03 (singlet, 3 H), 2.31 (multiplet, 1 H), 5.46 (doublet, 1 H), 6.95 ppm (singlet, 1 H).

Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.25; H, 11.06; N, 9.21.

(18) K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, **78**, 1640 (1956).

Oxidation produced 2-methylbutyric acid: $n^{25}D$ 1.4056; $[\alpha]^{25}D$ +15.11 ± 0.01° (neat); 74% optical purity. The isomerization to the 3 position occurred with 76% retention of configuration.

The glpc retention time and the ir and nmr spectra of the product obtained from reaction of 2,5-dimethylpyrrylmagnesium bromide with *sec*-butyl bromide were identical with those obtained from the 3-*sec*-butyl isomer produced on pyrolysis.

Registry No.—N-(1-Phenethyl)pyrrole, 17289-34-8; (+)-N-(1-phenethyl)pyrrole, 13245-05-1; N-(*sec*-butyl)-pyrrole, 17289-36-0; (+)-N-(*sec*-butyl)pyrrole, 13245-04-0; (+)-N-(1-phenylethyl)-2,5-dimethylpyrrole, 17289-38-2; (+)-N-(*sec*-butyl)-2,5-dimethylpyrrole, 17289-39-3; (+)-2-(1-phenylethyl)pyrrole, 13245-06-2; (+)-3-(1-phenylethyl)pyrrole, 13245-07-3; (+)-2-(*sec*-butyl)pyrrole, 17289-42-8; (+)-3-(*sec*-butyl)pyrrole, 17289-43-9; (+)-2-(1-phenylethyl)-3,5-dimethylpyrrole, 17289-44-0; (−)-3-(1-phenylethyl)-2,5-dimethylpyrrole, 17289-45-1; (+)-2-(*sec*-butyl)-3,5-dimethylpyrrole, 17289-46-2; (+)-3-(*sec*-butyl)-2,5-dimethylpyrrole, 17289-47-3.

Studies on Pyrimidine Derivatives and Related Compounds. LVIII.[1] Reaction of Dialkyl Acylphosphonates with 3-Benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Halides (Takamizawa Reaction 7)

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The novel reactions of 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium salts (**9a–c**) with diethyl benzoyl- or diethyl acetylphosphonate (**3a** or **b**) producing 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**8**) and 2-methyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**17**) afforded 2-(1-diethylphosphoroyl)benzyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium salts (**10a–c**) or 2-(1-diethylphosphoroyl)ethyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium bromide (**16**) as the intermediates. 3-Alkylimino-2,3-dihydro-4H-1,4-thiazine derivatives (**20–22** and **24**) were also obtained by the reaction of **10b** or **16** with ammonia or primary amines. The reaction of **10b** with dimethylamine gave 2-phenyl-3-dimethylamino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-4H-1,4-thiazine (**23**). The reaction of **16** with dimethylamine gave **17** unexpectedly. The rearrangement of **10b** to **8** was kinetically studied by measuring the successive changes in the ultraviolet absorption spectra. The mechanism of this novel reaction involving ring conversion was discussed. The reaction mechanism of thiamine with dialkyl acylphosphonates producing 1-alkyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′:4,5]pyrimido[2,3-*d*][1,4]thiazine (**4**) was also discussed briefly.

In previous papers,[2–4] we reported that the reaction of thiamine (B_1) with dialkyl acylphosphonate involving a novel conversion of thiazolium moiety into thiazine afforded tricyclic 1-alkyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′:4,5]pyrimido-[2,3-*d*][1,4]thiazine (**4**), which was quite easily hydrolyzed to give 2-alkyl-3-oxo-4-(2-methyl-4-aminopyrimidin-5-yl)methyl-5-methyl-6-(2-hydroxy)-ethyl-2,3-dihydro-4H-1,4-thiazine (**5**). 1,4-Thiazine derivatives (**7** and **8**) were directly obtained in fairly good yields in the case of thiazolium salts containing no functional groups such as the pyrimidine C-4 amino group (Scheme I). This is new reaction for dialkyl acylphosphonate. The present paper is aimed to elucidate the reaction mechanism of thiazolium salts with acylphosphonates using 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium halides and diethyl benzoyl- and diethyl acetylphosphonates. The information obtained here offers data useful for the elucidation of the Perkow reaction mechanism.

Reaction of Thiazolium Salts with Diethyl Benzoyl- and Diethyl Acetylphosphonate.—We already reported[5] that the reaction of the so-called "neutral form" of benzyl thiazolium salt (**6**) with diethyl benzoylphosphonate (**3a**) gave 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**7**) and its benzoate (**8**). In this paper the reactions of 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium halides (**9a–c**) with **3a** and diethyl acetylphosphonate (**3b**) in the presence of triethylamine in N,N-dimethylformamide are described.

The 1:1 adducts (**10a–c**) of **9a–c** and **3a** were obtained in approximately 80% yields by the reactions of **9a–c** with **3a**; each gave the nitrate (**10d**) on treat-

(1) Part LVII: A. Takamizawa, Y. Hamashima, S. Sakai, and S. Nagakura, *Bull. Chem. Soc. Jap.*, **41** (No. 9) (1968).

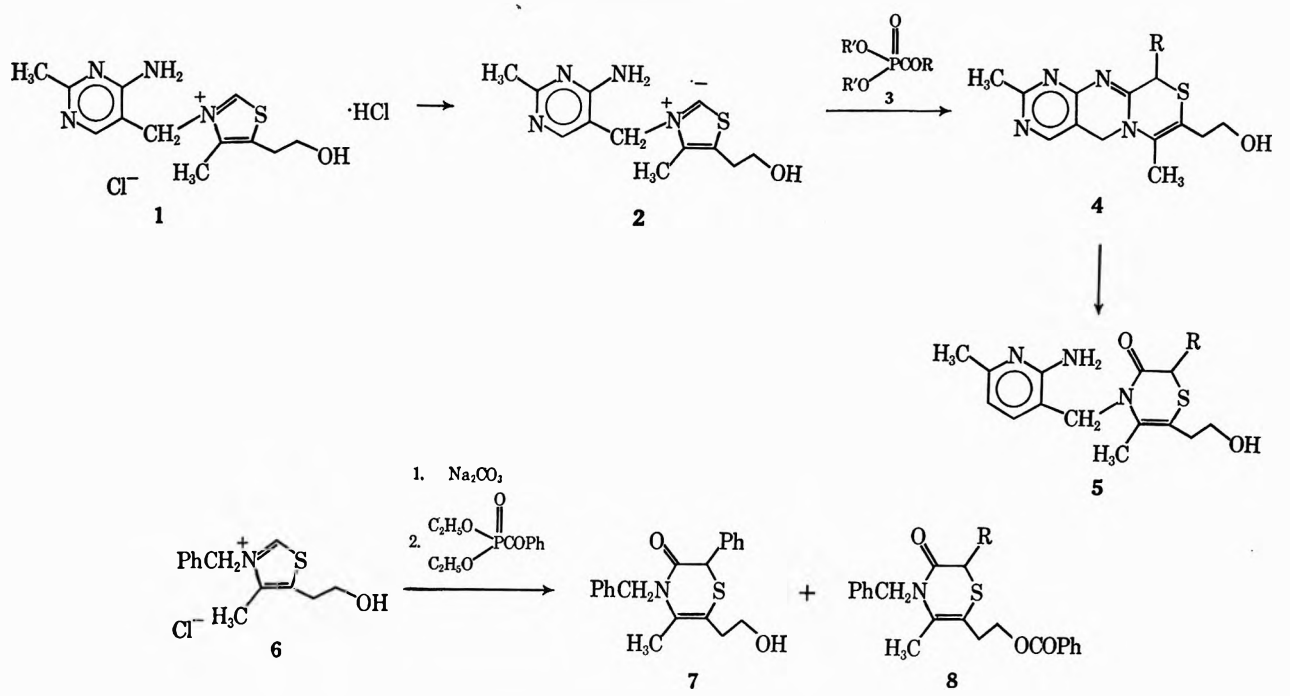
(2) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito and Y. Mori, *J. Org. Chem.*, **31**, 2951 (1966).

(3) A. Takamizawa, Y. Hamashima, Y. Sato, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **15**, 1178 (1967).

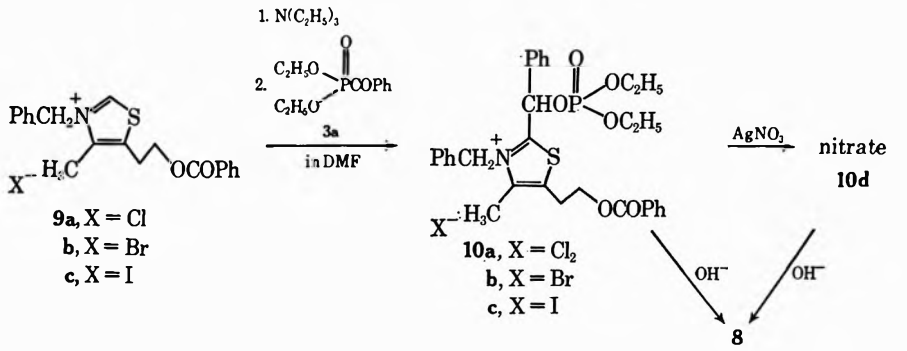
(4) A. Takamizawa, Y. Sato, and H. Sato, *ibid.*, **15**, 1183 (1967).

(5) A. Takamizawa and Y. Sato, *ibid.*, **14**, 742 (1966).

SCHEME I

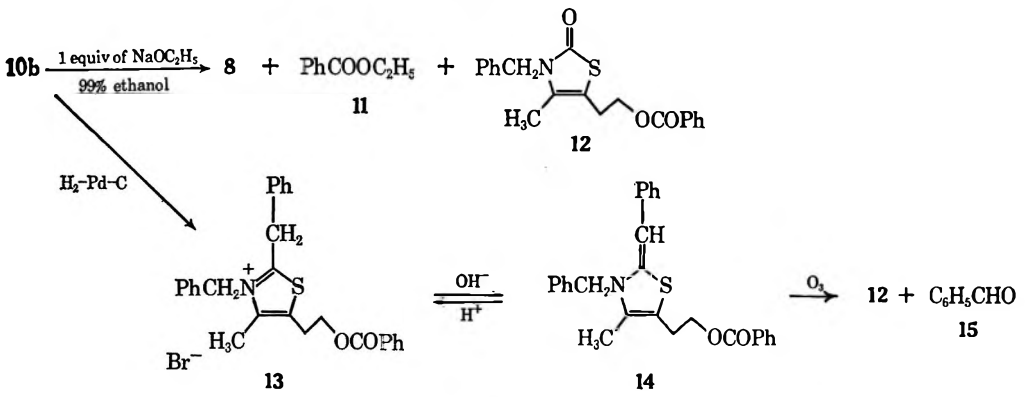


SCHEME II

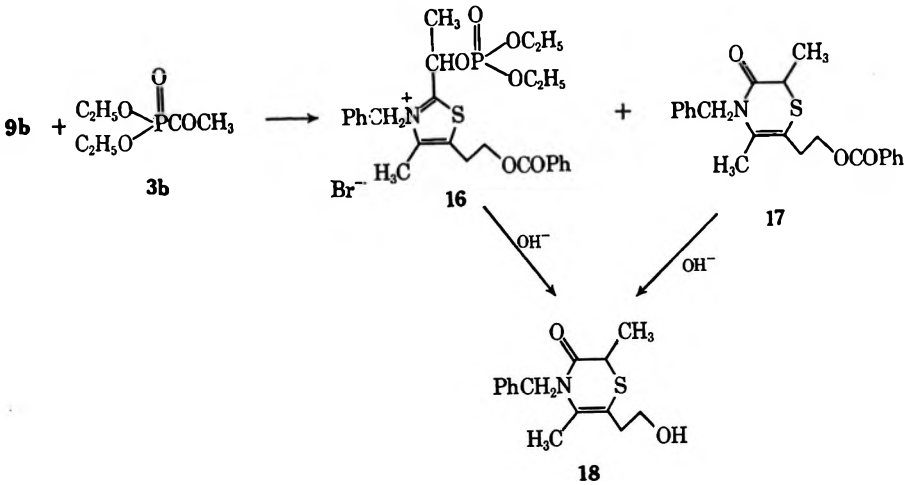


ment with silver nitrate and were easily converted into **8** by alkali (Scheme II). These facts reveal that **10a–d** are intermediates of a novel reaction leading to 1,4-thiazine derivatives from the reaction of thiazolium salts with acylphosphonate. The ir spectrum of **10a–d** showed strong ester bands, P=O and P—O—C, but no hydroxyl or carbonyl absorption band was observed. Accordingly, the diethoxyphosphinoyl group of **3a** can be thought to be introduced intact, though its benzoyl group may change the original form. There was no distinctive difference between the uv absorption spectrum of **10** and that of **9**. The nuclear magnetic resonance spectrum (nmr) of **10b**, for example, showed a 15 H multiplet signal at τ 1.95–2.83, a 1 H multiplet signal at 3.12–3.20, which did not disappear with an addition of deuterium oxide, a 4 H multiplet methylene signal at 6.12, a 6 H methyl signal of two ethoxyphosphinoyl groups as two triplets of doublets at 8.87 and 8.92 (J_{HH} = 7.0, J_{PH} = 1.1 Hz), a 2 H singlet methylene signal at 3.97, and a singlet methyl signal at 7.56. The latter two signals showed very similar signal patterns and chemical-shift values as **9b**, but no C-2 methine signal was detected. From the above data, **10b** might still have the thiazolium moiety, and **3a** was assumed to be substituted at the thiazole C-2 position in a form of $C_6H_5CHP(O)(OC_2H_5)_2$. In this case, there might be another possibility that **10** might have a six-membered-ring structure in view of its easy and facile conversion into a 1,4-thiazine derivative. This notion, however, was discarded on the basis of the following evidence. Ethyl benzoate (**11**) and 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolin-2-one (**12**) were obtained by careful treatment of **10b** with an equimolar amount of sodium ethoxide. Furthermore, hydrogenation of **10b** over a palladium–charcoal catalyst consumed an equimolar amount of hydrogen to give a colorless oily product (**13**), which was neutralized to afford **14**, (Scheme III). The ir absorption spectrum of **14** showed ester bands at 1713 and 1278 and strong bands due to conjugated double bond at 1573 and 1552 cm^{-1}. The uv absorption spectrum exhibited the absorption maxima at 229.5 mμ (ϵ 17,800), 267 (6110), and 365 (8510), but these bands disappeared by adding hydrochloric acid and reproduced the absorption curve of **13**, indicating that the highly conjugated system disappeared on protonation. The nmr spectrum of **14** showed a 1 H singlet at τ 4.63, and a 2 H singlet methylene signal at 5.18. These signals changed on a proton addition, namely, the signal at 4.63 disappeared with the concurrent appearance of a 2 H singlet at 5.68, and a 2 H singlet signal at 5.18 shifted to lower field (4.03). The behavior of these proton signals are explained as

SCHEME III



SCHEME IV



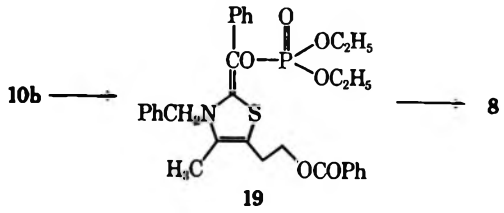
follows. The signal at τ 4.63 was assigned to a benzylidene proton at the thiazole C-2 and that of 5.18 to benzyl methylene protons at the nitrogen. The two groups changed into two benzyl groups owing to formation of a thiazolium moiety by adding acid. Furthermore, chemical evidence for the structure of **14** was obtained by ozonolysis of **14** which gave **12** and benzaldehyde (**15**) (Scheme III). Based on the data mentioned above the structure of **14** was determined to be 2-benzylidene-3-benzyl-4-methyl-5-(2-benzoyloxy)-ethylthiazoline.

Reaction of **9b** with **3b** was also found to proceed analogously, providing **16** in a moderate yield together with a small amount of **17** (Scheme IV). The elemental analysis of **16** corresponded to the 1:1 adduct of **9b** and **3b**. The ir spectrum showed strong ester bands at 1712 and 1280, P=O band at 1265, and P—O—C bands at 1026 and 969 cm^{-1}, but no hydroxyl absorption band was observed. The nmr signal showed a 2 H singlet methylene signal and a typical 4 H CH_3–CH< signal composed of a doublet and a quintet;[6] this splitting was caused by a coupling of the methine proton with phosphor nucleus. Treatment of **16** with alcoholic sodium hydroxide gave **18** in a good yield. These data indicated that **16** had an analogous structure to that of **10** and it was concluded to be that of 2-(1-diethylphosphoroyl)ethyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium bromide. Upon reconsidering the matter of **10b**, the existence of C_6H_5—$CHOP(O)(OC_2H_5)_2$ systems was confirmed. The structure of **17** was determined on the basis of the following evidence. The ir spectrum showed an amide carbonyl band at 1665 cm^{-1}. The uv absorption spectrum showed a curve very similar to that of **8**. The nmr signal showed a typical CH_3—CH< signal composed of a doublet and a quartet. These data indicated that **17** had a structure analogous to **8**, and it was concluded to be that of 2,5-dimethyl-3-oxo-4-benzyl-6-(2-benzyloxy)-ethyl-2,3-dihydro-4H-1,4-thiazine. Compound **17** was hydrolyzed to give **18**.

Kinetic Studies of the Rearrangement of 10b in Alkaline Medium.—In the process of obtaining **8** from **10** a deprotonation might first occur on the benzyl group substituted at the C-2 position of the thiazole moiety by an alkaline treatment in a similar manner as observed for the change from **13** to **14**. The absorption maxima at 229 and 276 mμ of **10b** immediately disappeared by the addition of alkali, and simultaneously the strong maximum appeared at 373.5 mμ. The new absorption spectrum returned to that of **10b** again by an immediate addition of acid. The intensity of the band at 373.5 mμ decreased slowly and finally disappeared, and the spectrum indicated a similar pattern to that of **8** (uv max 229 and 282 mμ). Accordingly, it is probable that **10b** may be rearranged to **8** *via* **19** as an intermediate (Scheme V). The rate of the rearrangement of **19** to **8** was determined by measuring the successive decrease in the absorption intensity at 373.5 mμ as a function of time. Compound **8** was ob-

(6) J. W. Emsley, J Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Ltd., Oxford, England, 1966, p 1062.

SCHEME V



tained in nearly theoretical yield upon degradation of **10b** in the similar reaction conditions (See Experimental Section). Figure 1 shows examples of the behavior at 15 and 5°. These rate constants were obtained under excess hydroxide concentrations. The logarithms of the observed ϵ at 15 and 5° for the rearrangement of **18** to **8** were plotted against time. Over the time range between 30 sec and 60 min the plots were found to fit to a straight line with a slope of −0.031 and −0.016. The mean values of k_{calcd} from the data of Figure 1 and the equation $\log \epsilon = -0.4343\,kt + \log \epsilon_0$ are 1.19×10^{-3} and 6.11×10^{-4} M^{-1} sec^{-1} at 15 and 5°, respectively.

Reactions of 10b and 16 with Amines.—The alkaline treatment of **10b** or **16** produced **8** or **17** in good yields. The reaction of **10b** with methylamine gave a colorless solid, whose structure was assumed to be **20** (Scheme VI) with regard to the reaction between **10b** and sodium hydroxide affording **8**. The ir spectrum showed ester bands at 1720 and 1278, and a C=N band at 1633 cm^{-1}. In the uv spectrum, the absorption maxima appeared at 228 mμ (ϵ 22,500), 282 (3840), and 301 (4150); the latter maximum shifted to 311 (3340) by adding hydrochloric acid. The nmr spectrum showed a 2 H AB-type quartet benzyl signal at τ 4.04 and 5.39 (J = 16.0 Hz), a 1 H singlet signal at 4.82, and a singlet N-methyl signal at 6.97. These signals were changed by adding several drops of concentrated hydrochloric acid; namely, the benzyl methylene signal shifted to τ 3.76 and 4.90 as the AB quartet (J = 16.0 Hz); the 1 H singlet signal at 4.48; and the N-methyl signal at 6.85 as a doublet (J = 5.5 Hz). These data mentioned above support the structural relation between **20** and **20a**. Another possibility of the structure with thiazoline moiety in **20′** or of the equilibria of **20′a** ⇌ **20′b** was excluded by the uv and nmr data. Accordingly, the structure of **20** was concluded to be that of 2-phenyl-3-methylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine. The reaction of **10b** with benzylamine afforded **21** as a colorless oil in a good yield. The hydrochloride of **21** was obtained as colorless needles. The reaction of **10b** with ammonia similarly gave **22** as an oil. The reaction of **10b** with dimethylamine afforded a light brown oil (**23**), whose structure was confirmed by the following data. The ir spectrum showed a strong C=C band at 1582 cm^{-1}. The absorption maxima in the uv region appeared at 231 mμ (ϵ 25,500), 281 (7240), and 365 (2500). These absorption maxima disappeared by adding acid with the concurrent appearance of maxima at 228 mμ (ϵ 22,800) and 332 (3490). The nmr spectrum showed a 2 H singlet methylene signal at τ 5.38 and a 6 H singlet N-dimethyl signal at 7.56. On an addition of a proton, these signals shifted toward lower field, the former appeared at τ 4.24 and 4.69 as AB-type quartet, and the latter at 6.60 as a broad singlet. Furthermore,

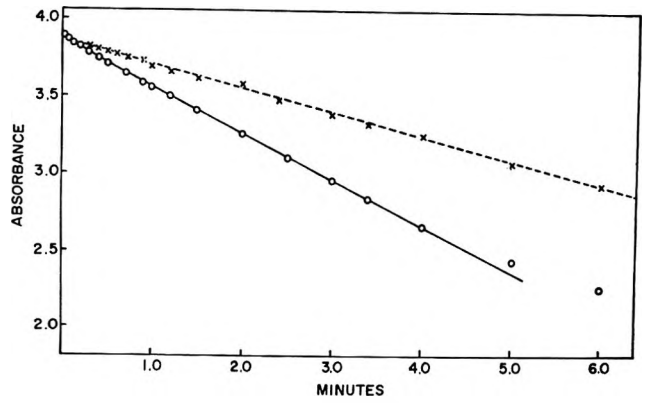


Figure 1.—Disappearance of 2-(1-diethylphosphoroyl)benzylidene-3-benzyl-4-methyl-5-(2-benzoyloxy)ethyl-4-thiazoline (**19**) at 15 (———) and 5° (– – – –).

a 1 H signal newly appeared at τ 4.17, which was assigned to the C-2 proton in **23a**. These spectral data indicate the unambiguous structure for **23** and the equilibrium between **23** and **23a**. The structures of **20**–**23** were also supported on the basis of the following evidence. The reaction of **16** with methylamine afforded **24** as colorless crystals. The ir spectrum showed a strong C=N band at 1619 cm^{-1}. The ultraviolet absorption spectrum showed maxima at 229 mμ (ϵ 20,800), 284 (4760), and 296 (5320) in a neutral medium; at 229 (20,400), 283 (2830), and 309 (3890) in an acidic medium. The nmr spectrum showed a 3 H singlet N-methyl signal at τ 6.99 and a typical 4 H CH_3—CH< signal as a doublet and a quartet. Contrary to our expectation **17** was obtained as an oil by the reaction of **16** with dimethylamine.

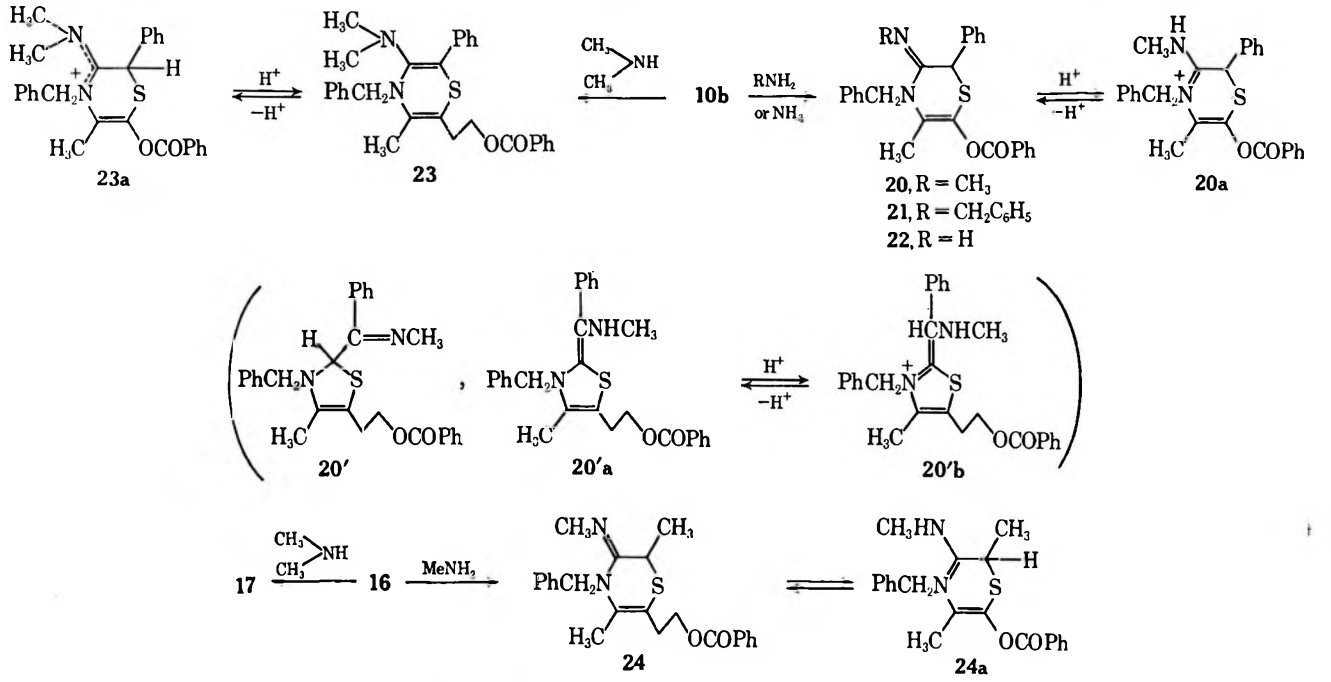
Discussion

As described above, **10** retains a thiazolium moiety which is expanded to give **8** by the presence of base. It seems probable that the reaction will proceed by way of Scheme VII. Previously we reported[7] that dialkyl acylphosphonates are convenient acylating agents. In this case, thiazolium ylide **a** produced by treatment of **9** with triethylamine reacts with the acylphosphonate to give betain **b**. This makes a nucleophilic attack on the pentavalent phosphorous to give a cyclic oxyphosphorane **c**. The benzyl carbon of the C_6H_5–C–P system in **c** is electron deficient; the rearrangement occurs easily and results in **10**. This assumption is supported by the fact that the reaction of **9** with **3b** proceeds more slowly than that of **9** with **3a** (see Experimental Section). In view of the spectral consideration mentioned above, it is obvious that **10** produces **d** by deprotonation, followed by a ring expansion to give **8**. Both spectral data and the experimental results support the assumption that the rearrangement reaction is first order.

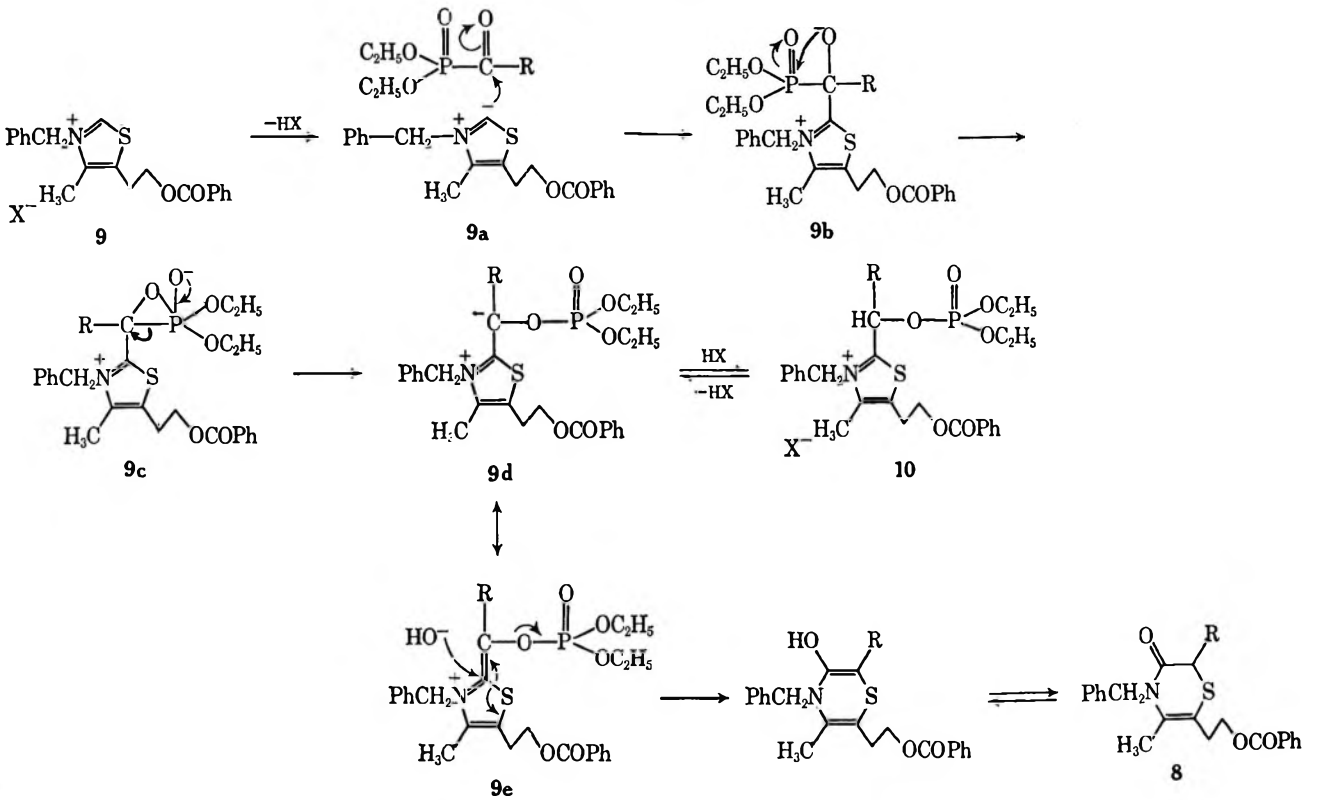
The mechanism of the reaction of thiamine with dialkyl acylphosphonate to give **4** can be easily and reasonably explained by the facts that **19**–**24** were produced from the reaction of **10b** or **16** with amines as described. In thiamine, the amino group at the pyrimidine C-4 position shows similar behavior to that of the amines described above and gives **4** by the way

(7) A. Takamizawa, Y. Sato, and S. Tanaka, *Yakugaku Zasshi*, **85**, 298 (1965).

SCHEME VI



SCHEME VII



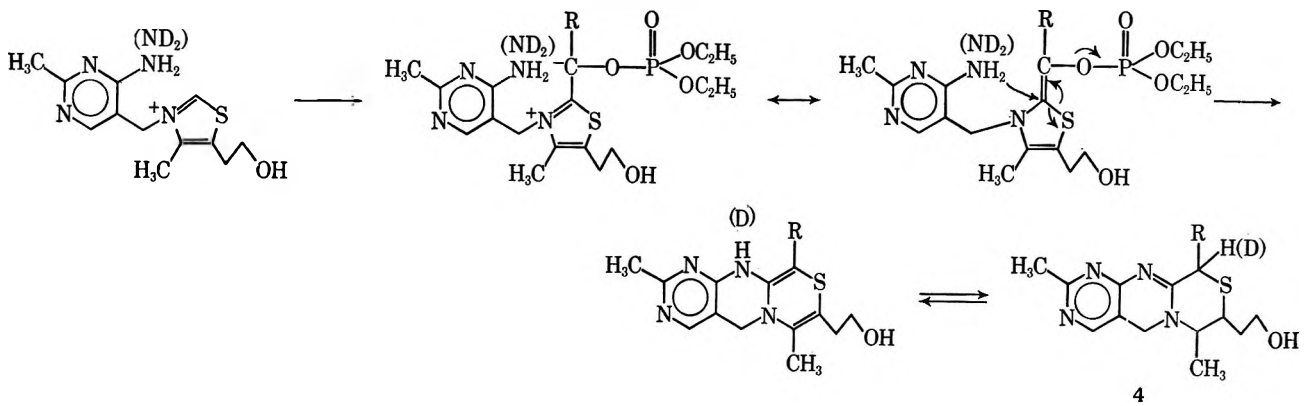
described in Scheme VIII. This assumption is also supported by the fact that, when deuterioaminothiamine was used, a deuterium on the pyrimidine C-4 amino group was introduced into the C-1 position of **4** as previously described.[2]

Various mechanisms have been reported on the Perkow reaction. Recently Hudson, *et al.*,[8] suggested that the enol phosphate formation proceeded most likely by the initial attack at carbonyl carbon followed by rearrangement of the phosphorous to carbonyl oxygen. More recently, from the data of the reaction of certain phenacyl bromides with triethyl phosphite, Borowitz, *et al.*,[9] suggested that the Perkow reaction involved an initial attack of triethyl phosphite on the carbonyl carbon followed by rearrangment to oxygen. The isolation of **10** and **16** in our case offers a suggestion for the elucidation of the Perkow reaction mechanism (Scheme IX).

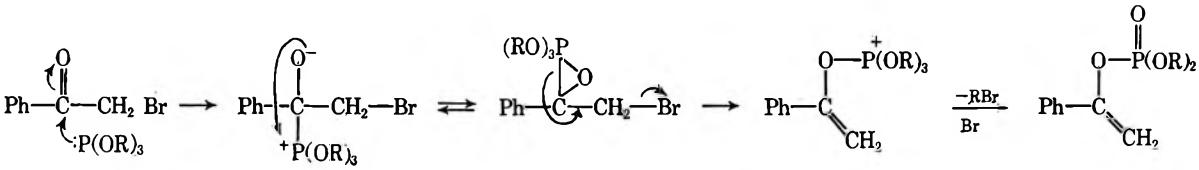
(8) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965).

(9) I. J. Borowitz, M. Anshel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

SCHEME VIII



SCHEME IX



Experimental Section[10]

2-(1-Diethylphosphoroyl)benzyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Halides (10a–c). 10a.—To an ice-cooled suspension of **9a** (3.73 g) and triethylamine (2.2 g) in N,N-dimethylformamide (40 ml) was added **3a** (2.42 g) in nitrogen atmosphere, and the mixture was stirred at 0–5° for 15 min; then the mixture reacted at room temperature for 15 hr resulting in a dark green solution. The solution was concentrated *in vacuo* leaving a green crystalline residue, which was washed with ether and acetone. The light green residue was recrystallized from acetonitrile or ethanol affording **10a** as colorless needles (5.18 g): mp 150–151° dec; ir (Nujol) 1716 and 1270 (COO), 1256 (P=O), and 1028, 1108, and 986 cm^{-1} (P—O—C).

Anal. Calcd for $C_{31}H_{35}ClNO_6PS$: C, 60.43; H, 5.72; Cl, 5.76; N, 2.28; P, 5.02; S, 5.20. Found: C, 60.12; H, 5.84; Cl, 6.06; N, 2.40; P, 4.83; S, 5.21.

10b was obtained by a method similar to that for **10a** using 2.01 g of **9b**, 1.1 g of triethylamine and 1.21 g of **3a** in N,N-dimethylformamide (20 ml). Recrystallization of the solid from ethanol gave colorless rhombs (2.83 g, 88%): mp 148° dec; uv max (95% C_2H_5OH) 230 mμ (ε 18,200), 271 (8720), and 276 (8740).

Anal. Calcd for $C_{31}H_{35}BrNO_6PS$: C, 56.36; H, 5.34; Br, 12.09; N, 2.12; P, 4.69; S, 4.85; C_2H_5O, 13.62. Found: C, 56.46; H, 5.43; Br, 11.84; N, 2.05; P, 4.39; S, 4.58; C_2H_5O, 13.64.

10c gave light brown needles (acetone): yield, 73.2%; mp 119° dec.

Anal. Calcd for $C_{31}H_{35}INO_6PS$: C, 52.62; H, 4.99; I, 17.95; N, 1.98; P, 4.32; S, 4.54. Found: C, 52.41; H, 5.14; I, 18.01; N, 1.92; P, 4.21; S, 5.12.

2-(1-Diethylphosphoroyl)benzyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Nitrate (10d).—To a solution of **10b** (0.21 g) in methanol (5 ml) was added 0.062 g of silver nitrate in water. Precipitated silver bromide was removed by centrifugation. The residue, after removal of the solvent, was extracted with chloroform. The extract was washed, dried, and concentrated leaving a colorless crystalline residue, which was recrystallized from methanol–benzene to give **10d** as colorless needles (0.15 g): mp 138–139°; ir (Nujol) 1340 and 1326 cm^{-1} (NO_3).

Anal. Calcd for $C_{31}H_{35}N_2O_9PS$: C, 57.93; H, 5.49; N, 4.36; P, 4.82; S, 4.99; Found: C, 57.85; H, 5.73; N, 4.26; P, 4.60; S, 5.78.

Similar reaction of **10a** or **10c** with silver nitrate also gave **10d** (83 and 62%, respectively).

Alkaline Degradation of 10a–d. General Procedure.—To 20 ml of 10% alcoholic sodium hydroxide (75%) was added 1.3 g of **10b**; the mixture was stirred at 10° for 2 hr, after which the mixture was concentrated and extracted with chloroform. The chloroform extract was washed, dried, and concentrated leaving a light brown oily residue, which crystallized on standing. Recrystallization from ether gave 0.79 g (89%) of **8** as colorless needles, mp 107–108°, which proved to be identical with an authentic sample by ir comparison.

Treatment of 10b with Equimolar Amount of Sodium Ethoxide.—To a cooled solution of 1.98 g of **10b** in 36 ml of ethanol was added dropwise 0.075 g of sodium in 6 ml of ethanol, and the mixture was stirred at −50° for 1.5 hr, after which the mixture was allowed to warm to room temperature and left overnight, The mixture was concentrated and extracted with chloroform. To the residue after removal of the solvent was added acetone precipitating colorless solid (0.45 g of **10b** recovered), which was filtered off and the filtrate was concentrated and submitted to silica gel chromatography. Elution with acetone gave a light brown oil, which was a mixture of three components. The mixture was rechromatographed over alumina and eluted with ether to give 0.04 g of ethyl benzoate (**11**) as the first fraction. From the second fraction was obtained 0.19 g of **8** as colorless crystals. From the following fraction was obtained 0.07 g of colorless crystals, mp 77–78°, which proved to be identical with **12** by mixture melting point and ir comparison.

Catalytic Hydrogenation of 10b with Palladium-Charcoal.—**10b** (0.66 g) was dissolved in 15 ml of methanol and hydrogenated at atmospheric pressure and room temperature over 1 g of 5% palladium-charcoal catalyst. Complete hydrogenation was observed after approximately 32 ml of hydrogen had been consumed within 15 min. The solution was freed of the catalyst by suction filtration and the filtrate was concentrated, neutralized, and extracted with chloroform. The crystalline residue after removal of the solvent was recrystallized from ether giving **14** as yellow plates (0.2 g): mp 107–108°; nmr ($CDCl_3$) τ 1.84–3.18 [m, 15, $(C_6H_5)_3$], 4.36 (s, 1, C_6H_5—CH=), 5.18 (s, 2, C_6H_5—CH_2—), 5.55 and 7.08 (t, 4, >—CH_2—CH_2—O—, J = 6.3 Hz), and 8.03 (s, 3, CH_3) in a neutral medium; 1.52–3.00 [m, 15, $(C_6H_5)_3$], 4.03 (s, 2, C_6H_5—CH_2—), 5.68 (s, 2, thiazole C_2—CH_2—C_6H_5), 5.50 and 6.61 (t, 4, >—CH_2—CH_2—O—, J = 6.2 Hz), and 7.52 (s, 3, CH_3) on addition of 2–3 drops of concentrated hydrochloric acid.

Anal. Calcd for $C_{27}H_{25}NO_2S$: C, 75.86; H, 5.90; N, 3.28; S, 7.49; mol wt, 427.54. Found: C, 75.93; H, 5.72; N, 3.29; S, 7.69; mol wt, 433 (chloroform).

Ozonolysis of 14.—Through a solution of **14** (0.05 g) in chloroform (15 ml) was passed 0.006 g of ozone at −30°; the mixture was stirred at the temperature for 30 min. The mixture was

(10) All melting points were obtained using a stirred Yamato Kagaku silicon oil bath. Infrared spectra were measured using a Jasco DS-201B recording spectrophotometer, and ultraviolet curves were obtained using a Hitachi EPS-3 recording spectrophotometer. Proton magnetic resonance spectra were obtained using a Varian A-60 apparatus with tetramethylsilane as the internal standard.

decomposed by the addition of 0.5 g of powdered zinc, 0.5 ml of acetic acid, and 1 ml of water. The mixture was filtered; the filtrate was neutralized with sodium carbonate; and the chloroform layer was separated. The residue after removal of the solvent was submitted to alumina chromatography and eluted with ether. From the first fraction was obtained 0.003 g of benzldehyde, which was identical with authentic benzaldehyde as shown by gas chromatographical identification. From the second fraction was obtained 0.005 g of colorless crystals, mp 76–78°, which were proved to be identical with **12** by infrared comparison.

2-(Diethylphosphoroyl)ethyl-3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium Bromide (16).—To a solution of 2.09 g of **9b** in 15 ml of N,N-dimethylformamide was added 1.1 g of triethylamine, and the mixture was stirred for 20 min, after which 0.9 g of **3b** was added; the mixture was allowed to react at room temperature for 8 hr and left overnight. The reaction mixture was concentrated *in vacuo*, and the resulting oil was extracted with acetone (0.27 g of triethylamine hydrobromide was obtained as insoluble material). The extract was concentrated; the residue, after washing with hot ether, was dissolved in chloroform and submitted to the silica gel column chromatography to yield **16** as a light brown oil (1.8 g): R_f 0.12 (SiO_2–methanol) and R_f 0.46 (SiO_2–acetone); nmr ($CDCl_3$) τ 1.92–2.97 [m, 10, $(C_6H_5)_2$], 3.90 (quintet, 1, CH_3–CH–O–P, $J_{HH} = J_{PH} = 6.5$ Hz), 4.02 (s, 2, $C_6H_5CH_2$–), 5.35 (t, 2, >CH_2–CH_2–O–, $J = 5.6$ Hz), 5.96 (quintet of doublets, 2, CH_3–CH_2–O, $J_{HH} = J_{PH} = 7.0$ Hz), 5.98 (quintet of doublets, 2, CH_3–CH_2–O, $J_{HH} = J_{PH} = 7.0$ Hz), 6.52 (t, 2, >CH_2–CH_2–O, $J = 5.6$ Hz), 7.54 (s, 3, CH_3), 8.05 (d, 3, CH_3–CH<, $J = 6.5$ Hz), 8.75 (triplet of doublets, 3, CH_3–CH_2–O, $J_{HH} = 7.1$ Hz, $J_{PH} = 1.0$ Hz), and 8.78 (triplet of doublets, 3, CH_3–CH_2–O, $J_{HH} = 7.1$ Hz, $J_{PH} = 1.0$ Hz).

Anal. Calcd for $C_{26}H_{33}BrNO_6PS$: C, 52.17; H, 5.56; Br, 13.35; N, 2.34; P, 5.18. Found: C, 53.00; H, 5.87; Br, 12.96; N, 2.41; P, 5.29.

The ether extract was submitted on alumina column chromatography. Elution with ether gave 0.35 g of **17** as a colorless oil: ir (film) 1718, 1276 (COO), and 1665 cm^{-1} (CO); uv max (95% C_2H_5OH) 229.5 mμ (ϵ 17,900), 276 (2890) shoulder, 282 (3130), 292 (2580) shoulder; nmr ($CDCl_3$) τ 1.93–2.63 [m, 10, $(C_6H_5)_2$], 2.82 (s, 5, C_6H_5–CH_2–), 4.91 and 5.55 (AB quartet, 2, C_6H_5–CH_2–, $J = 16.0$ Hz), 5.55 (t, 2, >CH_2–CH_2–O, $J = 6.5$ Hz), 6.60 (q, 1, CH_3–CH<, $J = 6.8$ Hz), 7.35 (t, 2, >CH_2–CH_2–O, $J = 6.5$ Hz), 8.07 (s, 3, CH_3), and 8.54 (d, 3, CH_3–CH<, $J = 6.8$ Hz).

Anal. Calcd for $C_{22}H_{23}NO_3S$: C, 69.27; H, 6.08; N, 3.67; S, 8.39. Found: C, 68.90; H, 6.21; N, 4.09; S, 8.58.

Alkaline Treatment of 16. A.—To a cooled solution of 0.3 g of sodium in 10 ml of ethanol was added dropwise an ethanol solution of **16** (1.0 g). The temperature was maintained for 1.5 hr below 5°, after which the mixture was stirred at room temperature for 2 hr. The residue, after removal of the solvent, was extracted with chloroform and chromatographed over alumina. Elution with ether gave 0.2 g of **18** as a colorless oil: R_f 0.42 (alumina–ether); ir (film) 3380, 1045 (OH), and 1652 cm^{-1} (CO); uv max (95% C_2H_5OH) 230 mμ (ϵ 5920) shoulder and 290 (2460); nmr ($CDCl_3$) τ 2.76–2.83 (m, 5, C_6H_5), 5.00 and 5.27 (AB quartet, 2, C_6H_5–CH_2–, $J = 16.5$ Hz), 6.58 (t, 2, >CH_2–CH_2–O, $J = 6.5$ Hz), 6.73 (q, 1, CH_3–CH<, $J = 7.1$ Hz), 7.67 (t, 2, >CH_2–CH_2–O, $J = 6.5$ Hz), 8.23 (s, 3, CH_3), and 8.66 (d, 3, CH_3–CH<, $J = 7.1$ Hz).

Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.96; H, 6.91; N, 5.05; S, 11.55. Found: C, 64.72; H, 7.17; N, 5.01; S, 11.50.

B.—A solution of **16** (0.3 g) in 15 ml of 10% sodium hydroxide–ethanol was warmed at 60° for 1.5 hr, after which the mixture was concentrated and extracted with chloroform. The extract was washed, dried, and concentrated leaving oily residue, which was chromatographed over alumina. Elution with ether gave 0.08 g of colorless oil, which proved to be identical with **18** obtained above (A) by infrared comparison.

2-Phenyl-3-methylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)-ethyl-2,3-dihydro-4H-1,4-thiazine (20) was obtained as colorless plates (ether) by a method similar to that mentioned using methylamine and **10b**: mp 123–124°; yield, 87.2%.

Anal. Calcd for $C_{28}H_{28}N_2O_2S$: C, 73.66; H, 6.18; N, 6.14; O, 7.01; S, 7.02; mol wt, 456.58. Found: C, 73.43; H, 6.22; N, 6.19; O, 7.29; S, 6.78; mol wt, 453 (acetone).

2-Phenyl-3-benzylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)-ethyl-2,3-dihydro-4H-1,4-thiazine (21) was obtained as light brown oil by a method similar to that mentioned using benzylamine and **10b**. The hydrochloride, was obtained as colorless needles from methanol–acetone: mp 198–200° dec; ir (Nujol) 1711, 1281 (COO), and 1586 cm^{-1} (C=N); nmr (D_2O) τ 2.15–2.80 [m, 10, $(C_6H_5)_2$], 2.86 (s, 5, C_6H_5), 3.53 and 4.86 (AB quartet, 2, $J = 17.1$ Hz), 4.86 (s, 1, C_6H_5—CH<), 5.03 and 5.45 (AB quartet, 2, $J = 16.0$ Hz).

Anal. Calcd for $C_{34}H_{33}ClN_2O_2S$: C, 71.78; H, 5.85; Cl, 6.23; N, 4.92; O, 5.62; S, 5.63. Found: C, 71.65; H, 5.97; Cl, 6.43; N, 4.99; O, 5.90; S, 5.58.

2-Phenyl-3-imino-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (22).—To an ice-cooled and stirred 8% alcoholic ammonia solution (20 ml) was added dropwise 1.0 g of **10b** in ethanol. The temperature was maintained for 1 hr below 5°, after which the mixture was stirred at room temperature for 2 hr. The residue, after removal of the solvent and excess of ammonia, was extracted with chloroform. The chloroform extract was washed, dried, and concentrated leaving an oily residue, which was not crystallized and not distillable. The hydrochloride (0.4 g) was obtained as colorless cubes [mp 190° dec; ir (Nujol) 1720, 1276 (COO) and 1598 cm^{-1} (C=N)].

Anal. Calcd for $C_{27}H_{27}ClN_2O_2S$: C, 67.70; H, 5.68; Cl, 7.40; N, 5.68; O, 6.68; S, 6.69. Found: C, 68.45; H, 5.96; Cl, 7.67; N, 5.77; O, 6.72; S, 6.76.

2-Phenyl-3-dimethylamino-4-benzyl-5-methyl-6-(2-benzoyloxy)-ethyl-4H-1,4-thiazine (23).—To a stirred and ice-cooled 10% dimethylamine solution in ethanol (20 ml) was added 1.5 g of **10b** in ethanol. The temperature was maintained for 2 hr below 5°, after which the mixture was stirred at room temperature for 5 hr. After removal of the solvent and excess of dimethylamine, the residue was extracted with chloroform. The chloroform extract was washed, dried, and concentrated leaving an oily residue. The residue was purified by alumina column chromatography, and **23** was obtained as a light brown oil (0.4 g).

Anal. Calcd for $C_{29}H_{30}N_2O_2S$: C, 74.01; H, 6.42; N, 5.95; S, 6.81. Found: C, 74.02; H, 6.65; N, 5.40; S, 6.55.

2-Methyl-3-methylimino-4-benzyl-5-methyl-6-(2-benzoyloxy)-ethyl-4H-1,4-thiazine (24).—To a cooled solution of **16** (1.0 g) in ethanol (15 ml) was added 10 ml of alcoholic methylamine (8.6%). The temperature of the mixture was maintained for 2 hr below 10°, after which the mixture was stirred at room temperature for 1 hr. After removal of the solvent and excess of methylamine the residue was extracted with chloroform. The chloroform extract was washed, dried, and submitted to the alumina-column chromatography. Elution with ether gave a mixture of two compounds as yellow oil (0.28 g), which was rechromatographed over silica gel. Elution with ether gave 0.025 g of colorless oil, which proved to be identical with **17** by infrared comparison. From the second fraction was obtained crystals, which were recrystallized from ether to give **24** as colorless rhombs (0.13 g): mp 90–92°; nmr ($CDCl_3$) τ 1.95–2.67 (m, 5, C_6H_5), 2.85 (s, 5, C_6H_5—CH_2—), 4.49 and 5.33 (AB quartet, 2, C_6H_5—CH_2—, $J = 16.0$ Hz), 5.58 (t, 2, >—CH_2—CH_2—O, $J = 6.3$ Hz), 5.95 (q, 1, CH_3—CH<, $J = 7.0$ Hz), 6.99 (s, 3, =N—CH_3), *ca.* 7.4 (m, 2, >—CH_2—CH_2—O), 8.06 (s, 3, C_5—CH_3), and 8.69 (d, 3, CH_3—CH<, $J = 7.0$ Hz); nmr ($CDCl_3$ + 3 drops of concentrated HCl) τ 1.96–2.63 (m, 5, C_6H_5), 2.77 (s, 5, C_6H_5—CH_2—), 4.23 and 4.87 (AB quartet, 2, C_6H_5—CH_2—, $J = 17.0$ Hz), 5.35 (t, 2, >—CH_2—CH_2—O, $J = 6.0$ Hz), 5.75 (q, 1, CH_3CH<, $J = 7.0$ Hz), 6.82 (d, 3, N—CH_3, $J = 5.0$ Hz), 7.23 (m, 2, >—CH_2—CH_2—O) and 8.57 (d, 3, CH_3—CH<, $J = 7.0$ Hz).

Anal. Calcd for $C_{23}H_{26}N_2O_2S$: C, 70.03; H, 6.64; N, 7.10; S, 8.12. Found: C, 70.17; H, 6.85; N, 7.04; S, 7.96.

Reaction of 16 with Dimethylamine.—To a solution of **16** (1.0 g) in ethanol (15 ml) was added 10 ml of alcoholic dimethylamine (10%) with stirring. The temperature was maintained for 3 hr below 10°, after which the mixture was stirred at room temperature for 5 hr. After removal of the solvent and excess of dimethylamine, the residue was extracted with chloroform. The chloroform extract was washed, dried, and submitted to the alumina chromatography.

Elution with ether gave brown oils, which were rechromatographed over silica gel. First 0.18 g of colorless oil was obtained, which proved to be identical with **17** obtained above by ir comparison. From the second fraction was obtained light brown crystals, which were recrystallized from ether to give 0.01 g of **12** as colorless crystals, mp 75–77°, undepressed by admixture with an authentic sample.

Alkaline Hydrolysis of 17.—A solution of **17** (0.5 g) and sodium hydroxide (1.0 g) in diluted ethanol (10 ml) was stirred at room

temperature for 5 hr; the mixture was concentrated and extracted with chloroform. The chloroform extract was washed, dried, and concentrated to leave light brown oil. The residue was chromatographed over alumina. Elution with ether gave 0.32 g of **18** as colorless oil, which proved to be identical with an authentic sample by ir comparison.

Kinetic and Rate Constant Measurements.—The rates of rearrangement of 2-(1-diethylphosphoroyl)benzyliden-3-benzyl-4-methyl-5-(2-benzoyloxy)ethyl-4-thiazoline (**19**) were measured by following the decrease of the intensity at 373.5 mμ, using a Hitachi EPS-3 spectrophotometer equipped with a thermostated cell holder. A solution containing 2.9 ml of 9.3×10^{-1} *M* **10b** in 95% ethanol was prepared in 4 ml with 1-cm cuvettes and temperature equilibration. Reaction was initiated by the addition of 0.1 ml of temperature-equilibrated solution of 6.06×10^{-2} *M* sodium hydroxide in 95% ethanol from a blow-out pipet, followed by rapid mixing with hands. The first reading of intensity was taken about 15 sec after the addition, and thereafter readings were taken at 10-sec intervals during 2 min, after which readings were taken at 30-sec intervals. All the plots of log ε against time were linear for at least 50 min. The rate constants were reproducible within ±4% of the average. The extinction coefficient of 19 at 373.5 mμ in 2×10^{-3} *N* NaOH at 15° was obtained by extrapolating of the plot of log ε against time to the moment at which sodium hydroxide solution was added into ethanolic solution of **10b**. Five determinations gave values between 8210 and 8450 M^{-1} cm^{-1}, with an average of 8300 M^{-1} cm^{-1}.

Product Identification.—The uv spectrum of a solution that initially contained 9.3×10^{-5} *M* **10b** in 95% ethanol containing 2×10^{-3} sodium hydroxide showed, after complete disappearance of the absorbance at 373.5 mμ, a band with uv max (95% C_2H_5OH) 229 mμ (ε 17,500) and 282 (3320). Under the same condition the spectrum of authentic 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**8**) had uv max (95% C_2H_5OH) 229 mμ (ε 18,000) and 282 (3410).

Registry No.—**10a**, 17511-94-3; **10b**, 17511-95-4; **10c**, 17511-96-5; **10d**, 17511-97-6; **14**, 17528-36-8; **16**, 17528-37-9; **17**, 17511-98-7; **18**, 17528-38-0; **20**, 17511-99-8; **21** HCl, 17512-00-4; **22**, 17528-39-1; **23**, 17512-01-5; **24**, 17512-02-6.

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Synthesis and Determination of the Absolute Configurations of the Enantiomeric 1,2-Epoxy-1-phenylcyclohexanes

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The enantiomeric forms of 1,2-epoxy-1-phenylcyclohexane have been prepared through a sequence involving conversion of the racemic epoxide into a mixture of 1-phenyl- and 2-phenyl-*trans*-2-dimethylaminocyclohexanols, separation and resolution of this mixture with tartaric and dibenzoyltartaric acids, and reconversion of the resolved amino alcohols into the epoxide. The absolute configurations and optical purities of the (+)-epoxide and of several other phenylcyclohexane derivatives have been determined through a series of stereospecific reactions leading to (+)-2-phenyladipic acid; application of the partial resolution method of Horeau to two of the intermediates has provided further confirmation for the stereochemical assignments.

The optically active forms of 1,2-epoxy-1-phenylcyclohexane (**2**) were needed for an extention of previous work on the stereochemistry of the ring opening of aryl-substituted cyclohexene oxides.[1-3] Since no practical method could be seen for a direct resolution of the racemic epoxide, a preparation involving cyclization of an appropriate optically active precursor appeared as the most promising approach. Racemic **2** was therefore treated with aqueous dimethylamine under pressure; this reaction had been repeatedly reported to give exclusively the amino alcohol **3**,[4-6] but it was found that the product actually consisted of a mixture of the two *trans* compounds **1** and **3**, in a ratio of about 1:2, and of some of the *cis* glycol **13**. The latter product evidently derives from the hydrolysis of **2**, which is known to proceed exclusively by *cis* opening of the ring in the absence of acids.[7]

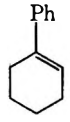
The necessity of separating the two amino alcohols **1** and **3** prior to their resolution introduced an unforeseen complication in the planned route to the optically active epoxide; luckily enough, however, it was found that the separation of isomers and the resolution could be easily carried out in one sequence, since the (+)-tartrate of (−)-**3** crystallized out in fairly good purity on treatment of the crude mixture of bases with (+)-tartaric acid. A subsequent treatment of the bases recovered from the mother liquor with (−)-dibenzoyltartaric acid gave the corresponding salt of (+)-**1**. The separation–resolution could be completed by further treatments with (−)-tartaric acid and (+)-dibenzoyltartaric acid, which led to the isolation of (+)-**3** and (−)-**1**. About 70% of the initial mixture was thus recovered in the form of bases of high optical purity.

The structures of the isomeric amino alcohols **1** and **3** were assigned on the basis of the fact that (+)-**1** was easily oxidized with Jones reagent to the ketone (−)-**4**, while (+)-**3** was recovered unchanged from a similar treatment.

The amino alcohols **1** and **3** were reconverted into the epoxide **2** through the corresponding quaternary hydroxides. Both (−)-**1** and (+)-**3** gave the dextrorotatory epoxide **2**; (+)-**1** and (−)-**3**, the levorotatory enantiomer. All four products had specific rotations of at least ±117°, the highest value observed being +121.2° (in benzene). The close coincidence of the four values indicates that 121.2° probably corresponds very nearly to optical purity. This was confirmed

(1) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965).
(2) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *ibid.*, **22**, 189 (1966).
(3) G. Berti, B. Macchia, and F. Macchia, *ibid.*, **24**, 1755 (1968).
(4) J. Levy and J. Sfiras, *Bull. Soc. Chim. Fr.*, **49**, 1837 (1931).
(5) A. M. Mandrou, P. Potin, and R. Wylde-Lachazette, *ibid.*, 1546 (1962).
(6) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 4835 (1963).
(7) C. L. Stevens, H. T. Hanson, and K. G. Taylor, *J. Amer. Chem. Soc.*, **88**, 2769 (1966).

by a sequence leading from (+)-**2** to (+)-2-phenyladipic acid (**10**). Reaction of (+)-**2** with potassium hydroxide in dimethyl sulfoxide–water gave the *trans* glycol (+)-**5**; it had been shown before with the racemic epoxide that this reaction yields exclusively the *trans* isomer.[8] Treatment of (+)-**5** with hydrogen chloride in chloroform led to the *trans* chlorohydrin (+)-**6**, which was reduced catalytically to (+)-*cis*-2-phenylcyclohexanol (**8**); the latter two reactions had been found to proceed with retention of configuration,[2] when applied to the racemic compounds. (+)-**8** was converted through the methylxanthate (+)-**7** into (+)-3-phenylcyclohexene (**9**), a reaction which was known to yield this olefin contaminated by less than 4% 1 isomer (**11**);[9,10] this was confirmed by glpc, which showed that in the product of the pyrolysis of (+)-**7** the ratio of **9** to **11** was 98:2. (+)-**9** was converted through oxidation with osmium tetroxide, followed by cleavage with chromium trioxide, into (+)-2-phenyladipic acid (**10**);[11] some 4-benzoylbutyric acid (**12**) was also formed. Since (+)-**10**



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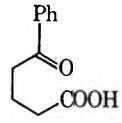

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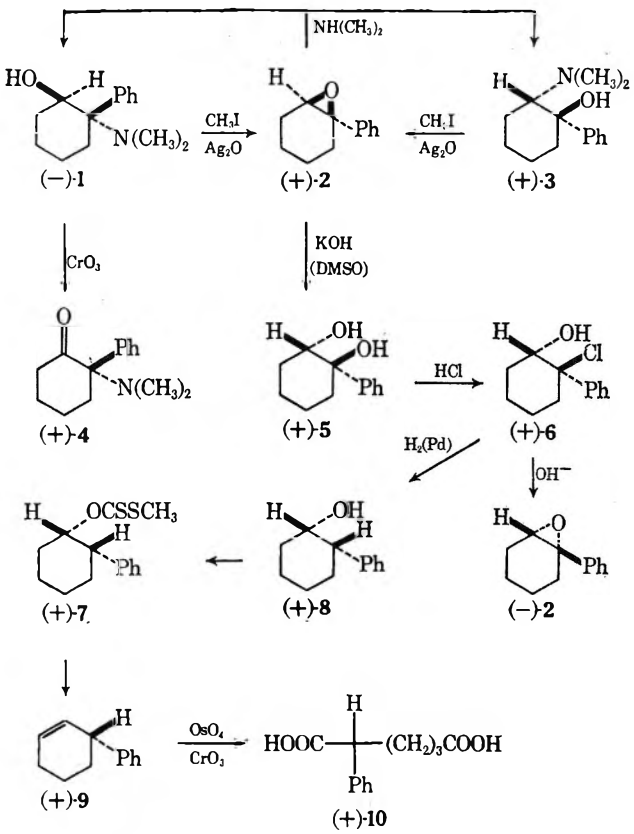
had been assigned the *S* configuration it was possible to deduce the absolute configuration of (+)-**2** and of all the compounds shown in Chart I.

CHART I

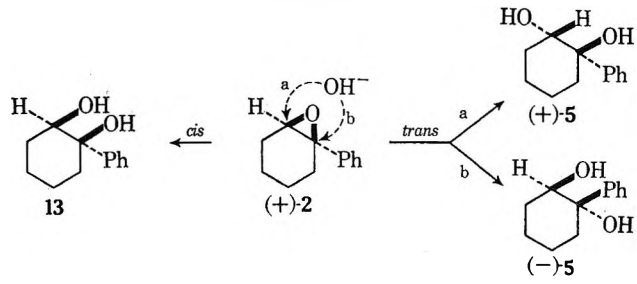


(8) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron Lett.*, 3421 (1965).
(9) E. R. Alexander and A. Mudrak, *J. Amer. Chem. Soc.*, **72**, 1810 (1950).
(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 103.
(11) L. Westman, *Ark. Kemi*, **12**, 167 (1958).

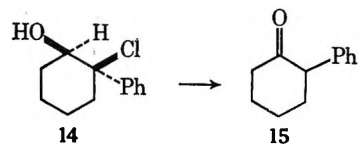
In all the reactions involved in the correlation between (+)-**2** and (+)-**10**, recrystallizations were avoided as much as possible to prevent changes in optical purity due to fractionations during purifications; crude mixtures were used for the subsequent steps, or, when necessary, purifications through absorption chromatography were employed. A recrystallization was used for the purification of the xanthate (+)-**7**; however, the purified ester was correlated directly with the precursor (+)-**8** through hydrolysis, and a corresponding correction was applied to the final calculation. Also the acid (+)-**10** had to be recrystallized to separate it from **12**, but it was possible to recover it completely, and no optical activity remained in the mother liquor.

A closer examination of the reactions in Chart I shows that, although several of them could take place with formation of more than one diastereoisomer, only the conversion of **2** into **5** (and possibly that of **9** into **10**) could lead to some racemization, since only one of two chiral atoms is involved in the other ones. As far as reaction **2** → **5** is concerned, three steric courses could be anticipated, as shown in Chart II;

CHART II



one, involving a *cis* opening of the oxirane ring to give the glycol **13**, would be rather unlikely for the alkaline hydrolysis of an epoxide and was ruled out by gas chromatographic analysis of the product. On the other hand, the *trans* opening could take place by attack either on C-2 (path) or C-1 (path b), leading, respectively, to (+)-**5** or (−)-**5**; if both modes of attack are operative some racemization must take place. This point was clarified by reconversion of the crude glycol into the epoxide **2**, through transformation into the chlorohydrin **6** and treatment of the latter with base. The displacement **5** → **6** had been shown to take place exclusively on the benzylic hydroxyl group and essentially in a *cis* stereospecific way;[2] however, even if some of the *cis* chlorohydrin (**14**) were formed, it would not interfere with the stereochemical correlation, as this compound would not give any epoxide in the treatment with base, the ketone **15** being formed instead. The epoxide obtained from



14 **15**

(+)-**6** was found after chromatographic purification to be enantiomeric with the starting epoxide, its specific rotation having been reduced to 88.6% of the initial value. For the reasons stated above the racemization

Table I

Configurations and Specific Rotations

Compound	Configuration	[α]D max obsd (temp, solvent)	[α]D max calcd on the basis of ±121.2° for 2
(−)-1	1*R*,2*S*	−31.9° (24°, benzene)	−31.9°
(+)-2	1*R*,2*R*	+121.2° (24°, benzene)	+121.2°
(+)-3	1*R*,2*S*	+14.9° (24°, benzene)	+14.9°
(−)-3 HCl	1*R*,2*S*	−24.9° (22°, water)	−24.9°
(−)-4	*S*	−65.9° (23°, benzene)	
(+)-5	1*R*,2*S*	+51.0° (27°, benzene)	+53.6°
(+)-6	1*S*,2*R*	+13.7° (24°, benzene)	+14.1°
(+)-7	1*S*,2*S*	+73.3° (29°, chloroform)	+76.6°
(+)-8	1*S*,2*S*	+97.8° (30°, benzene)	+102.2°
(+)-9	*R*	+149.7° (29°, benzene)	+159.6°
(+)-10	*S*	+61.0° (25°, abs ethanol)	+63.4°

can only take place in the passage from **2** to **5**; therefore the result indicates that this reaction goes for about 94% by path a and 6% by path b, in accordance with the fact that SN2-type displacements on epoxides are more sensitive to steric factors than to the bond-weakening effects caused by aryl substituents.[3,12] In the similar reaction between **2** and dimethylamine the percentage of attack on the benzylic carbon to give the amino alcohol **1** is higher; probably, in this case, in the presence of a weaker base the transition state has more of a "borderline SN2" character.[12]

The catalytic reduction of crude (+)-**6** gave mostly (+)-*cis*-2-phenylcyclohexanol (**8**) containing only a small amount of the *trans* isomer. The latter, which could originate either from a contamination of **6** with some **14**, or from an incomplete stereospecificity of the reduction, was easily eliminated by column chromatography.

When the specific rotation found for (+)-**10** was corrected for the racemization involved in the step **2** → **5** and for the changes in optical purity occurring in some of the purifications, a value of [α]D +63.4° was calculated for the acid **10** corresponding to a starting epoxide with [α]D +121.2°; the highest one reported in the literature for the acid is [α]D +63.8°,[11] a fact which confirms that 121.2° must be very near to the specific rotation for the optically pure epoxide **2**. Scheme I gives the numerical values used in the correlation of (+)-**2** with (+)-**10**, while Table I summarizes the specific rotations that were calculated for all compounds in Chart I.

Scheme I

Correlation of (+)-2 with (+)-10[a]

(+)-**2** (+116.6°; 96.2%) → (+)-**5** (. . . ; 85.2%)

↓

(+)-**8** (+87.1°; 85.2%) ← (+)-**6** (. . . ; 85.2%) → (−)-**2** (−103.3°; 85.2%)

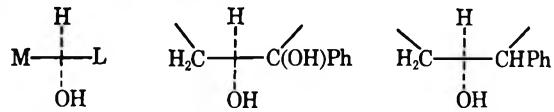
(+)-**8** (+92.9°; 90.9%) → (+)-**7** (+73.3°; 95.7%)[b] → (+)-**8** (+97.8°; 95.7%)

↓

(+)-**10** (+60.7°; 95.7%) ← (+)-**9** (+152.7°; 95.7%)[c]

[a] Values in parentheses indicate [α]D and optical purity, based on [α]D +121.2° for (−)-**2**. [b] Recrystallized product. [c] Corrected for the presence of 2% 1-phenylcyclohexene.

Since the absolute configuration of **10** had been determined by the method of quasiracemates,[11] which, although usually quite reliable, cannot be considered as a complete proof, we checked the configurational attributions by applying the partial resolution method of Horeau[13,14] to the alcohols (+)-**5** and (+)-**8**. In both cases the recovered 2-phenylbutyric acid was levorotatory, and the optical yield was around 50%. This is in good agreement with the assigned configurations as, according to the rules of Horeau, the recovery of levorotatory acid indicates configuration **16** for the chiral center, which would correspond to configurations **17** and **18** for C-2 of (+)-**5** and (+)-**8**. The tertiary hydroxy group of (+)-**5** is apparently not esterified even in the presence of a large excess of 2-phenylbutyric anhydride.



16 **17** **18**

It may also be pointed out that the configurational assignments discussed above are in good agreement with those that can be deduced from the semiempirical rules of Brewster for cyclohexane derivates.[15]

Experimental Section[16]

Reaction of 1,2-Epoxy-1-phenylcyclohexane [(±)-2] with Dimethylamine.—A mixture of (±)-**2**[1] (66 g, 0.38 mol) and 40% aqueous dimethylamine (250 ml, 2.2 mol) was heated at 150° for 24 hr in a magnetically stirred 1-l. autoclave. The product was extracted with three 200-ml portions of ether; the ether solution, after washing with water (200 ml) and thorough extraction with 1 *N* hydrochloric acid, left on evaporation a neutral crystalline residue (12.5 g) of slightly impure 1-phenyl-*cis*-cyclohexane-1,2-diol (**13**).[1] The acidic extract was made alkaline with 32% aqueous ammonia and extracted three times with 200 ml of ether; the ether was evaporated, and the residue was distilled; the product [54 g; bp 100–120° (0.2 mm); n^{24}D 1.5478] was a mixture of 1-phenyl-*trans*-2-dimethylaminocyclohexanol (**3**) and 2-phenyl-*trans*-2-dimethylaminocyclohexanol (**1**).

Separation and Resolution of the Mixture of 1 and 3.—A solution of the mixture of amino alcohols described above (66.1 g, 0.30 mol) in 312 ml of 95% ethanol was heated at 60–70° and treated with (+)-tartaric acid (47 g, 0.31 mol) in 312 ml of 95% ethanol. The precipitate was collected after one night. Salt A (20 g) was obtained: mp 177–179°; [α]^{23}D +29.2° (*c* 1.28, H_2O). A sample was crystallized repeatedly from ethanol to give pure (1*S*,2*R*)-1-phenyl-*trans*-2-dimethylaminocyclohexanol (+)-tartrate: needles; mp 180–183°; [α]^{24}D +30.1° (*c* 1.35, H_2O).

Anal. Calcd for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37. Found: C, 58.23; H, 7.39.

The mother liquor of salt A was evaporated to dryness *in vacuo;* the residue was taken up in 900 ml of water, treated with 10% aqueous sodium hydroxide (200 ml), and extracted with ether. The mixture of bases obtained on evaporation of the ether layer (54.1 g) was dissolved in 95% ethanol (300 ml) and water (55 ml), treated with a hot solution of (−)-dibenzoyltartaric acid monohydrate (96.6 g, 0.257 mol) in ethanol (330

(12) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(13) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(14) R. Weidmann and A. Horeau, *Bull. Soc. Chim. Fr.*, 117 (1967).

(15) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5483, 5493 (1959).

(16) Melting points were determined on a Kofler hot stage and are uncorrected. Ir spectra were taken with a Perkin-Elmer Infracord Model 137 or a Perkin-Elmer 237 grating spectrophotometer and uv spectra with a Beckman Model DU spectrophotometer. Gas–liquid partition chromatograms were run on a Carlo Erba Fractovap Model GV apparatus with a flame ionization detector. Optical rotations were determined with a Perkin-Elmer 141 photoelectric polarimeter. Comparisons between compounds were made on the basis of their ir spectra. Petroleum ether refers to the fraction with bp 30–50°. Magnesium sulfate was used as the drying agent, unless stated otherwise.

ml) and water (55 ml), and stored overnight. (1*S*,2*R*)-2-Phenyl-*trans*-2-dimethylaminocyclohexanol (−)-dibenzoyltartrate (salt B, 20.5 g) crystallized out. An analytical sample was obtained from ethanol–water as blades: mp 190–192°; $[\alpha]^{24}D$ −32.3° (*c* 1.0, N,N-dimethylformamide).

Anal. Calcd for $C_{32}H_{35}NO_9$: C, 66.54; H, 6.11. Found: C, 66.16; H, 6.24.

The free bases (44 g), recovered as described above from the mother liquor of salt B, were dissolved in ethanol (210 ml) and treated with (−)-tartaric acid (30 g) in ethanol (210 ml) to yield practically pure (1*R*,2*S*)-1-phenyl-*trans*-2-dimethylaminocyclohexanol (−)-tartrate (salt C, 32.8 g): mp 180–181°; $[\alpha]^{24}D$ −30.2° (*c* 0.52, H_2O).

Anal. Calcd for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37. Found: C, 58.34; H, 7.52.

The free bases (22.6 g), recovered from the mother liquor of salt C, dissolved in ethanol (200 ml) and water (33 ml), and treated with (+)-dibenzoyltartaric acid monohydrate (38.0 g) in ethanol (200 ml) and water (33 ml), yielded (1*R*,2*S*)-2-phenyl-*trans*-2-dimethylaminocyclohexanol (+)-dibenzoyltartrate (salt D, 24.9 g, mp 186–188°), which was crystallized from ethanol–water to give blades: mp 192–193°; $[\alpha]^{25}D$ +26.8° (*c* 0.56, N,N-dimethylformamide).

Anal. Calcd for $C_{32}H_{35}NO_9$: C, 66.54; H, 6.11. Found: C, 66.51; H, 6.11.

(1*S*,2*R*)-(−)-1-Phenyl-*trans*-2-dimethylaminocyclohexanol [(−)-3].—A solution of salt A (20.0 g) in water (200 ml) was treated with 10% aqueous NaOH (50 ml) and extracted with ether. The washed (H_2O) and dried ether extract gave after evaporation an oily residue of (−)-**3** (11.6 g, 18% yield, calculated on the starting mixture of amino alcohols), $[\alpha]^{23}D$ −14.9° (*c* 1.29, C_6H_6). The hydrochloride, prepared with hydrogen chloride in ether, was crystallized from ethanol–ether: mp 160–161° [(±)-**3** HCl, lit.[7] mp 204–206°]; $[\alpha]^{22}D$ +24.6° (*c* 0.33, H_2O).

Anal. Calcd for $C_{14}H_{22}ClNO \cdot {}^1/_2H_2O$: C, 63.50; H, 8.76; N, 5.29. Found: C, 63.54; H, 8.92; N, 4.93.

(1*R*,2*S*)-(+)-1-Phenyl-*trans*-2-dimethylaminocyclohexanol [(+)-3].—The base obtained from salt C (19.0 g, 28% yield) was an oil, $[\alpha]^{24}D$ +14.9° (*c* 1.06, C_6H_6). The corresponding hydrochloride was crystallized from ethanol–ether: mp 159–160°; $[\alpha]^{22}D$ −24.9° (*c* 0.56, H_2O).

Anal. Calcd for $C_{14}H_{22}ClNO \cdot {}^1/_2H_2O$: C, 63.50; H, 8.76; N, 5.29. Found: C, 63.42; H, 8.78; N, 5.16.

(1*S*,2*R*)-(+)-2-Phenyl-*trans*-2-dimethylaminocyclohexanol [(+)-1].—The base obtained as above from salt B (7.7 g, 12% yield), $[\alpha]^{23}D$ +26.3° (*c* 1.10, C_6H_6), was crystallized repeatedly from petroleum ether to a constant specific rotation to give a product: mp 75–76.5° [(±)-1, lit.[17] mp 78–80°]; $[\alpha]^{25}D$ +31.3° (*c* 0.97, C_6H_6).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.79; H, 9.57.

(1*R*,2*S*)-(−)-2-Phenyl-*trans*-2-dimethylaminocyclohexanol [(−)-1].—The base obtained from salt D (8.4 g, 13% yield) had $[\alpha]^{24}D$ −30.7° (*c* 1.25, C_6H_6). Repeated crystallizations from petroleum ether gave a sample: mp 75.5–77°; $[\alpha]^{24}D$ −31.9° (*c* 1.59, C_6H_6).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.80; H, 9.96.

(*S*)-(−)-2-Dimethylamino-2-phenylcyclohexanone [(−)-4].—A solution of (+)-1 (0.174 g), $[\alpha]^{25}D$ +31.3° in acetone (5 ml), was oxidized with Jones reagent[18] (0.20 ml), diluted with water after 1 min, made alkaline with aqueous ammonia, and extracted with ether. Evaporation of the ether left an oily residue (0.140 g), ir (neat) 1710 cm^{-1} (C=O), which was converted into the picrate of (−)-4. The salt was crystallized from ethanol: mp 187–188° [(±)-4 picrate, lit.[17] mp 199–200°].

Anal. Calcd for $C_{20}H_{22}O_8N_4 \cdot H_2O$: C, 51.72; H, 5.21; N, 12.06. Found: C, 51.70; H, 5.26; N, 12.05.

A solution of the purified picrate (70 mg) in ether (20 ml) was washed with five 5-ml portions of 10% aqueous sodium hydroxide, then with water, dried, and evaporated; the residue of (−)-4 (26 mg) had $[\alpha]^{23}D$ −65.9° (*c* 0.26, C_6H_6).

(+)-3 was recovered unchanged from a similar treatment.

(1*S*,2*S*)-(−)-1,2-Epoxy-1-phenylcyclohexane [(−)-2]. A.—A solution of (−)-**3** (4.0 g, $[\alpha]^{23}D$ −14.9°) and methyl iodide (22.8 g) in absolute methanol (40 ml) was refluxed 1 hr, then evaporated to dryness *in vacuo* to give the methiodide of (−)-**3** (6.95 g). An analytical sample was obtained by crystallization from methanol–ether: mp 206–207° [(±)-**3** methiodide, lit.[7] mp 212–214°]; $[\alpha]^{20}D$ +11.1° (*c* 0.28, C_2H_5OH).

Anal. Calcd for $C_{15}H_{24}INO$: C, 49.86; H, 6.70; N, 3.88. Found: C, 49.80; H, 6.80; N, 4.06.

The crude methiodide (6.85 g) in water (200 ml) was shaken for 5 hr with silver oxide freshly prepared from 15.0 g of silver nitrate. The mixture was filtered; the precipitate was washed with ether; the ether was evaporated; and the residue was added to the aqueous solution, which was steam distilled. The distillate was extracted with ether, and the ether evaporated to give (−)-**2** (2.43 g): $[\alpha]^{24}D$ −119.6° (*c* 1.85, C_6H_6); $[\alpha]^{35}D$ −75.5° (*c* 0.70, $CHCl_3$); $[\alpha]^{35}D$ −119.0° (neat).

B.—(+)-**1** (6.94 g, $[\alpha]^{23}D$ +30.9°) gave, when treated as described in A, 12.8 g of the methiodide of (+)-**1**: mp 137–139° (from acetone) [(±)-methiodide, lit.[17] mp 144–146°]; $[\alpha]^{25}D$ +31.4° (*c* 0.87, C_2H_5OH).

Anal. Calcd for $C_{15}H_{24}INO$: C, 49.86; H, 6.70. Found: C, 49.55; H, 6.38.

The methiodide, treated as described in A, gave 4.50 g of crude (−)-**2**, $[\alpha]^{25}D$ −108.0° (*c* 1.08, C_6H_6), which was distilled over a little potassium hydroxide[1] to give the pure product (3.9 g): bp 121° (1.5 mm); $n^{26}D$ 1.5419 [lit.[1] bp 118° (0.5 mm); $n^{19}D$ 1.5430]; $[\alpha]^{26}D$ −117.3° (*c* 1.28, C_6H_6).

(1*R*,2*R*)-(+)-1,2-Epoxy-1-phenylcyclohexane [(+)-2].—A method recently described by Stevens, *et al.*,[7] for the preparation of (±)-**2** was used.

A.—A solution of (+)-**3** (17.7 g, $[\alpha]^{24}D$ +14.9°) in methanol (130 ml) was converted by 1-hr reflux with methyl iodide (36 g) into the methiodide: mp 204–205° (after crystallization from methanol–ether); $[\alpha]^{22}D$ −11.5° (*c* 0.36, C_2H_5OH).

Anal. Calcd for $C_{15}H_{24}INO$: C, 49.86; H, 6.70; N, 3.88. Found: C, 49.52; H, 6.96; N, 3.57.

The crude methiodide was dissolved in ethanol (1800 ml) and treated with a suspension of silver oxide, prepared from silver nitrate (21.3 g) and sodium hydroxide (11.2 g) in water (550 ml). The mixture was shaken for 2 hr and filtered. The filtrate and the residue were extracted with petroleum ether; the combined and dried (K_2CO_3) extracts were evaporated to give (+)-**2** (11.7 g), $[\alpha]^{25}D$ +116.0° (*c* 0.84, C_6H_6). A part of this product (0.2 g) was purified by chromatography through a 15 × 20 cm column of neutral alumina (grade II). The first 100-ml eluate (hexane) yielded pure (+)-**2** (0.090 g), $[\alpha]^{24}D$ +121.2° (*c* 0.78, C_6H_6). The low recovery was due to partial decomposition of the epoxide during the chromatography to products which were, however, retained by the column.

B.—(−)-**1** (0.309 g, $[\alpha]^{26}D$ −31.6°), when treated in the same manner, gave, after chromatography of the final product, (+)-**2** (0.062 g), $[\alpha]^{25}D$ +119.9° (*c* 0.60, C_6H_6).

(1*R*,2*S*)-(+)-1-Phenyl-*trans*-cyclohexane-1,2-diol [(+)-5].—A solution of (+)-**2** (5 g, $[\alpha]^{25}D$ +116.0°) in dimethyl sulfoxide (100 ml) and 10 *N* aqueous potassium hydroxide (18 ml) was heated for 70 hr at 100°.[8] The mixture was evaporated to dryness *in vacuo*, and the residue extracted with 200 ml of ether. The extract was washed with 100 ml of water and evaporated to give 4.6 g of crude (+)-**5**, $[\alpha]^{23}D$ +40.8° (*c* 0.49, C_6H_6). Repeated crystallizations from chloroform–hexane gave a sample: mp 79–80° [(±)-**5**, lit.[1] mp 98.5–100°]; $[\alpha]^{27}D$ +51.0° (*c* 0.37, C_6H_6).

A sample of the crude (+)-**5** (0.5 g) was purified by chromatography through a 1.5 × 40 cm column of neutral alumina (grade II). Elution with 7:3 benzene–ether gave chemically pure (+)-**5**, $[\alpha]^{24}D$ +45.7° (*c* 0.54, C_6H_6).

(1*S*,2*R*)-(+)-2-Phenyl-*trans*-2-chlorocyclohexanol [(+)-6].—(+)-**5** (0.577 g, $[\alpha]^{28}D$ +49.3°) was treated with a 0.1 *N* solution of hydrogen chloride in chloroform (130 ml).[2] After 3 hr the solution was washed with saturated $NaHCO_3$ and water and was evaporated *in vacuo*. The residue was crystallized repeatedly from petroleum ether to give (+)-**6** (0.360 g): mp 44.5–45° [(±)-**6**, lit.[2] mp 89–91°]; $[\alpha]^{24}D$ +13.7° (*c* 0.58, C_6H_6).

Conversion of (+)-6 into (−)-2.—A solution of (+)-**6** (0.496 g, $[\alpha]^{25}D$ +13.7°) in methanol (20 ml) was titrated with 0.1 *N* aqueous sodium hydroxide (phenolphthalein). After 15 min the reaction was complete, the theoretical amount of base having been consumed. Dilution with water, extraction with chloroform, and evaporation of the dried extract *in vacuo* gave an oily residue (0.36 g), the ir spectrum of which was identical with that of **2**. It was passed through a 1.5 × 20 cm column of neutral alumina

(17) C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. D. Pillai, and J. W. Stoddard, *J. Org. Chem.*, **31**, 2593 (1966).

(18) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(grade II); the first 200 ml of eluate (hexane) yielded pure (−)-**2**, $[\alpha]^{25}D$ −117.5° (*c* 1.00, C_6H_6).

(1*S*,2*S*)-(+)-*cis*-2-**Phenylcyclohexanol** [(+)-**8**].—A preliminary test was made on (±)-**6** (0.23 g) which was hydrogenated in ethanol (40 ml) over 5% palladium on calcium carbonate (0.2 g) at room temperature and pressure. After 1 hr the catalyst was filtered off; the solution was evaporated to dryness *in vacuo;* and the residue crystallized from petroleum ether to give (±)-**8**, mp 41–42° (lit.[19] mp 41–42°). The same reaction was repeated with (+)-**6**, $[\alpha]^{24}D$ +12.7°, and the crude product (1.32 g), $[\alpha]^{24}D$ +78.9° (*c* 0.59, C_6H_6), was dissolved in hexane and chromatographed through a 1.5 × 26 cm column of neutral alumina (grade II). Elution with hexane (3600 ml) and 7:3 hexane–benzene (1200 ml) gave (+)-**8** (0.770 g): liquid; $[\alpha]^{20}D$ +92.9° (*c* 1.18, C_6H_6). Further elution with hexane–benzene (1500 ml) and with benzene (700 ml) yielded *trans*-2-phenylcyclohexanol (36 mg): $[\alpha]^{31}D$ +47.6° (*c* 1.56, C_6H_6). A final elution with ether gave (+)-**5** (140 mg).

Direct Correlation of (+)-8 with (+)-2.—The reactions described above were repeated without purification of the intermediates, in the following way. (+)-**2** (0.504 g, $[\alpha]^{25}D$ +116.6°, purified through chromatography) was converted into crude (+)-**5** {0.449 g, $[\alpha]^{22}D$ +43.7° (*c* 1.14, C_6H_6)}, 0.437 g of which was treated with hydrogen chloride in chloroform, as described above, to give crude (+)-**6** (0.405 g). A part of this (0.086 g) was reconverted with sodium hydroxide into the epoxide, which was purified through chromatography, $[\alpha]^{25}D$ −103.3° (*c* 0.694, C_6H_6). The rest of the crude (+)-**6** (0.32 g) was reduced catalytically, as above, to a crude product, which was subjected to chromatography to give pure (+)-**8**: liquid; $[\alpha]^{27}D$ +87.1° (*c* 0.288, C_6H_6). The purity was checked through tlc (SiO_2 F 254 Merck, benzene), a single spot being observed; the *trans* isomer of **8** can easily be detected under these conditions, as it has a smaller R_f value.

(1*S*,2*S*)-(+)-*cis*-2-**Phenylcyclohexanol Methylxanthate** [(+)-**7**].—The method of Alexander and Mudrak[20] for the preparation of the corresponding racemic compound was followed. A solution of (+)-**8**, $[\alpha]^{29}D$ +92.9° (0.535 g, 3.0 mmol), in anhydrous ether (5 ml) was shaken for 70 hr at room temperature with sodium (0.100 g, 4.35 mg-atom) cut in thin slices; carbon disulfide (0.72 g, 9.1 mmol) was slowly added; excess sodium was eliminated mechanically; stirring was continued for 30 min; methyl iodide (2.0 g, 14.4 mmol) was added; and the mixture was stirred for 46 hr, more methyl iodide (0.25 g) being added after 24 and 44 hr. The mixture was filtered and evaporated *in vacuo*, and the residue (0.760 g) was chromatographed through a 1.4 × 22 cm column of neutral alumina (grade II). Hexane (300 ml) eluted (+)-**7** (0.66 g), $[\alpha]^{31}D$ +67.9° (*c* 1.82, $CHCl_3$), which was crystallized from ethanol at −10° to give the pure product (0.49 g): mp 57.5–58.5° [(±)-**7**, lit.[20] mp 49–50°]; $[\alpha]^{29}D$ +73.3° (*c* 0.44, $CHCl_3$).

Anal. Calcd for $C_{14}H_{18}OS_2$: C, 63.11; H, 6.81. Found: C, 62.81; H, 6.77.

A solution of the pure (+)-**7** (81 mg) was refluxed for 100 min with 3% potassium hydroxide in ethanol (3 ml), then diluted with water (10 ml), and extracted with hexane (30 ml). Evaporation of the extract and chromatography of the residue through alumina gave (+)-**8** (16 mg), $[\alpha]^{30}D$ +97.8° (*c* 1.07, C_6H_6).

(*R*)-(+)-**3-Phenylcyclohexene** [(+)-**9**].—(+)-**7** (0.400 g, $[\alpha]^{29}D$ +73.3°) was heated for 40 min at 210° and 5 min at 240°. The residue was extracted with hexane and chromatographed through neutral alumina (1 × 24 cm, grade I). The first 80 ml of eluate gave (+)-**9** as a colorless oil (0.087 g): $[\alpha]^{29}D$ +149.7° (*c* 0.53, C_6H_6); uv max (95% C_2H_5OH) 248 and 252.5 mμ (ε 635 and 653) [(±)-**9**, lit.[21] uv max 253 mμ (ε 653); 1-phenylcyclohexene, uv max 247 mμ (ε 12,940)]; the ir bands reported in the literature[22] for (±)-**9** were all present, those reported for 1-phenylcyclohexene absent or barely visible. Glpc analysis (2-m column, i.d. 3 mm, of 1% neopentyl glycol succinate on silanized Chromosorb W 80–100 mesh, 100°) indicated that the product consisted of 98% **9** and 2% 1-phenylcyclohexene (**11**) (relative retention times 1:1.97). Preliminary tests had shown that the passage through alumina does not cause any conversion of **9** into **11**.

(*S*)-(+)-**2-Phenyladipic Acid** [(+)-**10**].—A solution of (+)-**9** (70 mg, 0.44 mmol), $[\alpha]^{29}D$ +149.7°, in ether (3 ml) and pyridine (0.26 ml) was treated with osmium tetroxide (120 mg, 0.46 mmol) in ether (3 ml). After 6 days the brown precipitate was collected, dissolved in methylene chloride (10 ml), treated with sodium hydroxide (0.20 g) and mannitol (0.50 g) in water (8 ml), and shaken until the color disappeared. Evaporation of the organic layer gave a mixture of diastereoisomeric 3-phenyl-*cis*-cyclohexane-1,2-diols (0.085 g), mp 86–88°, which was dissolved in acetone (5 ml) and oxidized with 0.49 ml of Jones reagent.[18] After 5 min saturated sodium chloride was added, and the solution was extracted with ether. The ether layer was washed with saturated sodium chloride, dried, and evaporated to give a solid residue (75 mg). Crystallization from benzene gave (+)-**10**: needles (30 mg); mp 152–153.5°; $[\alpha]^{25}D$ +61.0° (*c* 0.39, absolute C_2H_5OH) (lit.[11] mp 153–155°, $[\alpha]^{25}D$ +63.8°). From the mother liquor, after treatment with charcoal and dilution with petroleum ether, another 4.5 mg of (+)-**10**, $[\alpha]^{25}D$ +59.0°, was obtained. Complete evaporation of the mother liquor gave an optically inactive product which was crystallized from water to give 4-benzoylbutyric acid (**12**), mp 118–120° (lit.[23] mp 119–123.5°); it was identical with an authentic sample of **12**, prepared by permanganate oxidation of 1-phenylcyclopentene.

Determinations of Absolute Configurations through Partial Resolution. A.—According to the method of Horeau, a solution of 2-phenylbutyric anhydride (0.506 g, 1.63 mmol) in pyridine (5 ml) was added to (+)-**5** (74.6 mg, 0.39 mmol, $[\alpha]^{26}D$ +49.6°). After 18 hr at room temperature 2 drops of water was added; the mixture was heated 30 min on a steam bath and after addition of benzene (6 ml) titrated with 0.1 *N* sodium hydroxide (phenolphthalein), 30.2 ml being consumed; the esterification yield was 62%. The water layer was washed with benzene, acidified with hydrochloric acid, and extracted with three 15-ml portions of benzene. The benzene extract was evaporated, and the residue brought to a volume of 5 ml with benzene: $[\alpha]^{28}D$ −0.377° (1 dm); optical yield 50%.

B.—The same treatment was repeated on the alcohol (+)-**8** (32.8 mg, $[\alpha]^{23}D$ +94.6°) with 109 mg of 2-phenylbutyric anhydride in 1 ml of pyridine [0.1 *N* sodium hydroxide (6.23 ml); esterification yield 45%; recovered 2-phenylbutyric acid (in 2.0 ml of benzene), $[\alpha]^{26}D$ −0.304° (1 dm); optical yield 47%].

Registry No.—(+)-**1**, 17539-99-0; (+)-**1** methiodide, 17540-00-0; (+)-**1** (−)-dibenzoyltartrate, 17540-01-1; (−)-**1**, 17540-02-2; (−)-**1** (+)-dibenzoyltartrate, 17540-03-3; (+)-**2**, 17540-04-4; (−)-**2**, 5775-23-5; (+)-**3**, 17540-06-6; (+)-**3** HCl, 10276-01-4; (+)-**3** methiodide, 17540-21-5; (+)-**3** (−)-tartrate, 17540-08-8; (−)-**3**, 17540-09-9; (−)-**3** HCl, 17540-10-2; (−)-**3** methiodide, 10276-02-5; (−)-**3** (+)-tartrate, 17540-12-4; (−)-**4**, 17540-13-5; (−)-**4** picrate, 17540-14-6; (+)-**5**, 17540-15-7; (+)-**6**, 5775-43-9; (+)-**7**, 17540-17-9; (+)-**8**, 17540-18-0; (+)-**9**, 17540-19-1; (+)-**10**, 17540-20-4.

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(19) C. C. Price and J. V. Karabinos, *J. Amer. Chem. Soc.*, **62**, 1159 (1940).
(20) E. R. Alexander and A. Mudrak, *ibid.*, **72**, 1810 (1950).
(21) R. Y. Mixer and W. G. Young, *ibid.*, **78**, 3379 (1956).
(22) E. L. Eliel, J. W. McCoy, and C. C. Price, *J. Org. Chem.*, **22**, 1533 (1957).
(23) R. C. Gilmore, Jr., and W. J. Horton, *J. Amer. Chem. Soc.*, **73**, 1411 (1951).

Studies in the Pyrolysis of N-Formylacetamides. The Imide–Isoimide Rearrangement

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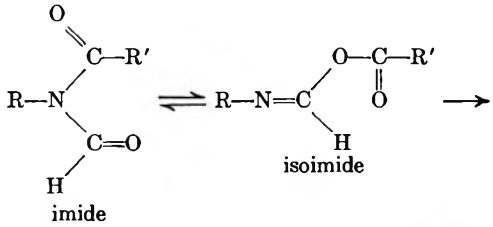
The purpose of this investigation is to obtain basic information on the reaction of substituted formamides giving isocyanides. Imide–isoimide equilibria were studied by an analysis of the thermal decomposition products of N-alkyl- (or -aryl-) N-formylacetamides. Relative yields in decarbonylation (arising from imide) *vs.* isocyanide formation (arising from isoimide) in the pyrolysis of N-phenyl-, N-*n*-butyl-, N-*sec*-butyl-, and N-cyclohexyl-N-formylacetamides were found to be >99:<1, 86:14, 57:43, and 51:49, respectively. Nitriles rather than isocyanides were isolated because of the isomerization which occurs at high temperatures. It is concluded that the quantities of amide and nitrile isolated may be the net result of a number of reactions: imide–isoimide reversible rearrangement, isoimide α elimination (possibly reversible), imide decarbonylation (irreversible), isocyanide–nitrile isomerization (irreversible), and imide regeneration from isocyanide and acid through formamide and acetic anhydride. Among the imides studied both an electronic and a steric effect appear to be operating.

It has been indicated that pyrolysis of N-alkyl- (or -aryl-) N-formylamides gives isocyanides because of the characteristic odor which accompanied the reaction.[2,3] Mumm detected an intensive odor of isocyanide in the decarbonylation of N-formylbenzanilide, but he did not report isolating the product. Similarly Wheeler[4] claimed that pyrolysis of N-formylstearanilide gave phenyl isocyanide and stearic acid, but he gave no supporting details. Isocyanide production in these reactions gives evidence of an imide–isoimide rearrangement (eq 1).[5]



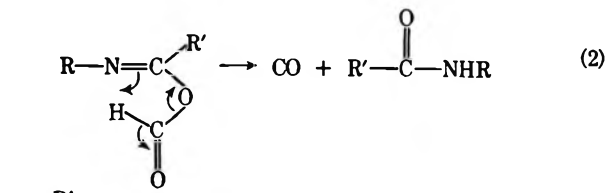
$$R—N{\equiv}C + R'COOH \quad (1)$$

The formation of isoimides as transient intermediates (which rearrange to the imide or which yield products logically derived from isoimide structures) is widely reported.[6-13] Isoimides have been isolated when the function is part of a five-membered ring which also contains a carbon–carbon double bond[14] or when the nitrogen bears a 2,4-dinitrophenyl group.[15] These isoimides rearrange *via* an oxygen to nitrogen acyl migration; when heated, however, the rearrangement observed for the cyclic case may depend on acid or base catalysis.[15]

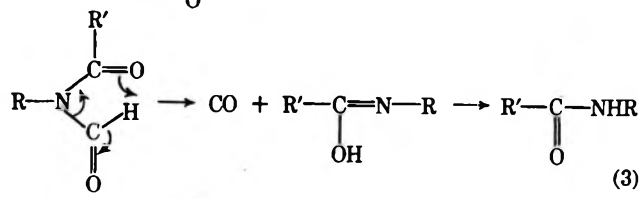
Mumm and coworkers,[2] postulated a reversible imide–isoimide rearrangement to explain three pyrolysis reactions. Expressing Mumm's specific examples in general terms the reactions are pyrolysis of acyclic imides to carboxylic acids and nitriles, pyrolysis of N-alkyl- (or -aryl-) N-formylamides to carboxylic acids and nitriles, pyrolysis of N-alkyl- (or -aryl-) N-formylamides to the N-alkyl- (or -aryl-) amides and carbon monoxide, and the pyrolysis of N-alkyl- (or -aryl-) N-formylamides to isocyanides and carboxylic acids.

For the pyrolysis of acyclic imides, Sheehan and Corey[9] have written a reversible imide–isoimide rearrangement as a part of the mechanism in agreement with Mumm's postulate. More extensive studies have recently been explained by postulating a concerted mechanism which omits a discrete isoimide intermediate, though the authors consider a path through an isoimide intermediate as a possible limiting case.[16]

In the pyrolysis of N-alkyl- (or -aryl-) N-formylamides to N-alkyl- (or -aryl-) amides, a decarbonylation mechanism for Mumm's postulated isoimide[2,3] can be written (eq 2). However, decarbonylation could also occur directly from the imide (eq 3).



(2)



(3)

For the pyrolysis of N-alkyl- (or -aryl-) N-formylamides to isocyanides, a mechanism is difficult to write unless prior rearrangement to an isoimide occurs. The isoimide can then undergo an α elimination (eq 1). The existence of this pyrolysis reaction gives the best evidence for a reversible imide–isoimide equilibrium

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(2) O. Mumm, H. Hesse, and H. Volquartz, *Ber.*, **48**, 379 (1915).

(3) O. Mumm, *ibid.*, **43**, 886 (1910).

(4) H. L. Wheeler, *Am. Chem. J.*, **18**, 695 (1896).

(5) Isocyanide formation by α elimination from an isoformimide is analogous to the mechanism postulated for isocyanide formation from nitrogen-substituted formamides by phosphorus and sulfur halides with tertiary amine. See I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).

(6) F. Cramer and K. Baer, *ibid.*, **93**, 1231 (1960).

(7) C. L. Stevens and M. E. Munk, *J. Amer. Chem. Soc.*, **80**, 4065 (1958).

(8) H. H. Wasserman and M. B. Floyd, *Tetrahedron*, **22** (**S 7**), 441 (1966).

(9) J. C. Sheehan and E. J. Corey, *J. Amer. Chem. Soc.*, **74**, 4555 (1952).

(10) C. G. Overberger and E. Sarlo, *ibid.*, **85**, 2446 (1963).

(11) D. S. Kemp, *Tetrahedron*, **23**, 2001 (1967).

(12) A. Kornhauser and D. Keglevic, *ibid.*, **18**, 7 (1962).

(13) T. Shono, M. Kimura, Y. Ito, K. Nishida, and R. Oda, *Bull. Chem. Soc. Jap.*, **37**, 635 (1964), and L. R. Walters, E. G. Podrebarac, and W. E. McEwen, *J. Org. Chem.*, **26**, 1161 (1961), claim preparation of several isoimides based on the position of ir absorption bands. This may not be sufficiently conclusive evidence for the isoimide structure.

(14) W. R. Roderick and P. L. Bhatia, *ibid.*, **28**, 2018 (1963). E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **31**, 1311 (1966); 1317 (1966).

(15) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965); D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, **89**, 637 (1967).

(16) W. S. Durrell, J. A. Young, and R. D. Dresdner, *J. Org. Chem.*, **28**, 831 (1963).

at high temperatures. In order to investigate Mumm's postulated equilibrium,[2,3] to determine quantitatively the relative importance of decarbonylation *vs.* isocyanide formation as pyrolysis pathways, and to investigate the formation of isocyanides from substituted formamides, we studied the pyrolysis of N-phenyl-, N-*n*-butyl-, N-*sec*-butyl-, and N-cyclohexyl-N-formylacetamides.

Results and Discussion

Starting materials were synthesized by acetylating the appropriate formamide derivative with acetyl chloride. The N-formylacetamides were pyrolyzed by passing them through copper or glass tubes at 400°. Experimental results are summarized in Tables I and II.

TABLE I
PRODUCTS OBTAINED IN THE PYROLYSIS OF N-SUBSTITUTED N-FORMYLACETAMIDES

Nitrogen substituent	Acetamide, % yield	Nitrile, % yield	Acetic acid, % yield
Phenyl[a]	99	1	
n-Butyl[a]	75	12	13
n-Butyl[b]	74	10	16
sec-Butyl[a]	40	30	30
Cyclohexyl[a]	34	35	31

[a] Copper tube. [b] Glass tube.

TABLE II
RELATIVE REACTION PATHS IN THE PYROLYSIS OF N-SUBSTITUTED N-FORMYLACETAMIDES

Nitrogen substituent	Decarbonylation	Isocyanide–acid formation
Phenyl	99	1
n-Butyl	86	14
sec-Butyl	57	43
Cyclohexyl	51	49

Additional experiments were performed in conjunction with the N-(*n*-butyl)-N-formylacetamide pyrolysis reactions and included a variety of sealed-tube reactions (eq 4–8).

$$n\text{-}C_4H_9NHCHO \xrightarrow[30\ min]{380^\circ} \text{no reaction} \quad (4)$$

$$n\text{-}C_4H_9N(COCH_3)CHO \xrightarrow[30\ min]{365^\circ} n\text{-}C_4H_9NHCOCH_3 + \text{high pressure (CO)} \quad (5)$$
(100%)

$$n\text{-}C_4H_9NC + CH_3COOH \xrightarrow[30\ min]{325^\circ} n\text{-}C_4H_9NHCOCH_3 + n\text{-}C_4H_9CN + n\text{-}C_4H_9NHCHO \quad (6)$$
(80%) (10%) (10%)

$$n\text{-}C_4H_9NC \xrightarrow[15\ min]{310^\circ} n\text{-}C_4H_9CN \quad (7)$$
(100%)

$$n\text{-}C_4H_9NHCHO + (CH_3CO)_2O \xrightarrow[30\ min]{350^\circ} n\text{-}C_4H_9NHCOCH_3 + CH_3COOH + \text{high pressure (CO)} \quad (8)$$
(50%) (50%)

If the reaction represented in eq 5 is not allowed to proceed to completion, then the odor of isocyanide is detectable upon opening the tube.

General Considerations.—The results are conveniently discussed in terms of Scheme I. Although the experimental information required to fulfill the necessary conditions for unimolecular reaction mechanisms[17] has not been determined, we postulate that the imide decarbonylation and the isoimide α elimination (isocyanide–acid formation) reactions are unimolecular. The agreement within experimental error of the results for pyrolysis of the *n*-butyl derivative in both the copper and glass tube supports the conclusion that the reactions whose rates determine the product ratios are homogeneous.

A mechanism for the formation of nitrile and carboxylic acid from the imide is difficult to conceive without the isoimide α elimination and the isocyanide isomerization. The four-centered cyclic transition state for the reversible imide–isoimide equilibrium (Scheme I) is that proposed by Curtin and Miller[15] for the isoimide–imide rearrangement.

The quantities of amide and nitrile isolated may be the net result of a number of possible reactions: imide–isoimide reversible rearrangement, isoimide α elimination (possibly reversible), imide decarbonylation (irreversible), isocyanide–nitrile isomerization (irreversible), and imide regeneration from formamide and acetic anhydride (formed from isocyanide and acid). Though all these rates and their dependence upon the R group is not known, an explanation of the general features of the R-group influence upon reaction pathway can be proposed which seems logical in view of already determined isocyanide isomerization rates[18–20] and the electronic and steric effects of the R groups.

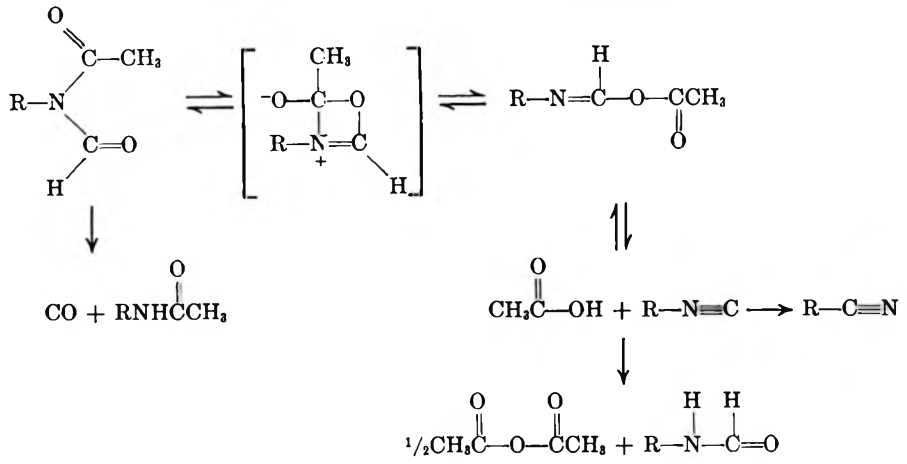
Isocyanide Isomerization.—The thermal unimolecular isomerization of isocyanides to nitriles explains the presence of the nitriles as the products of the pyrolysis.[18–20] Several of the isocyanides in this study were so completely isomerized under the exact conditions of imide pyrolysis that their odor was barely detectable in the nitrile product. Furthermore, isomerization rate constants can be estimated for the isocyanides by using the Arrhenius parameters for methyl isocyanide reported by Schneider and Rabinovitch[18] and the influence of the nitrogen substituent on the isomerization rate reported by Casanova, *et al.*[20] Thus an estimated lower limit is $k = 5\ \text{sec}^{-1}$, a number sufficiently large to explain the exclusive formation of nitrile.

Kohlmaier[19] and Rabinovitch determined the *p*-tolyl isocyanide gas phase isomerization rate to be $75 \times 10^{-5}\ \text{sec}^{-1}$ at 200°. Casanova, *et al.*,[20] showed phenyl isocyanide isomerization rates in diglyme to be only slightly dependent upon a *para* substituent, suggesting that the gas phase isomerization rate of phenyl isocyanide is probably very similar to that of *p*-tolyl isocyanide. They also determined the ethyl and *sec*-butyl isocyanide gas phase isomerization rates to be 10.4×10^{-5} and $3.45 \times 10^{-5}\ \text{sec}^{-1}$, respectively, at 200°. Thus comparison of gas phase isomerization constants gives this order: phenyl > *n*-alkyl > *sec*-alkyl. It is interesting to note that the rate of nitrile

(17) A. Maccoll, *Advan. Phys. Org. Chem.*, **3**, 96 (1965).
(18) F. W. Schneider and B. S. Rabinovitch, *J. Amer. Chem. Soc.*, **84**, 4215 (1962).
(19) G. Kohlmaier and B. S. Rabinovitch, *J. Phys. Chem.*, **63**, 1793 (1959).
(20) J. Casanova, Jr., N. D. Werner, and R. E. Schuster. *J. Org. Chem.*, **31**, 3473 (1966).

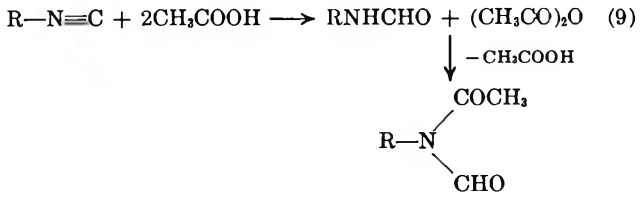
SCHEME I

CONSEQUENCES OF THE IMIDE–ISOIMIDE REARRANGEMENT



formation relative to the rate of decarbonylation is *sec*-alkyl > *n*-alky > phenyl for imide pyrolysis, which is achieved *in spite of* the order of isocyanide isomerization rates. One might have expected a greater contribution from isocyanide chemical reactions in the case of the compounds which isomerize at lower rates.

Isocyanide Chemical Reactions.—Isomerization to nitrile may not be the only reaction of the isocyanide formed. Isocyanide and acid may revert into imide if the α elimination is a reversible reaction or if a second pathway through formamide and acetic anhydride[21] is operative (eq 9). Sealed-tube reactions (eq 6 and 8)

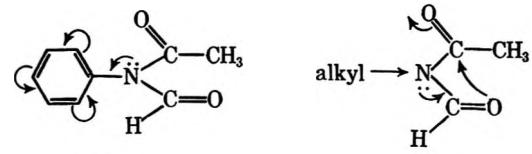


(9)

show that these reaction sequences are possible and conceivably could be present in the flow method pyrolysis. If imide originally decomposing to isocyanide and acid does re-form and decarbonylate, then the amount of nitrile isolated would be less than the case if the isocyanide reaction was exclusively isomerization.

Isocyanide isomerization may not compete favorably with the reaction of isocyanide and acid in the sealed-tube experiments. Thus, the higher pressures obtained by pyrolysis in a sealed tube may so enhance the re-formation of imide that decarbonylation is the only net reaction observed (note eq 5). Heating the imide to temperatures near its boiling point at atmospheric pressure gave a gas-evolving, isocyanide-smelling, rapidly darkening solution. Knowledge of the reactions possible for a solution of the parent imide, its corresponding amide and formamide, isocyanide, nitrile, acetic acid, and acetic anhydride between 100 and 200° discouraged further investigation.

Electronic Effects.—An electronic effect seems best able to explain the near absence of nitrile in the pyrolysis of the phenyl-substituted imide. The electron density of the nitrogen atom can affect the imide's ability to achieve the transition state shown in Scheme I. For the phenyl imide, the nitrogen electron density is significantly decreased by electron delocalization into the benzene ring (structure A). This is in comparison

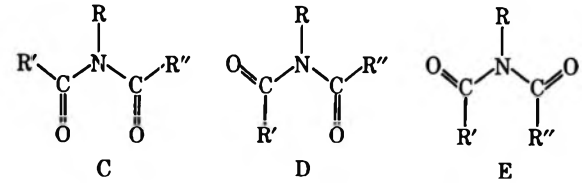


A B

to the alkyl-substituted imides in which the nitrogen electron density (as well as the ability of the imide to achieve the transition state for isomerization to isoimide) is increased by an inductive effect (structure B). We suggest that these electronic effects are responsible for the higher amide/nitrile ratio for the phenyl imide compared with those for the alkyl imides.

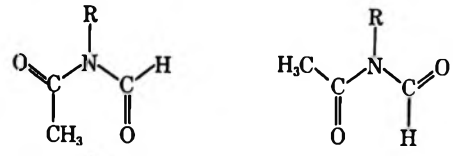
The same argument now based on the relative inductive effects of primary *vs.* secondary alkyl groups may contribute to the increase of nitrile yield in going from *n*-butyl to *sec*-butyl and cyclohexyl. However, steric considerations may also be important.

Steric Effects.—The rotational barrier of the amide bond[22] leads to three possible conformers for an imide.



C D E

Dipole moment data support assignment of conformation D to N-methyldiformamide, diacetamide, and N-methyldiacetamide.[23] Though not determined, it is likely that the D conformation (I or II) can also be assigned to the imides of this study. Monosubstituted



I II

(21) A. Gautier, *Ann. Chim. Phys.*, **17**, 224 (1869).

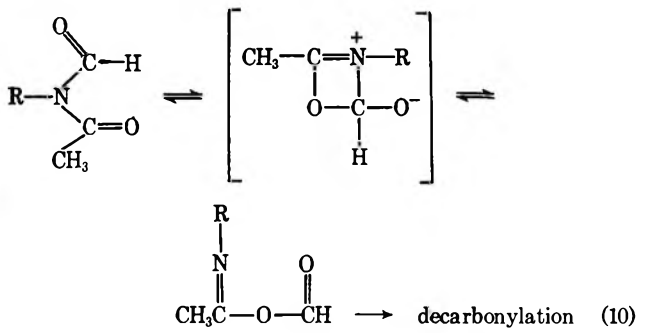
(22) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 366.

(23) C. M. Lee and W. D. Kumler, *J. Amer. Chem. Soc.*, **84**, 571 (1962).

formamides are predominantly *trans* and show a small trend toward the *cis* conformer with increasingly bulky substituents.[24] In unsymmetrical disubstituted formamides, the formyl hydrogen is *cis* to the bulkier substituent.[25]

Though the amide bond will no longer show *cis–trans* isomerism at the temperature of this pyrolysis,[26] the steric considerations can still be used to deduce the trend of conformation with the R group. Thus as one goes from a primary to secondary alkyl group, the trend will be toward a conformation I-D-like character even though rotation may occur. This is precisely the trend in conformation favorable for producing a trend toward rearrangement to an isoimide.

Isoacetimide Intermediates.—As mentioned previously, a unimolecular mechanism for decarbonylation can be written from either an isoimide (eq 2) or an imide (eq 3). As the trend in nitrile/amide ratio agrees with factors favoring isoformimide formation, rearrangement to isoformimide appears to be the rate-determining step for degradation to nitrile and acid. In view of this it is tempting to try to exclude the possibility of an isoacetimide in the decarbonylation mechanism (eq 10) by using an argument based on



(10)

inherent electronic or steric properties of a specific imide. For example, for the phenyl imide, the nitrile/amide ratio was much smaller than for alkyl imides because the lower electron density on nitrogen is unfavorable for rearrangement to the isoformimide. One would thus expect rearrangement to the isoacetimide. Because decarbonylation is rapid in comparison to nitrile formation, one is tempted also to exclude isoacetimide as a decarbonylation intermediate in favor of the alternative mechansim involving imide.

Experimental Section[27]

The pyrolysis apparatus was a gas chromatograph equipped with a 6 ft × 0.25 in. copper or glass tube in place of the usual column. Sufficient pyrolysis products were then obtained by multiple injection of reactant using a helium carrier gas flow rate of 60 ml/min and an oven temperature of 400°. The time of passage through the tube varied between 2 and 25 sec. The combined products were collected at ice–water temperature and separated by preparative glpc 20 ft × $^3/_8$ in. column, 30% SE-30 on $^{45}/_{60}$ Chromosorb W). The identity of each peak was determined by comparison of its retention time and ir spectrum with those of an authentic sample. Quantitative analyses were obtained with an estimated uncertainty of 3% by measuring peak areas using a Disc integrator.

The sealed-tube reactions were performed using 10-mm heavy-walled glass tubing. In a typical run, 0.10 ml of reactant was degassed and the tube was sealed under vacuum. After the appropriate length of time in the oven (see eq 4–8) the tube components were separated by preparative glpc. Product identification was based on glpc retention times and comparison of ir spectra with those of authentic samples.

N-Formylacetanilide.—Formanilide (24.2 g, 0.20 mol) was dissolved in 250 ml of methylene chloride and cooled in ice. Pyridine (31.7 g, 0.40 mol) and acetyl chloride (31.4 g, 0.40 mol) were added, and the mixture was stirred at room temperature for 1 hr. The mixture was then extracted twice with 100-ml and once with 50-ml portions of water. The methylene chloride solution was dried (Na_2SO_4) overnight, stripped with a rotary evaporator, and distilled with a spinning-band column giving 26.0 g (80%) of the imide: bp 81–82° (0.035 mm) [lit.[4] bp 157–158° (23 mm)]. The product was recrystallized from ether–ligroin: softens at 53°; mp 55° (lit.[4] mp 56°); ir ($CHCl_3$) 5.89 and 5.80 μ (C=O).

N-(*n*-Butyl)-N-formylacetamide.—N-Butylformamide (20.2 g, 0.20 mol) and acetyl chloride (62.7 g, 0.80 mol) were mixed and stirred at reflux for 5 hr, while protected from moisture. After the reaction solution stood at room temperature for 30 hr, the acetyl chloride was stripped off with a rotary evaporator. The residue was distilled through a spinning-band column giving 19.2 g (67%) of the imide: bp 74.5–75.5° (0.70–0.75 mm); $n^{23}D$ 1.4513; ir (neat) 1720 and 1670 cm^{-1} (C=O).

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.9; H, 9.3; N, 9.7.

Reduction of N-(*n*-Butyl)-N-formylacetamide.—To substantiate that reaction of acetyl chloride with N-monosubstituted formamide leads to imide rather than isoimide, N-(*n*-butyl)-N-formylacetamide was reduced with lithium aluminum hydride in THF to *n*-butyl-, ethyl-, or methylamine. The product was purified by vpc (39%) and then was alkylated with *n*-butyl iodide to give di(*n*-butyl)ethylmethylammonium iodide (77%): mp 178–179° (lit.[28] mp 176–178°) (recrystallized from EtOAc).

N-(*sec*-Butyl)-N-formylacetamide.—*sec*-Butylformamide (20.3 g, 0.20 mol) was dissolved in 200 ml of methylene chloride and pyridine (23.7 g, 0.30 mol). The solution warmed and turned yellow upon the start of acetyl chloride addition. The solution was then cooled in ice; a white salt formed when the acetyl chloride addition (17.3 g, 0.22 mol) was completed. The mixture was stirred at room temperature; an additional 10 ml of acetyl chloride and 5 ml of pyridine were added since glpc showed an incomplete reaction. The white salt was again filtered off, and the solution was concentrated. More white salt formed and was filtered off. The residue was vacuum distilled to give 22.2 g (77%) of imide: bp 53.5° (0.10 mm). The product was slightly impure by glpc and was purified by preparative glpc: $n^{23}D$ 1.4517; ir ($CHCl_3$) 5.98 and 5.80 μ sh (C=O).

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.5; H, 9.3; N, 9.9.

N-Cyclohexyl-N-formylacetamide.—Cyclohexylformamide (25.5 g, 0.20 mol) was dissolved in 250 ml of methylene chloride and pyridine (31.7 g, 0.40 mol). Acetyl chloride (31.4 g, 0.40 mol) was slowly added with ice cooling. A white salt formed immediately. The mixture turned light yellow and was allowed to stand for 1 hr. The mixture was poured into a separatory funnel and was washed three times each with 100 ml of water. The methylene chloride solution was dried (Na_2SO_4), concentrated, and distilled through a spinning-band column giving 23.2 g (68%) of imide: bp 74–75° (0.20 mm); $n^{23}D$ 1.4872; ir (neat) 1720 and 1672 cm^{-1} (C=O).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.8; H, 9.0; N, 8.3.

Pyrolysis of N-Formylacetanilide.—The imide was injected in 48-μl aliquots. White crystals, mp 109–113°, formed in the collector bottle without purification (acetanilide mp 113–115°). The collector bottle was washed with a small amount of $CHCl_3$. An ir spectrum of the $CHCl_3$ solution was identical with that of acetanilide except for a small peak at 4.48 μ, identical with that of benzonitrile. Glpc of the $CHCl_3$ solution gave a small peak with a retention time identical with that of benzonitrile, and a

(24) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 337 (1964)
(25) L. A. LaPlanche and M. T. Rogers, *ibid.*, **85**, 3728 (1963).
(26) R. C. Neuman, Jr., and L. B. Young, *J. Phys. Chem.*, **69**, 2570 (1965).
(27) Infrared spectra of N-(*n*-butyl)-N-formylacetamide and N-cyclohexyl-N-formylacetamide were obtained by Dr. R. A. Mackay, Edgewood Arsenal, from neat liquids between KRS-5 plates using a Perkin-Elmer Model 521 spectrophotometer. A study of the effect of metal ion complexation on the carbonyl stretching frequencies of these imides will be published later. Other ir data reported in the present paper were obtained using a Beckman IR-5A spectrophotometer. Boiling points are uncorrected.
(28) S. Wawzonek, J. Chua, E. L. Yeakey, and W. McKillip, *J. Org. Chem.*, **28**, 2376 (1963).

very large peak with a retention time identical with that of acetanilide.

Pyrolysis of N-(*n*-Butyl)-N-formylacetamide. Copper Tube.—The imide (228 mg, 1.59 mmol) was injected in 50-μl aliquots. The products (186 mg) were collected in ice and analyzed by glpc. Product weight corrected for carbon monoxide loss from 85% of the starting material was 224 mg.

Glass Tube.—The imide (228 mg, 1.59 mmol) was injected in 50-μl aliquots. The products (195.5 mg) were collected in ice and analyzed by glpc. Product weight corrected for carbon monoxide loss from 85% of the starting material was 234 mg.

Pyrolysis of N-(*sec*-Butyl)-N-formylacetamide.—The imide (461 mg, 3.22 mmol) was injected in 45-μl aliquots. The products (433 mg) were collected in ice and analyzed by glpc. The product weight corrected for carbon monoxide loss with 33% unreacted starting material and 57% of the reacted imide decarbonylating was 467 mg.

Pyrolysis of N-Cyclohexyl-N-formylacetamide.—The imide (980 mg, 5.80 mmol) was injected in 45-μl aliquots. The products (802 mg) were collected in ice and analyzed by glpc. The weight corrected for carbon monoxide loss with 8% unreacted starting material and 51% of the reacted imide decarbonylating was 880 mg.

Registry No.—N-(*n*-Butyl)-N-formylacetamide, 17604-86-3; N-(*sec*-butyl)-N-formylacetamide, 17604-87-4; N-cyclohexyl-N-formylacetamide, 17604-88-5.

Acknowledgment.—Elemental analyses were performed by the Analytical Chemistry Department, Chemical Research Laboratory, Edgewood Arsenal.

Synthetic Routes to Cyclopropyl-Substituted Azoalkanes. Some Reactions of Cyclopropylcarbinyl Cyanates, Isocyanates, Benzoates, and *p*-Nitrobenzoates

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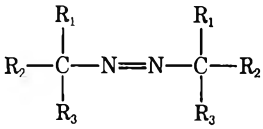
Received January 29, 1968

The syntheses of substituted azomethanes with one, two, and three cyclopropyl substituents on each methyl carbon (1a-e) have been approached *via* a variety of pathways starting from the appropriate cyclopropylcarbinols. We discuss complicating reactions which arise from the ready ionization of compounds such as tricyclopropylcarbinyl isocyanate and from ring-opening reactions of cyclopropyl carbonium ions. The most generally successful route to these azoalkanes involved ammonolyses of cyclopropylcarbinyl esters followed by oxidative coupling of the resulting amines by treatment with iodine pentafluoride. A second promising synthetic route converts a ketone into an azine to which chlorine is added to give an azo-α-chloroalkane. Replacement of the chlorine by an alkyl substituent occurs readily with alkylmagnesium bromides, under conditions which lead to regeneration of the azine on treatment with the corresponding alkylmagnesium iodide.

In connection with a kinetic study of the rates of formation of substituted cyclopropylcarbinyl radicals,[1] we have synthesized the following tertiary alkylazo compounds: 2,2′-dicyclopropyl-2,2′-azopropane (**1a**), 1,1,1′,1′-tetracyclopropyl-1,1′-azoethane (**1b**), 1,1,1′,1′-tetracyclopropyl-1,1′-azoisobutane (**1c**), and 1,1,1,1′,-1′,1′-hexacyclopropylazomethane (**1e**). This paper describes the synthesis of these compounds and the attempted synthesis of 1,1′-dicyclopropyl-1,1′-diisopropyl-1,1′-azoisobutane (**1d**).



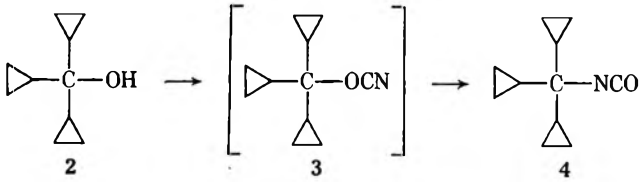
1a, $R_1 = R_2 = CH_3$; R_3 = cyclo-C_3H_5
b, $R_1 = CH_3$; $R_2 = R_3$ = cyclo-C_3H_5
c, $R_1 = i$-C_3H_7; $R_2 = R_3$ = cyclo-C_3H_5
d, $R_1 = R_2 = i$-C_3H_7; R_3 = cyclo-C_3H_5
e, $R_1 = R_2 = R_3$ = cyclo-C_3H_5
f, $R_1 = R_2 = R_3 = CH_3$
g, $R_1 = R_2 = CH_3$; $R_3 = C_6H_5$

Two possible synthetic approaches were considered likely to provide attractive routes to compounds such as **1**. The method of Esser, Rastadter, and Reuter[2] involves treatment of the appropriate isocyanate with excess hydrogen peroxide and leads directly to the azo compound. The method of Stevens[3] involves oxidative coupling of the appropriate amine with iodine pentafluoride. The latter method has been used to prepare the tertiary alkyl-substituted azo compounds 2,2′-azoisobutane[3,4] (**1f**) and azocumene[4] (**1g**).

Kauer and Henderson[5] have developed a method for preparation of isocyanates which involves treatment of an alcohol with sodium hydride followed by cyanogen chloride to give the aliphatic cyanates. The cyanates rearrange to the isocyanates on treatment with boron trifluoride etherate or, in some cases, simply on distillation.

$$ROH \xrightarrow{NaH} RO^-Na^+ \xrightarrow{ClCN} ROCN \xrightarrow{BF_3\cdot Et_2O} RNCO$$

Amine Syntheses.—Employing the method of Kauer and Henderson,[5] with only slight modification, we were able to prepare tricyclopropylcarbinyl isocyanate (**4**). The rapid rearrangement of **3** to **4** is suggested by our failure to detect any cyanate (**3**). Treatment of the isocyanate with hydrogen peroxide did not yield the desired azo compound. Instead, an almost quantitative yield of tricyclopropylcarbinol (**2**) was returned.



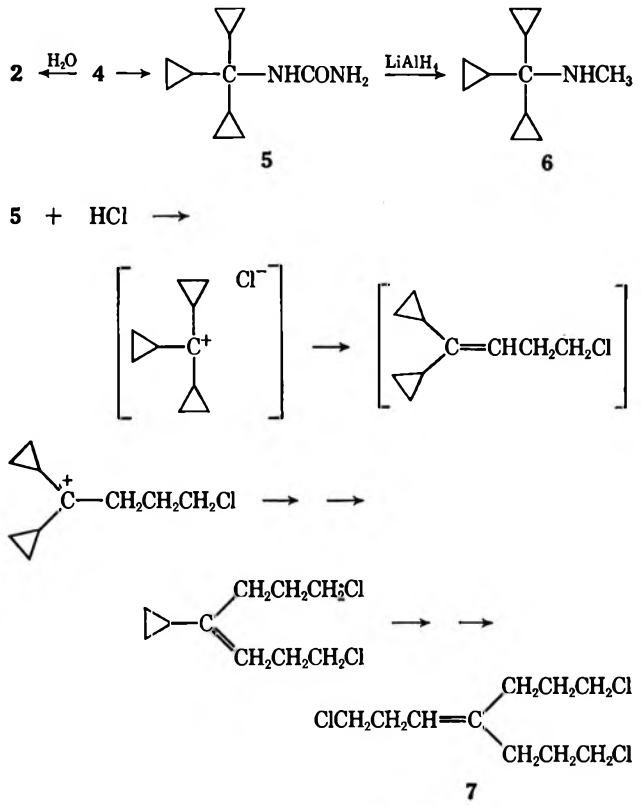
2 **3** **4**

It is possible that the isocyanate is hydrolyzed in the aqueous hydrogen peroxide solution even though attempts were made to remove all water. Hydroly-

(1) J. C. Martin, John E. Schultz, and Jack W. Timberlake, *Tetrahedron Lett.*, 4629 (1967).
(2) H. Esser, K. Rastadter, and G. Reuter, *Chem. Ber.*, **89**, 685 (1956).
(3) T. E. Stevens, *J. Org. Chem.*, **26**, 2531 (1961).
(4) S. F. Nelsen and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966).
(5) J. C. Kauer and W. W. Henderson, *ibid.*, **86**, 4732 (1964).

sis of the isocyanate in water–tetrahydrofuran also gave only **2**. The ionization of alkyl isocyanates is usually not rapid enough to compete with attack of nucleophile at the isocyanate carbon. In this case, however, the great stability of the tricyclopropyl carbonium ion apparently provides sufficient driving force to effect the ionization.[6] It was hoped that because of the facile ionization of **4**, treatment with ammonia would give tricyclopropylcarbinylamine. Instead, the isocyanate reacted in the manner usual for isocyanates, and the only isolated product was the substituted urea (**5**). The urea was unreactive toward dilute aqueous acid, and treatment with concentrated acid solution gave only 1,7-dichloro-4-(3-chloropropyl)-3-heptene (**7**), probably by the sequence of steps outlined in Scheme I.

SCHEME I

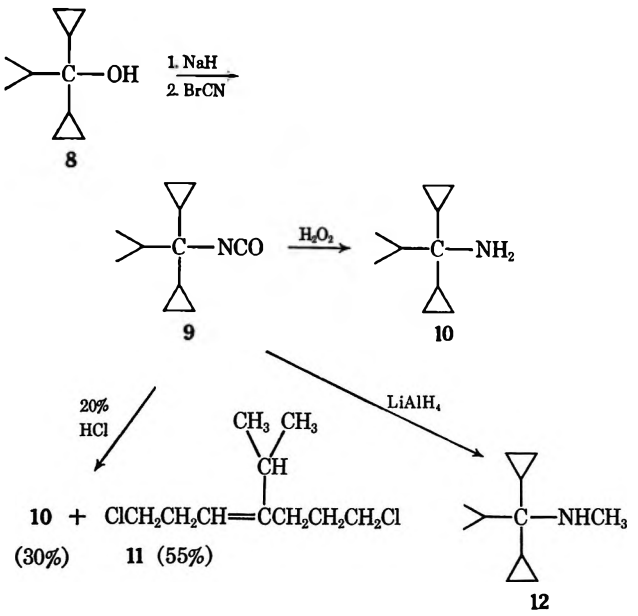


Isocyanate **4** was reduced by lithium aluminum hydride to yield N-methyl-N-tricyclopropylcarbinylamine (**6**).

Isopropyldicyclopropylcarbinyl isocyanate (**9**) was prepared in the same manner as tricyclopropylcarbinyl isocyanate. Again, isomerization of the cyanate intermediate was so rapid that its isolation was impossible. Treatment of the isocyanate with hydrogen peroxide did not yield the desired azo compound, nor did it hydrolyze in an analogous manner to **2** to isopropyldicyclopropylcarbinol (**8**). Instead, the only isolated product was isopropyldicyclopropylcarbinylamine (**10**). In contrast to **4**, **9** is unreactive toward water in refluxing tetrahydrofuran, and treatment with 20% hydrochloric acid yields a mixture of **10** (30%) and 1,7-dichloro-4-isopropyl-3-heptene (**11**, 55%). Isocyanate **9** was also reduced to the corresponding

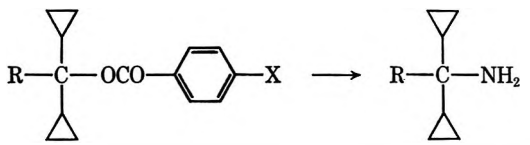
(6) R. Breslow in "Molecular Rearrangement," Vol. 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, Chapter 4.

SCHEME II



methylamine (**12**) by action of lithium aluminum hydride (Scheme II).

Although hydrolysis of **9** gave low yields of **10**, a more convenient route was found which not only gave **10** in high yield but which could be adapted for synthesis of tricyclopropylcarbinylamine (**16**) and methyldicyclopropylcarbinylamine (**17**). Ammonolysis of benzoate (**13**) or *p*-nitrobenzoate esters (**14** and **15**) in anhydrous liquid ammonia at room temperature gave the corresponding amines **16**, **10**, and **17** in high yield. The driving force provided by the cyclopropyl substituents apparently makes ionization to the carbonium ion more rapid than nucleophilic attack on the carbonyl group by ammonia.



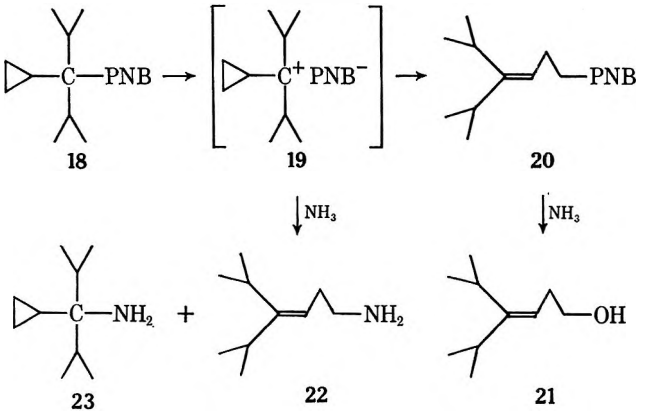
13, R = cyclo-C_3H_5; X = H
14, R = *i*-C_3H_7; X = NO_2
15, R = CH_3; X = NO_2

16, R = cyclo-C_3H_5
10, R = *i*-C_3H_7
17, R = CH_3

Significantly different results were obtained from the ammonolysis of diisopropylcyclopropylcarbinyl *p*-nitrobenzoate (**18**) in liquid ammonia. The ester was less reactive, and the ammonia solution had to be heated to 50° before appreciable disappearance of ester could be observed. The product yields were determined by glpc to be 36% 5-methyl-4-isopropyl-3-hexenol (**21**), 42% 6-amino-2-methyl-3-isopropyl-3-hexene (**22**), and 17% diisopropylcyclopropylcarbinylamine (**23**) (Scheme III). There was also one other amine component present in about 2% yield which was not identified. The structure of **21** is apparent from its elemental analysis and spectral data. Carbinol **21** has been reported as a product from the hydrolysis of 5-methyl-4-isopropyl-3-hexenyl *p*-nitrobenzoate (**20**).[7] The structural proof for amines **22** and **23**, although less rigorous, is evident from consideration of the spectral data. A mixture of the two amines, after

(7) H. Hart and J. M. Sandri, *J. Amer. Chem. Soc.*, **81**, 320 (1959).

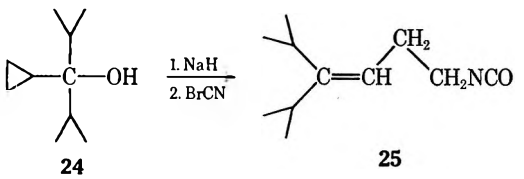
SCHEME III



purification by glpc, gave a satisfactory elemental analysis. The nmr of 6-amino-2-methyl-3-isopropyl-3-hexene (22) shows a single-proton triplet at δ 5.0 (vinyl proton), a three-proton multiplet at 2.38–3.10 (the methylene protons are adjacent to the amine group and the methine proton is on the isopropyl group which is *cis* to the vinyl proton),[8,9] a three-proton multiplet at 1.91–2.37 (the methylene protons are α to the double bond and the methine proton on the isopropyl group is *trans* to the vinyl proton), a two-proton broad peak at 1.54 (amine protons), and a twelve-proton doublet at 0.96 (methyl protons on the isopropyl groups).

Although the higher temperature employed for ammonolysis of **18** may have some effect in determining the different product distribution, the most important factor is more likely to be the greater difference in charge distribution in the carbonium ion formed by ionization of ester **18** relative to the ions from esters **13–15**. The formation of carbinol **21** is best accounted for by postulating internal return from the ion pair (**19**) to form the ring-opened *p*-nitrobenzoate ester (**20**) which then undergoes ammonolysis by attack at the carbonyl position to give the cleavage products 5-methyl-4-isopropyl-3-hexenol and *p*-nitrobenzamide. Hart[7] has found the same behavior for solvolysis of diisopropylcyclopropylcarbinyl *p*-nitrobenzoate in a variety of solvents. He found that the amount of rearranged ester (**20**) decreases as the dissociating power of the solvent increases. Although it is possible that all three products, carbinol **21** and amines **22** and **23**, arise from the rearranged ester **20**,[10] it is more likely that amines **22** and **23** arise from competition of ammonia with the *p*-nitrobenzoate anion for the initially formed cyclopropylcarbinyl cation. This is in accord with the observed lack of reactivity of 5-methyl-4-isopropyl-3-hexenyl *p*-nitrobenzoate (**20**), and supports the rationale that once formed it reacts *via* carbonyl attack of ammonia to yield carbinol. The preponderance of ring-opened amine in the ammonolysis of **13–15** appears to parallel the amount of positive charge expected on the methylenes in the cyclopropyl rings of the carbonium ions. The two isopropyl groups in **19** may also be so much more sterically demanding than cyclopropyl groups that attack by nucleophile on the ring becomes favored over attack at the tertiary carbon atom.

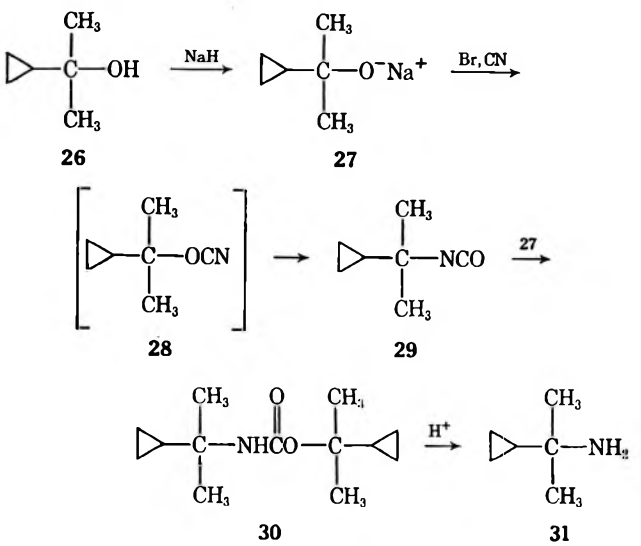
An attempted preparation of diisopropylcyclopropylcarbinylamine *via* the isocyanate was also unsuccessful. Treatment of diisopropylcyclopropylcarbinol with sodium hydride and cyanogen bromide gave a mixture of unstable products. The only component which was isolated (38%) was tentatively identified as 5-methyl-4-isopropyl-3-hexenyl isocyanate (**25**) from its ir and



nmr spectra. The ir spectrum showed intense absorption at 2260 cm^{-1} (NCO). The nmr showed a single-proton triplet at δ 5.08 (vinyl proton), a two-proton triplet at 3.24 (methylene protons α to the isocyanate group), a four-proton multiplet at 1.81–2.94 (methylene protons α to the double bond and the isopropyl methine protons), a doublet at 1.01, (J = 7 cps, methyl protons), and a small absorption from an impurity at 0.45. The impurity (less than 5%) could be diisopropylcyclopropylcarbinyl isocyanate.

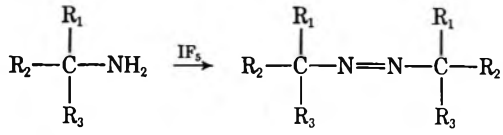
Dimethylcyclopropylcarbinylamine (**31**) was prepared by acid hydrolysis of the carbamate (**30**) produced from treatment of the carbinol (**26**) with sodium hydride and cyanogen bromide. It is noteworthy that, even though there is only one cyclopropyl group to delocalize the charge in the rearrangement of cyanate to isocyanate, no ring-opened products are formed. Apparently the less sterically demanding methyl groups (relative to isopropyl) allow attack by NCO^- at the tertiary carbon atom rather than on the ring. The isocyanate, once formed, is not appreciably sterically hindered toward attack by the unreacted alkoxide (**27**), and the major product is the carbamate (**30**) (Scheme IV). In the earlier isocyanate preparations no carbamate was observed.

SCHEME IV



(8) R. B. Bates, R. H. Carnighan, R. O. Rakutis, and H. J. Schauble, *Chem. Ind.* (London), 1020 (1960).
(9) R. B. Bates, and D. M. Gale, *J. Amer. Chem. Soc.*, **82**, 5949 (1960).
(10) K. L. Servis and J. D. Roberts, *ibid.*, **87**, 1331 (1965).

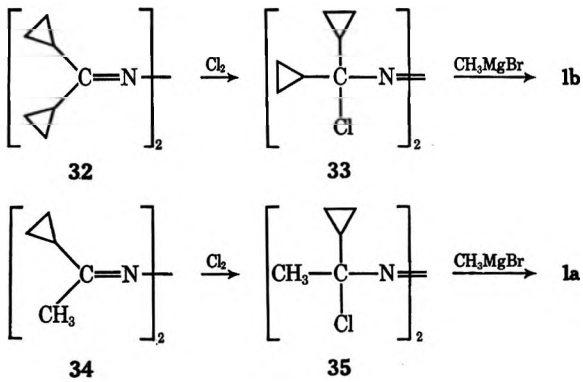
Azo Compounds.—In all cases the amines (**10, 16, 17,** and **31**) underwent oxidative coupling to the corresponding azo compounds **1a–c** and **1e** by treatment with iodine pentafluoride.



10, 16, 17, 31 **1a–c, 1e**

Compounds **1a** and **1b** were also prepared from the appropriate chloroazo compounds, **33** and **35**. Such compounds can readily be prepared by the method of Goldschmidt and Acksteiner[11,12] and Benzing[13] by action of chlorine on the azine. Compounds **33** and **35** were prepared in this manner from the corresponding ketazines **32** and **34**. Treatment of **33** with methylmagnesium iodide did not provide the desired azo compound, **1b**. Instead, the chloroazo compound was transformed into ketazine **32**. It was found that use of methylmagnesium bromide instead of methylmagnesium iodide did give **1b** from **33** and **1a** from **35** (Scheme V).

SCHEME V



32 **33** **34** **35**

It is possible that, in cases where the desired amines are difficult or impossible to prepare, this may be the preferred method for preparation of tertiary alkylazo compounds of type **1**.

Experimental Section

Tricyclopropylcarbinyl Isocyanate (4).—The method of Hart and Sandri[14] was used to prepare tricyclopropylcarbinol, **1**, bp 85° (10 mm) [lit.[14] bp 85° (10 mm)], in 83% yield. The isocyanate was prepared according to the general method of Kauer and Henderson[5] with several modifications.

To 3.5 g (0.146 mol) of sodium hydride in 30 ml of tetrahydrofuran was added dropwise tricyclopropylcarbinol (10.2 g, 0.067 mol) in 20 ml of tetrahydrofuran. After the addition (2 hr) the reaction mixture was refluxed for 8 hr. The mixture was cooled in an ice bath, and a tetrahydrofuran solution of cyanogen bromide (20.0 g, 0.189 mol) was added. The mixture was stirred at room temperature for 1 hr and suction filtered. Solvent removal and distillation gave 9.5 g of clear liquid, bp 74–76° (2.5 mm). Analysis by glpc (SE-30 on Chromosorb W, column temperature 140°) showed the liquid to be a 4:1 mixture of isocyanate **4** and tricyclopropylcarbinol which was not separated by a second, more careful distillation. Attempted column chromatography on silica gel and elution with benzene resulted in an increase in the amount of carbinol from hydrolysis of the isocyanate on the column. A small sample was purified for analytical and spectroscopic purposes by glpc, but for the reactions listed below samples of 80–90% purity were used [nmr ($CDCl_3$) δ 0.75–1.24 (m, 3.7, methine cyclopropyl protons), 0.27–0.69 (m, 11.83, methylene cyclopropyl protons)].

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.91. Found: C, 74.50; H, 8.58; N, 8.11.

To the above mixture of **4** and **1** (500 mg) was added 1.5 ml of water and 5 ml of tetrahydrofuran. The mixture was refluxed with stirring for 11 hr. The reaction mixture was extracted with ether and dried over magnesium sulfate. After removal of the ether and tetrahydrofuran *in vacuo* there remained 480 mg of a liquid whose ir and nmr spectra and glpc retention time, under conditions which would allow tricyclopropylcarbinylamine, tricyclopropylcarbinol, and tricyclopropylcarbinyl isocyanate to be distinguished, were identical with those of an authentic sample of trieyclopropylcarbinol.

N-Methyl-N-tricyclopropylcarbinylamine (6).—To lithium aluminum hydride (0.8 g, 0.021 mol) in 25 ml of sodium-dried ether was added tricyclopropylcarbinyl isocyanate of approximately 90% purity (2.07 g, 0.0117 mol, assuming 100% isocyanate) in 10 ml of ether. The solution was refluxed for 90 min, then hydrolyzed with water. The ether layer was dried, and hydrogen chloride gas passed over the surface. The resulting white salt was filtered, washed with several small portions of ether, and dissolved in 30% potassium hydroxide solution. Ether extracts of the basic solution were dried over magnesium sulfate, and the ether was removed *in vacuo*. The resulting yellow liquid was purified by preparative glpc on a 5-ft column of Carbowax 20M at 150° to give 1.32 g (68%) of amine **6**: nmr ($CDCl_3$) δ 3.39 (s, 2.88, $-CH_3$), 0.08–0.85 (m, 16.12, NH_2 and cyclopropyl protons, integral reduced to 15.08 on shaking with D_2O).

Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found: C, 80.19; H, 11.44; N, 8.18.

Tricyclopropylcarbinylurea (5).—To an isocyanate mixture of approximately 90% purity (3.45 g, 0.0195 mol) in a Carius tube was added approximately 20 ml of anhydrous ammonia. The tube was sealed and allowed to stand at room temperature for 50 hr. After evaporation of the ammonia the oily solid that remained was recrystallized three times from a 4:1 mixture of hexane and chloroform. There was obtained 2.78 g (69%) of tricyclopropylcarbinylurea as colorless needles: mp 120.5–121°; nmr ($CDCl_3$) δ 4.88–5.30 (broad signals, 2.77, NH_2 and NH), 0.72–1.23 (m, 3.03, methine protons), and 0.14–0.69 (m, 11.98, methylene protons).

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.35; N, 14.42. Found: C, 67.89; H, 9.34; N, 14.49.

Tricyclopropylcarbinylurea (1.15 g, 5.93 mmol) was stirred for 10 hr with 20 ml of concentrated hydrochloric acid. The reaction was made basic and extracted with ether. The ether layer was dried and removed *in vacuo* to yield 1.40 g of crude 1,7-dichloro-4-(3-chloropropyl)-3-heptene identified by comparison of ir and nmr spectra with those of an authentic sample (*vide infra*).

1,7-Dichloro-4-(3-chloropropyl)-3-heptene (7).—To tricyclopropylcarbinol (5.07 g, 0.03 mol) was added 25 ml of concentrated hydrochloric acid. The suspension was stirred at room temperature for 8 hr and extracted with ether. The ether layer was dried over magnesium sulfate and removed *in vacuo*. After distillation through a 30-cm Holzman column, there was obtained 5.54 g (76%) of 1,7-dichloro-4-(3-chloropropyl)-3-heptene: bp 110–112° (0.25 mm); nmr ($CDCl_3$) δ 5.27 (t, 1.02, J = 7.0 Hz, vinyl proton), 3.50 (t, 5.88, J = 6.0 Hz, $-CH_2-$ α to chlorine), 1.55–2.70 (m, 10.01, $-CH_2-$ β to chlorine and $-CH_2-$ γ to chlorine).

Anal. Calcd for $C_{10}H_{17}Cl_3$: C, 49.30; H, 7.03. Found: C, 49.60; H, 7.06.

Isopropyldicyclopropylcarbinyl Isocyanate (9).—Isopropyldicyclopropylcarbinol was prepared according to the method of Hart and Sandri in 74% yield, bp 77–78° (10 mm) [lit.[7] bp 75° (10 mm)]. The isocyanate was prepared by the same procedure used for tricyclopropylcarbinyl isocyanate. After chromatography on silica gel there was obtained a 68% yield of the isocyanate contaminated with 5% (by glpc) of an unknown impurity. Preparative glpc on a 5-ft 20% SE-30 on Chromosorb W column at 120° was used to prepare a sample for elemental and spectroscopic analyses: nmr ($CDCl_3$) δ 1.72–2.22 [m, 1.0, $-CH(CH_3)_2$], 1.02 [d, $CH(CH_3)_2$] superposed on 0.68–1.20 (m,

(11) S. Goldschmidt and B. Acksteiner, *Chem. Ber.*, **91**, 502 (1958).
(12) S. Goldschmidt and B. Acksteiner, *Ann. Chem.*, **618**, 173 (1958).
(13) E. Benzing, *ibid.*, **631**, 1 (1960).
(14) H. Hart and J. M. Snadri, *Chem. Ind.* (London), 1014 (1956).

cyclopropyl methine protons) (total integral 8.0), 0.22–0.53 (m, 8.0, cyclopropyl $-CH_2-$).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.97; H, 9.45; N, 8.05.

A small sample of isopropyldicyclopropylcarbinyl isocyanate was shown to be stable toward water in refluxing tetrahydrofuran by reisolating the sample and examining its nmr and ir spectra and glpc retention time on a Carbowax 20M column, under conditions which would allow the carbinol, amine, and isocyanate to be distinguished.

To an ether solution of hydrogen peroxide (2 ml of 83% H_2O_2 dissolved in 40 ml of ether and dried over sodium sulfate)[15] was added 2 drops of triethylamine and 256 mg (1.43 mmol) of isopropyldicyelopropylcarbinyl isocyanate. The reaction was stirred at room temperature for 4 hr. After extracting the mixture with three 20-ml portions of water, the ether layer was dried over magnesium sulfate and concentrated. There was obtained in this manner 190 mg (87%) of a liquid whose nmr and ir spectra were identical with those of isopropyldicyclopropylcarbinylamine, *vide infra*.

1,7-Dichloro-4-isopropyl-3-heptene (11).—To 11.2 g (0.0625 mol) of isopropyldicyclopropyl isocyanate in 30 ml of tetrahydrofuran was added 15 ml of 20% hydrochloric acid. The solution was refluxed for 36 hr. The tetrahydrofuran solution was concentrated, and the acidic solution was extracted with ether. The ether layer was washed with 5% sodium hydroxide and dried, and the ether removed *in vacuo*. The dark red-brown oil was distilled to give 8.0 g (65%) of a colorless liquid identified as 1,7-dichloro-4-isopropyl-3-heptene: nmr ($CDCl_3$) δ 4.98–5.47 (m, 0.95, C=CH—), 3.30–3.77 (m, 3.88, CH_2 α to chlorine), 1.58–3.02 [m, 7.24, CH_2 α to double bond, plus CH_3 α to double bond and β to chlorine plus $-CH(CH_3)_2$], 1.02 [d, 5.95, J = 7.0 Hz, $-CH(CH_3)_2$].

Anal. Calcd for $C_{10}H_{18}Cl_2$: C, 57.42; H, 8.67. Found: C, 57.18; H, 8.68.

The acid solution was made basic and extracted with ether. The ether layer was dried, and hydrogen chloride gas was passed over the surface. The resulting white solid was filtered, washed with ether, and dissolved in 30% aqueous potassium hydroxide. The amine was extracted with ether. After drying the ether and removing it *in vacuo*, there remained 2.90 g (29%) of isopropyldicyclopropylcarbinylamine (10), *vide infra*.

N-Methyl-N-isopropyldicyclopropylcarbinylamine (12).—To 0.6 g (0.0158 mol) of lithium aluminum hydride in 30 ml of sodium dried ether was added 1.1 g (6.14 mmol) of isopropyldicyclopropylcarbinyl isocyanate in 10 ml of ether. The reaction was refluxed for 4 hr and hydrolyzed with 30 ml of water. The ether layer was dried over magnesium sulfate and concentrated. The clear liquid was purified by preparative glpc on a 3.5-ft SE-30 on Chromosorb W column at 120° to give 790 mg (77%) of the amine, 12: nmr ($CDCl_3$) δ 2.30 (s, 2.96, NCH_3), 1.97 [quintet, 0.99, J = 7.0 Hz, $-CH(CH_3)_2$], 0.98 [d, 6.21, J = 7.0 Hz, $-CH(CH_3)_2$], 0.08–0.80 (m, 10.90, cyclopropyl protons plus NH).

Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 78.90; H, 12.57; N, 8.57.

Tricyclopropylcarbinylamine (16).—Crude tricyclopropylcarbinyl benzoate, **13**, was prepared in 90% yield according to the method of Hart and Law[16] and was used without further purification. Into each of four Carius tubes (30 cm in length and 25 mm in diameter), containing equal portions of 20.28 g (0.0793 mol) of this ester, was condensed approximately 25 ml of anhydrous ammonia. After standing at room temperature for 10 days, the tubes were opened, and the ammonia was allowed to evaporate. The residue was taken up in 400 ml of ether and extracted with several portions of 10% sodium hydroxide. The ether layer was dried over magnesium sulfate and concentrated to yield 12.0 g (100%) of a yellow liquid. The amine was converted into its hydrochloride salt and reconverted into the amine with 30% potassium hydroxide. There was obtained after distillation 10.9 g (91%) of tricyclopropylcarbinylamine, bp 85° (11 mm). The nmr spectrum shows continuous absorption between 9.00 and 9.90.

Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.15; H, 11.25; N, 9.08.

A small portion of the hydrochloride salt was recrystallized from a 4:1 mixture of ethyl acetate and ethanol.

Anal. Calcd for $C_{10}H_{18}NCl$: C, 63.98; H, 9.67; N, 7.46. Found: C, 64.03; H, 9.61; N, 7.49.

1,1,1,1′,1′,1′-Hexacyclopropylazomethane (1e).—The general method used was that of Stevens[3] with several modifications.

Tricyclopropylcarbinylamine (3.84 g, 0.0265 mol) in 20 ml of olefin-free pentane was added dropwise to a solution of iodine pentafluoride (2.0 ml, 0.026 mol) and pyridine (10.25 g, 0.130 mol) in 75 ml of pentane cooled to 0° in an ice bath. After the addition, the solution was stirred at 0° for 15 min and then at room temperature for 45 min. Work-up was effected by adding 40 ml of a 10% potassium hydroxide solution and separation of the hydrocarbon layer. The aqueous layer was extracted with several 50-ml portions of pentane. After washing the pentane extracts with two 50-ml portions of water, two 50-ml portions of 5% sodium thiosulfate solution, and two additional 50-ml portions of water, the solution was dried over magnesium sulfate and the pentane removed *in vacuo*. The viscous yellow oil was chromatographed on 120 g of base washed alumina, eluting with hexane. The resulting yellow oil was recrystallized from a methanol–ether mixture (10:1) by cooling in Dry Ice and centrifuging the crystals. After three recrystallizations there was obtained 1.45 g (38%) of 1,1,1,1′,1′,1′-hexacyclopropylazomethane: mp 17–18.5°; bp 100° (0.25 mm) dec; uv max (cyclohexane) 386 mμ (ϵ 41); nmr ($CDCl_3$) δ 0.65–1.09 (m, 5.7, cyclopropyl methine), 0.12–0.64 (m, 24.3, cyclopropyl methylene).

Anal. Calcd for $C_{20}H_{30}N_2$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.24; H, 9.94; N, 9.52.

Further elution of the column with ethyl acetate gave 1.6 g (42%) of tricyclopropylcarbinol which was identified by comparison of its ir and nmr spectra with those of an authentic sample.

Isopropyldicyclopropylcarbinylamine (10).—To a suspension of potassium metal (5.3 g, 0.135 g-atom) in 300 ml of ether was added dropwise isopropyldicyclopropylcarbinol (20.86 g, 0.135 mol) dissolved in 50 ml of ether. The mixture was stirred at room temperature for 18 hr. The flask was cooled in an ice bath and *p*-nitrobenzoyl chloride (25.1 g, 0.1355 mol) in 100 ml of ether was added rapidly. The solution was stirred at room temperature for 1 hr and suction filtered. The solvent was removed, and the solid was recrystallized from hexane to yield 30.2 g (74%) of isopropyldicyclopropyl *p*-nitrobenzoate, mp 108–110° (lit.[7] mp 114–1151).

The same ammonolysis procedure was followed as was employed to make tricyclopropylcarbinylamine.

From 29.03 g (0.0784 mol) of the *p*-nitrobenzoate, there was obtained 10.8 g (90%) of pure isopropyldicyclopropylcarbinylamine: bp 86–87° (10 mm); nmr ($CDCl_3$) δ 1.55 [m, 0.99, $-CH(CH_3)_2$] 1.00 [d, 6.24, $-CH(CH_3)_2$], 0.45–0.85 (m, 2.34, cyclopropyl methine), 0.05–0.40 (m, 9.43, cyclopropyl methylene plus N–H).

Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.11; H, 12.37; N, 9.05.

A small amount of the amine hydrochloride salt was recrystallized from an ethyl acetate and ethanol mixture (8:1).

Anal. Calcd for $C_{10}H_{20}NCl$: C, 63.30; H, 10.63; N, 7.38. Found: C, 63.39; H, 10.59; N, 7.48.

1,1,1′,1′-Tetracyclopropyl-1,1′-azoisobutane (1c).—The azo compound was prepared in an identical manner with that described for 1,1,1,1′,1′,1′-hexacyclopropylazomethane.

From 6.12 g (0.04 mol) of isopropyldicyclopropylcarbinylamine, 3.3 ml (0.042 mol) of iodine pentafluoride, and 16.6 g (0.21 mol) of pyridine there was obtained, after chromatography and two recrystallizations from methanol–ether (9:1), 3.62 g (60%) of 1,1,1′,1′-tetracyclopropyl-1,1′-azoisobutane: nmr ($CDCl_3$) δ 2.00 [m, 2.17, $CH(CH_3)_2$], 0.95 [d, 12.11, $-CH(CH_3)_2$], 0.10–0.85 (m, 19.72, cyclopropyl protons).

Anal. Calcd for $C_{20}H_{34}N_2$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.37; H, 11.23; N, 9.51.

Methyldicyclopropylcarbinyl *p*-Nitrobenzoate (15).—Methyldicyclopropylcarbinol was prepared by the method of Hart and Sandri in 85% yield, bp 64° (15 mm) [lit.[7] bp 45° (4 mm)]. The *p*-nitrobenzoate was prepared by the same method used for synthesis of isopropyldicyclopropylcarbinyl *p*-nitrobenzoate.

From 24.2 mg (0.192 mol) of methyldicyclopropylcarbinol, 7.51 g (0.192 g-atoms) of potassium, and 35.52 g (0.192 mol) of *p*-nitrobenzoyl chloride was obtained, after recrystallization from hexane, 32.5 g (62%) of methyldicyclopropylcarbinyl *p*-nitrobenzoate as fluffy colorless needles: nmr ($CDCl_3$) 8.03–8.52 (m, 4.07, phenyl C–H), 1.52 (s, 3, CH_3), 1.60–1.80 (m,

(15) M. Hanack and H. Eggensperger, *Angew. Chem.*, **74**, 116 (1962).
(16) H. Hart and P. S. Law, *J. Amer. Chem. Soc.*, **86**, 1957 (1964).

1.8, cyclopropyl methine), 0.30–0.80 (m, 8.15, cyclopropyl methylene). The ester has no well-defined melting point. It changes crystalline structure between 100 and 165°, from needles to plates, the latter melting at 225–230°.[17]

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.63; H, 6.26; N, 5.18.

Methyldicyclopropylcarbinylamine (17).—The same procedure was followed that was employed for tricyclopropylcarbinylamine.

From 25 g (0.095 mol) of methyldicyclopropylcarbinyl *p*-nitrobenzoate there was obtained 9.22 g (82%) of methyldicyclopropylcarbinylamine: bp 50° (12 mm); nmr ($CDCl_3$) δ 0.96 (s, 3.38, CH_3), 0.40–0.95 (m, 3.86, cyclopropyl methine plus N–H), 0.29 and 0.20 (m, 7.81, cyclopropyl methylenes).

Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.90; H, 12.19; N, 11.13.

1,1,1′,1′-Tetracyclopropyl-1,1′-azoethane (1b).—The compound was prepared in an identical manner with that described for 1,1,1,1′,1′,1′-hexacyclopropylazomethane.

From methyldicyclopropylcarbinylamine (5.75 g, 0.046 mol), iodine pentafluoride (3.8 ml, 0.05 mol), and pyridine (19.75 g, 0.25 mol) there was obtained, after chromatography and two recrystallizations from absolute methanol at −80°, 3.17 g (56%) of 1,1,1′,1′-tetracyclopropyl-1,1′-azoethane: bp 80–81° (0.25 mm); uv max (cyclohexane) 378 mμ (ϵ 34); nmr ($CDCl_3$) δ 0.82 (s, 6.10–CH_3), 0.75–1.25 (m, 3.9, cyclopropyl methine), 0.10–0.55 (m, 16.0, cyclopropyl methylene).

Anal. Calcd for $C_{16}H_{26}N_2$: C, 77.99; H, 10.64; N, 11.37. Found: C, 78.17; H, 10.82; N, 11.45.

Diisopropylcyclopropylcarbinyl *p*-Nitrobenzoate (18).—Diisopropylcyclopropyl carbinol was prepared in 66% yield by the method of Hart and Sandri, bp 70–73° (10 mm) [lit.[7] bp 75° (10 mm)]. The corresponding *p*-nitrobenzoate was prepared by a slight modification of the method used for preparation of isopropyldicyclopropylcarbinyl *p*-nitrobenzoate.

From 3.12 g (0.02 mol) of diisopropylcyclopropylcarbinol, 1.0 g (0.0417 mol) of sodium hydride, and 3.7 g (0.02 mol) of *p*-nitrobenzoyl chloride there was obtained, after recrystallization from hexane, 4.0 g (66%) of diisopropylcyclopropylcarbinyl *p*-nitrobenzoate, mp 90–92° (lit.[7] mp 91–92°).

Ammonolysis of Diisopropylcyclopropylcarbinyl *p*-Nitrobenzoate (18).—The method employed was similar to the one used for preparation of isopropyldicyclopropylcarbinylamine.

Diisopropylcyclopropylcarbinyl *p*-nitrobenzoate (4.0 g, 0.0131 mol) was sealed in two Carius tubes with approximately 25 ml of anhydrous ammonia in each. After heating in a water bath at 50° for 10 days, the tubes were opened and the ammonia was allowed to evaporate. The residue was taken up in 200 ml of ether and washed with several portions of 10% potassium hydroxide solution. The ether layer was dried over magnesium sulfate and concentrated to give 1.91 g of yellow liquid. The mixture was analyzed on an Aerograph A-90-P3 glpc employing a 3-ft column packed with 20% diisodecylphthalate on base-washed firebrick at 146° with a helium flow rate of 50 cc/min. The mixture consisted of three major components (94.3%), identified in order of increasing retention times as, 6-amino-2-methyl-3-isopropyl-3-hexene (45%), diisopropylcyclopropylcarbinylamine (12.9%), and 5-methyl-4-isopropyl-3-hexenol-1 (36.4%). No diisopropylcyclopropylcarbinol was detected.

The carbinol was separated by chromatography of a small portion of the mixture on a silica gel column (50:1 weight ratio) by eluting with benzene–ethyl acetate (2:1). The clear liquid that eluted first was purified by preparative glpc on a 5-ft 20% Carbowax 20M on Chromosorb W column. It was identified as 5-methyl-4-isopropyl-3-hexenol[7] (21): nmr ($CDCl_3$) δ 5.11 (t, 1.00 J = 7.5 Hz; C=CH), 3.29–3.69 (m, 300 $-CH_2OH$), 2.57–3.07 [m, 1.12, $-CH(CH_3)_2$ *cis* to vinyl C—H],[8,9] 2.05–2.50 [m, 3.00, allylic CH_2 plus CH_2 plus $CH(CH_3)_2$ *trans* to vinyl C—H],[8,9] 1.02 [d, 11.88, J = 7.0 Hz, $-CH(CH_3)_2$].

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.83; H, 12.89.

The amine portion of the original mixture was purified by conversion into the hydrochloride salts and reconversion into the amines. The amines were collected by preparative glpc on a Carbowax 20M column.

Anal. Calcd for $C_{10}H_{21}N$: C, 77.34; H, 13.63; N, 9.02. Found: C, 77.23; H, 13.70; N, 9.24.

Purification of 6-amino-3-isopropyl-2-methyl-3-hexene was carried out by preparative glpc on a 3-ft 20% diisodecylphthalate on base-washed firebrick column: nmr ($CDCl_3$) ϵ 5.10 (t, 0.95 C=CH), 2.38–2.10 [m, 2.95 $-CH_2-$N plus $-CH(CH_3)_2$ *cis* to vinyl C—H], 1.91–2.37 [m, 2.95 allylic CH_2 plus $CH(CH_3)_2$ *trans* to vinyl C—H], 1.54 (m, 2.05, N—H), 0.96 [d, 12.13, $-CH(CH_3)$].

Purification of diisopropylcyclopropylcarbinylamine was effected using the same base-washed diisodecylphthalate column; nmr ($CDCl_3$) δ 1.53–2.17 [m, 2.17, $-CH(CH_3)_2$], 1.38 (m, 1.80 –NH), 0.94 and 0.90 [pair of doublets, 11.80, J = 7.0 Hz, two $-CH(CH_3)_2$].

5-Methyl-4-isopropyl-3-hexenyl Isocyanate (25).—The method was similar to that used for preparation of **4**.

From diisopropylcyclopropylcarbinol (5.2 g, 0.0333 mol), sodium hydride (2.4 g, 0.1 mol), and cyanogen bromide (12 g, 0.112 mol) was obtained, after work-up, 5.5 g of viscous red liquid.

The nmr of this liquid shows less than 15% of the molecules to have the cyclopropyl rings still intact.

A portion of the product (2.5 g) was chromatographed on 88 g of silica gel and eluted with benzene. The component which eluted first (1.19 g) was flash distilled to give 1.05 g (38%) of a colorless liquid which gradually turned red upon standing. The nmr and ir spectra are consistent for 5-methyl-4-isopropyl-3-hexenyl isocyanate: nmr ($CDCl_3$) δ 5.08 (t, 0.95, C=CH), 3.24 (t, 1.99 $-CH_2NCO$), 1.81–2.94 [m, 4.07, allylic CH_2 plus $CH(CH_3)_2$], 1.01 [d, 11.97, J = 7 Hz, $-CH(CH_3)_2$], 0.45 (impurity, less than 5%, probably diisopropylcyclopropylcarbinyl isocyanate).

Dimethylcyclopropylcarbinyl-N-(dimethylcyclopropylcarbinyl)-carbamate (30).—Dimethylcyclopropylcarbinol was prepared according to literature methods in 73% yield, bp 120–123° (760 mm) [lit.[18,19] bp 121–122°, 123–124° (760 mm)]. The carbinol (5.0 g, 0.05 mol) in 5 ml of tetrahydrofuran was added to sodium hydride (2.4 g, 0.1 mol) suspended in 50 ml of tetrahydrofuran. After refluxing for 10 hr, a solution of cyanogen bromide (15 g, 0.14 mol) in 50 ml of tetrahydrofuran was added rapidly to the ice-cooled alkoxide solution. The reaction was stirred at room temperature for 1 hr. After suction filtration, the tetrahydrofuran and excess cyanogen bromide were removed *in vacuo*, and the resulting viscous dark red liquid was vacuum distilled through a 30-cm Holzman column. After collecting 1.8 g of forerun, presumably dimethylcyclopropylcarbinyl isocyanate (the forerun showed a very strong infrared absorption at 2240 cm^{-1}), we collected 3.1 g (55%) of dimethylcyclopropylcarbinylcarbamate as a colorless viscous liquid: bp 95–96° (1.8 mm); nmr ($CDCl_3$) δ 4.45 (m, 0.82–NH) 1.17 and 1.31 (two singlets, 12.73, $-CH_3$), 1.17 (m, 12.23, $-CH_3$), 0.69–1.17 (m, 1.86, cyclopropyl methine), 0.30–0.41 (m, 8.09, cyclopropyl methylene).

Anal. Calcd for $C_{13}H_{53}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.34; H, 10.40; N, 6.61.

Dimethylcyclopropylcarbinylamine (31).—The most facile procedure for isolating the amine was to hydrolyze the crude carbamate described above before distillation.

From 30 g (0.3 mol) of dimethylcyclopropylcarbinol, 12 g (0.5 mol) of sodium hydride, and approximately 70 g of cyanogen bromide was isolated 28.6 g of dark red liquid. To the crude carbamate, cooled in an ice bath, was added approximately 50 ml of concentrated hydrochloric acid. The reaction was magnetically stirred and heated at 60° for 8 hr, cooled, and washed with three 50-ml portions of ether. The acid layer was cooled in an ice bath and made basic (pH > 11) with potassium hydroxide pellets. After extraction with ether and concentration by distillation through a Vigreux column, the amine was converted into the hydrochloride salt and recrystallized from ethyl acetate–ethanol, 8.05 g (53%): mp 223–225° dec; nmr ($CDCl_3$) δ 5.15 (s, 2.75, –NH), 1.75 (s, 6.30, CH_3), 0.95–1.30 (m, 0.75 cyclopropyl methine), 0.40–0.72 (m, 4.20, cyclopropyl methylene).

Anal. Calcd for $C_6H_{14}NCl$: C, 53.13; H, 10.40; N, 10.33. Found: C, 53.15; H, 10.64; N, 10.11.

1,1′-Dicyclopropyl-2,2′-azopropane (1a).—Dimethylcyclopropylcarbinylamine hydrochloride (7 g, 0.0518 mol) was dissolved in 20 ml of water, made basic (pH > 11) with potassium hydroxide pellets, and extracted with 50 ml of olefin-free hexane.

(17) P. D. Bartlett and E. B. Lefferts, *J. Amer. Chem. Soc.*, **77**, 2804 (1955).

(18) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1962).

(19) R. Van Volkenburg, K. W. Greenless, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **71**, 172 (1949).

The hexane was dried over magnesium sulfate, filtered, and added dropwise to an ice-cooled mixture of iodine pentafluoride (4.7 ml, 0.061 mol) and pyridine (24.1 g, 0.305 mol). After work-up, chromatography on 200 g of base-washed alumina, and distillation, there was obtained 2.23 g (44%) of 1,1′-dicyclopropyl-2,2′-azopropane: bp 43–45° (1.0 mm); uv max (cyclohexane) 372 mμ (ε 22); nmr ($CDCl_3$) δ 1.03 (s, CH_3), superposed on 0.77–1.38 (m, total 14.10, cyclopropyl methine), 0.25–0.32 (m, 7.90, cyclopropyl methylene).

Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.14; H, 11.44; N, 14.63.

Cyclopropylmethylcarbinylazine (34).—To cyclopropyl methyl ketone (8.4 g, 0.1 mol) in 30 ml of pentane was added anhydrous hydrazine (1.7 ml, 0.053 mol). The solution was refluxed for 24 hr and dried over calcium chloride, and the pentane was removed *in vacuo*. Distillation gave 4.44 g (54%) of cyclopropylmethylcarbinylazine: bp 76° (1.5 mm); nmr ($CDCl_3$) δ 1.76 (s, 5.6, $-CH_3$) 1.18–1.70 (m, 2.4, cyclopropyl methine), 0.50–0.90 (m, 8.0, cyclopropyl methylene).

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 73.01; H, 9.84; N, 17.20.

1,1′-Dichloro-1,1′-dicyclopropyl-1,1′-azoethane (35).—The azo compound was prepared by the method of Goldschmidt and Acksteiner.[11,12] After three recrystallizations from pentane at −30° there was obtained a 57% yield of the azo compound, mp 43–50°, presumably as a mixture of isomers: nmr ($CDCl_3$) δ 1.82 (s, 6.05, $-CH_3$), 1.30–1.75 (m, 1.95, cyclopropyl methine), 0.40–0.80 (m, 8.00, cyclopropyl methylene).

Anal. Calcd for $C_{10}H_{16}N_2Cl_2$: C, 51.07; H, 6.86; N, 11.91. Found: C, 50.91; H, 6.73; N, 11.83.

Dicyclopropylcarbinylazine (32).—The azine was prepared according to the method of Hart and Curtis in 78% yield, mp 91–91.5° (lit.[20] mp 92–93°).

1,1′-Dichloro-1,1,1′,1′-tetracyclopropylazomethane (33).—The azo compound was prepared in 72% yield by the procedure described for 1,1′-dichloro-1,1′-dicyclopropyl-1,1′-azoethane: mp 48–52°; nmr ($CDCl_3$) δ 1.32–1.90 (m, 4.09, cyclopropyl methines), 0.35–0.85 (m, 15.91, cyclopropyl methylenes).

Anal. Calcd for $C_{14}H_{20}N_2Cl_2$: C, 58.54; H, 7.02; N, 9.75. Found: C, 58.52; H, 7.14; N, 9.72.

Reaction of 1,1′-Dichloro-1,1,1′,1′-tetracyclopropylazomethane with Methylmagnesium Bromide.—To 1,1′-dichloro-1,1,1′,1′-tetracyclopropylazomethane (250 mg, 0.871 mmol) in 20 ml of sodium-dried ether was added methylmagnesium bromide (2 ml of approximately 3 *M* solution, 6 mmol). The solution was stirred at room temperature for 30 min and treated with water. The ether layer was dried, and the ether was removed *in vacuo*. The resulting liquid was chromatographed on 20 g of base-washed alumina to give 110 mg (51%) of a compound whose nmr and ir spectra were identical with those of 1,1,1′,1′-tetracyclopropyl-1,1′-azoethane.

It was found that addition of the chloroazo compound to a Grignard reagent generated from methylmagnesium iodide gave only dicyclopropylcarbinylazine in 85% yield.

Reaction of 1,1′-Dichloro-1,1′-dicyclopropyl-1,1′-azoethane with Methylmagnesium Bromide.—To 1,1′-dichloro-1,1′-dicyclopropyl-1,1′-azoethane (1.17 g, 5 mmol) in 35 ml of sodium-dried ether was added excess methylmagnesium bromide (5 ml of approximately 3 *M* solution, 15 mmol). After a slight induction period the reaction refluxed gently for several minutes. The solution was stirred for 2 hr at room temperature and hydrolyzed with water. The ether layer was dried over magnesium sulfate, concentrated, and chromatographed on 100 g of base-washed alumina to give 710 mg (73%) of a compound whose nmr and ir spectra were identical with those of 1,1′-dicyclopropyl-2,2′-azopropane.

(20) H. Hart and O. E. Curtis, *ibid.*, **78**, 112 (1956).

Registry No.—**1a**, 17396-98-4; **1b**, 17396-99-5; **1c**, 17397-00-1; **1e**, 17397-01-2; **4**, 17397-02-3; **5**, 17397-03-4; **6**, 17397-04-5; **7**, 17397-05-6; **9**, 17397-06-7; **10**, 17397-07-8; **11**, 17397-08-9; **12**, 17397-09-0; **15**, 17414-37-8; **16**, 17397-21-6; **17**, 17397-10-3; **18**, 17397-11-4; **21**, 17396-20-2; **25**, 17396-19-9; **30**, 17397-12-5; **31** HCl, 17397-13-6; **33**, 17397-14-7; **34**, 17397-15-8; **35**, 17397-16-9; **10** HCl, 17397-17-0; **16** HCl, 17397-18-1; 6-amino-2-methyl-3-isopropyl-3-hexene, 17397-19-2; diisopropylcyclopropylcarbinylamine, 17397-20-5.

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Alkyl-Substitution Effects in the Photochemistry of 2-Cyclohexenones[1]

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The scope of photochemical lumirearrangement in alkyl-substituted 2-cyclohexenones has been investigated. The rearrangement occurs only if the fourth carbon atom of the 2-cyclohexenone ring is fully alkyl substituted. If this requirement is not met, photodimers are the major products. The substituent requirement is necessary but not sufficient to ensure rearrangement as the presence of other substituents either retard or inhibit the reaction.

Photochemical Reactions of Conjugated Ketones.—In recent years the scope and mechanistic aspects of conjugated ketone photochemistry has received a great deal of attention. Photoreactions involving *cis–trans* isomerization,[3,4] molecular rearrangement,[5] dimerization,[6,7] solvent addition,[8] cycloaddition,[9] and reduction[10] have been reported.

The most widely investigated group of compounds possessing this chromophore has been the substituted cyclohexenone type, and in this series the characteristic rearrangements are the lumirearrangement[5] and cyclo-

(1) This work was supported in part by Public Health Service Grant No. G 0709, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) National Institutes of Health Predoctoral Fellow, 1965–1967.

(3) P. E. Eaton and K. Lin, *J. Amer. Chem. Soc.*, **86**, 2087 (1964); **87**, 2052 (1965).

(4) E. J. Corey, M. Tada, R. LaMahieu, and L. Libit, *ibid.*, **87**, 2051 (1965).

(5) O. L. Chapman, *Advan. Photochem.*, **1**, 323 (1963).

(6) O. L. Chapman, P. J. Nelson, R. W. King, D. J. Trecker, and A. A. Griswold, *Rec. Chem. Progr.*, **28**, 167 (1967), and references therein.

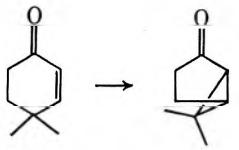
(7) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968), and references therein.

(8) B. J. Ramey and P. D. Gardner, *J. Amer. Chem. Soc.*, **89**, 3949 (1967).

(9) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *ibid.*, **86**, 5570 (1964).

(10) H. Koller, G. P. Rabold, K. Weiss, and T. K. Muhkerjee, *Proc. Chem. Soc.*, 332 (1964).

butanone formation.[11-13] The lumirearrangement is an example of a bond-switching reaction in which a cyclohexenone is transformed into a bicyclo[3.1.0]hexan-2-one as shown below. The rearrangement has been



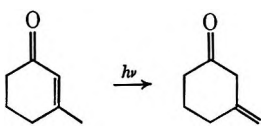
found to proceed in a stereospecific manner[14] and in low quantum yield,[15] but the scope and generality of the process has not been evaluated. The present study was undertaken to evaluate these qualities of the photoreaction.

In Table I, the series of 2-cyclohexenones studied are categorized in groups having the same pattern of alkyl substitution, *e.g.*, C-2 substitution, C-3 substitution, etc. The products from the irradiations of each member of a group were found to be similar, and the types of reactions found are readily classifiable into the groups. From this Table I, a striking correlation between alkyl substitution and photoproduct type can be seen.

Group A.—The photochemistry of cyclohexenone has been studied in detail, and recent results[6] show that no monomeric products are formed under the usual "lumirearrangement condition." The dimeric products found have been suggested to arise from triplets, and the ground-state enones apparently exist as aggregates and possibly excimer formation leads directly to the dimers. The ratio between the two cyclobutane-type dimers that are formed is effected by solvent polarity.

Group B.—The irradiation of **2**, using Vycor-filtered light, yielded 44% of dimer plus polymer with a total of only 6% of several volatile photoproducts being formed. Ketone **2** reacted very slowly when Corex-filtered light was used. This slow rate of reaction is consistent with the reported slow rate for the cycloaddition reaction of **2** with isobutylene.[9]

Group C.—With a single substituent at C-3, dimerization is the principal reaction. When the group is methyl (as in **3** and **4**), a 1,3-hydrogen rearrangement from the methyl group to C-2 of the ring occurs[16,17] to yield the exocyclic β,γ isomer in 10% yield. Similar



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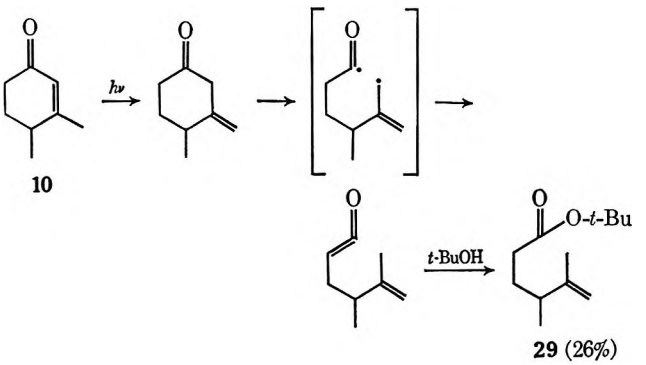
hydrogen migration was not found with ethyl, isopropyl, and *t*-butyl substituents at C-3. Irradiation of benzene solutions of the 3-ethyl (**5**) and 3-isopropyl derivations (**6**) yielded dimers, but under the same conditions 3-isopropyl-6-methyl (**7**) and 3-*t*-butyl (**8**) derivations were stable to the light. More forcing conditions, however, using Vycor-filtered light in *t*-butyl alcohol yielded nonmonomeric materials from **7** and **8**. Apparently, excessive steric hindrance can slow the reaction to the point where demotion from the triplet to ground state is the only efficient process open to the molecule, or less likely, decrease the efficiency of $S_1 \rightarrow T_1$ intersystem crossing.

Group D.—Monoalkyl sulbstitution at C-4 does not confer any special facility for photorearrangement of a 2-cyclohexenone. Dimeric products and traces of monomeric products were obtained on uv irradiation of **9**.

Group E.—Monosubstitution at both C-3 and C-4 does not induce the lumirearrangement in 2-cyclohexenones. Hydrogen migration, followed by further photorearrangement, was found in **10** which has the C-3 methyl group, shown in group C to be important for photochemical deconjugation.[17] None of the bicyclic compounds **11–14** showed any tendency toward hydrogen migration, a feature that is consistent with the results from **5–8**, the side-chain homologs of the 3-methyl-2-cyclohexenones.

The actual photoproduct isolated from the irradiation of **10** was the *t*-butyl ester **29**, identical with a synthetic sample (see Experimental Section), and the mechanism of its formation is thought to be as shown below.

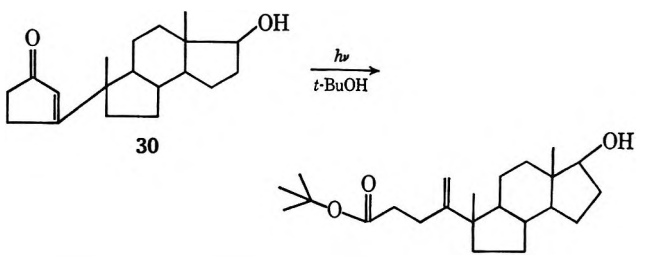


10

29 (26%)

Chemical deconjugation[18] of **10** yielded the $\Delta^{3,4}$ isomer which did not yield **29** upon irradiation. Thus, the $\Delta^{3,4}$ isomer does not appear to be involved in the photochemical reactions of **10**. The α cleavage of β,γ-unsaturated ketones and the formation of ketenes, as proposed here, have ample precedent in the literature.[19,20] Irradiation of **10** in slightly acidic *t*-butyl alcohol did not increase the yield of **29**.

The photochemical formation of **29** from **10** is the first example of such a reaction from a 2-cyclohexenone; an analogous formation of a *t*-butyl ester from the 3-substituted 2-cyclopentenone **30** has been reported.[21]

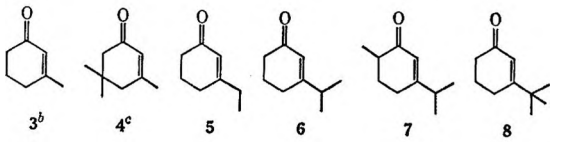
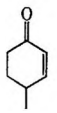
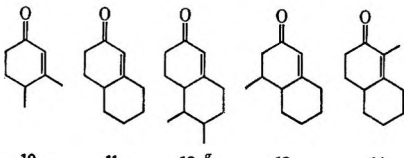
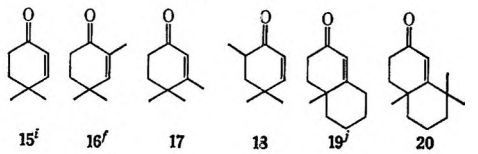
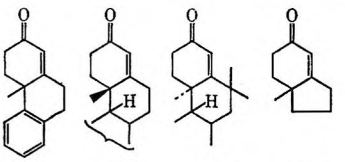
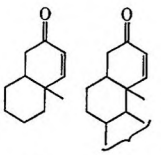


30

(11) H. E. Zimmerman and D. J. Sam, *J Amer. Chem. Soc.*, **88**, 4114, 4905 (1966).
(12) J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 2864 (1960).
(13) V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, *Tetrahedron*, **21**, 607 (1965).
(14) O. L. Chapman, J. B. Sieja, and W. J. Welstead, *J. Amer. Chem. Soc.*, **88**, 161 (1966).
(15) H. E. Zimmerman, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley, and M. Semmelhack, *ibid.*, **88**, 1965 (1966).
(16) See footnote *b*, Table I.
(17) See reference in footnote *c*, Table I.
(18) H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, 669 (1962).
(19) J. R. Williams and H. Ziffer, *Chem. Commun.*, 194 (1967).
(20) J. R. Williams and H. Ziffer, *ibid.*, 469 (1967).
(21) See reference in footnote *l*, Table I.

TABLE I

COMPOUNDS IRRADIATED GROUPED BY SUBSTITUTION PATTERN

Group	Compounds	Photoreaction
A	 1[a]	Dimerize
B	 2	Dimerize
C	 3[b] 4[c] 5 6 7 8	Dimerize,[d] deconjugate[e]
D	 9[f]	Dimerize
E	 10 11 12a[g] 12b[h] 13 14	Dimerize, hydrogen abstraction
F	 15[i] 16[f] 17 18 19[j] 20	Lumirearrange, deconjugate, or unreactive
	 21[k] 22a[l] 22b[n] 22c[o] 23[m] 24	
G	 25 26a[p] 26b[q]	Dimerize
H	 27	Dimerize
I	 28	Dimerize

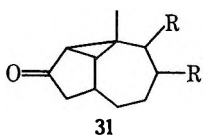
[a] See ref 6. [b] Y. Yamada, H. Uda, and K. Nakanishi, *Chem. Commun.*, 423 (1966). [c] Irradiation reported by P. W. Jennings, Ph.D. Dissertation, University of Utah, 1965; *Dissertation Abstr.*, **26**, 698 (1965). [d] Irradiation of 3-methyl-, 3,5-dimethyl-, and 3-methyl-6-isopropyl-2-cyclohexenone in concentrated solutions (20–50% by volume) has been reported to yield dimeric materials. W. Treibs, *Chem. Ber.*, **63**, 2738 (1930); *J. Prakt. Chem.*, **138**, 299 (1933). [e] Deconjugation only found in the 3-methyl-2-cyclohexenones **3** and **4**. [f] T. A. Rettig, Ph.D. Dissertation, Iowa State, 1966; *Dissertation Abstr.*, **B27**, 114 (1966). [g] **12a** = 3,17-diketo-Δ^4-androstane. [h] **12b** = 19-nortestosterone. [i] Also reported by O. L. Chapman, T. A. Rettig, A. A. Griswold, A. I. Dutton, and P. Fitton, *Tetrahedron Lett.*, 2049 (1963). [j] Also reported by Zimmerman in ref 15. [k] See ref 14 and 15. [l] **22a** = testosterone; reported also by B. Nann, D. Gravel, R. Schorta, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **46**, 2473 (1963). [m] **23** = 10-α-testosterone; reported by H. Wehrli, R. Wenger, K. Schaffner, and O. Jeger, *ibid.*, **46**, 678 (1963). [n] **22b** = testosterone; reported also by Nann, *et al.*, in footnote *l* above. [o] **22c** = cholestenone; reported by B. A. Shoulders, W. W. Kwie, W. Klyne, and P. D. Gardner, *Tetrahedron Lett.*, **21**, 2973 (1965), and by Chapman in footnote *i*. [p] **26a** = 3-keto-Δ^1-cholestene. [q] **26b** = 3-keto-Δ^1-17β-hydroxyandrostene; reported by P. J. Kropp as a private communication from O. L. Chapman in "Organic Photochemistry," O. L. Chapman, Ed., M. Dekker, Inc., New York, N. Y., 1967, p 74.

With the bicyclic members of group E, in addition to dimerization, an important photochemical reaction is hydrogen abstraction to yield saturated ketones. Solvent "dimers" resulting from the abstraction could be isolated. Irradiation of **11** in glyme, dioxane, cyclohexane, acetone, and *t*-butyl alcohol yielded only varying amounts of decalones (2:1, *trans/cis* ratio) and dimers (see Experimental Section). No rearranged products were found.

Group F.—This is the only group of 2-cyclohexenones in which lumirearrangement has been found. Compounds **15**, **18**, **19**, **21**, **22a**, **22b**, **22c**, and **24** all form bicyclo[3.1.0]hexanones *via* the lumiproduct pathway. In each case, it is an inefficient process, a quantum yield of 4×10^{-3} and 8×10^{-3} has been reported for **19** and **21**.[15] From the bicyclic examples **19** and **24**, it can be seen that the size of the B ring (five or six members) is not critical for lumirearrangement, though the lumiproduct yield in **24** is considerably higher than that in **19**. This result is thought to be due to the photochemical stability of the lumiproduct from **24** and not due to an intrinsic difference in the lumirearrangements of each enone. Small amounts of dimer (2%) were found in the case of **19**.

Hydrogen migration within the cyclohexenone ring is blocked by the two C-4 substituents in this class of substituted cyclohexenones, and double-bond migration into the B ring of polycyclic members of the group has been found only in 10α-testosterone (**23**).[22] Compound **20** contains all the requirements for rearrangement, but **20** also has the geminal-methyl substituents in the B ring, a position which is not expected to effect rearrangement by any mechanism proposed to date. This compound, however, would not undergo lumirearrangement even under vigorous conditions (Vycor filter), and the material was completely stable to the reaction conditions. Irradiation of 3,4,4-trimethyl-2-cyclohexenone (**17**) also did not undergo molecular rearrangement, instead a slow dimerization or polymerization were the only reactions found. Similar results have been reported[23] for compound **16**, and it would appear that excessive alkyl substitution beyond the 4,4-dimethyl requirement sometimes causes the molecule to be photochemically less reactive.

Group G.—Compounds **25**, **26a**, and **26b** all contain the 4,4-dialkyl substitution of group F but did not undergo skeletal rearrangement. These constitute further exceptions to the apparent substitution requirement of group F. The cause of this lack of reactivity is unknown but may be related to the strain of the lumiproduct **31** which would be formed. The products



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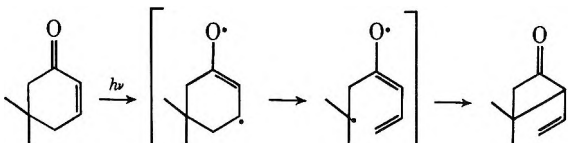
from the irradiation of **25** and **26a** were extremely complex mixtures of ketonic material which failed to resolve into any recognizable spot on tlc. The products from **25** were shown to be dimeric by mass spectrometry.

Group H.—The absence of a lumirearrangement in **4** and **27** shows that the ability of the migrating group to stabilize an intermediate carbonium ion or radical is insufficient to cause rearrangement. Furthermore, this type of substitution by stabilization of electron deficiency of C-5 did not enhance a skeletal rearrangement of the type shown for **27** and found for verbenone[12] and 4,5-diphenyl-2-cyclohexenone.[11] The enone **27** yielded one major crystalline dimer of the cyclobutane type, and the only volatile photoproduct produced (4%) was 3-*t*-butoxy-5,5-dimethylcyclohexanone (**32**). This probably arises formally by a similar reaction to the methanol addition to Pummerer's ketone (**33**).[24]



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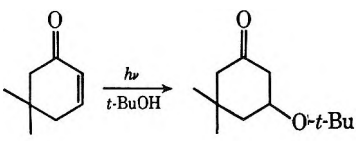

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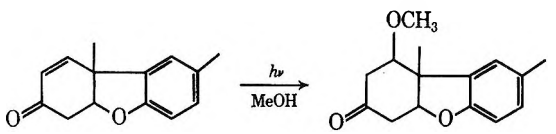

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Group I.—Irradiation of compound **28** did not differ from that of the parent compound 2-cyclohexenone. Only nonmonomeric material was formed.

Lumirearrangement.—As can be seen from Table I, the results from this series of cyclohexenones conclusively points to a striking substitution requirement. Only compounds belonging to group F show any tendency toward skeletal rearrangement of any kind. Lumiproducts are formed only in 2-cyclohexenones which have bis alkyl substitution at the fourth carbon atom of the enone ring. That this substitution requirement is not sufficient to ensure lumirearrangement can be seen from the enones in group G as well as enones **16**, **17**, and **20** in group F, all of which have more alkyl substitution than required and all of which fail to rearrange. Lumirearrangement is thus a very specific reaction, highly dependent on substituents peripheral to the 2-cyclohexenone ring. In the absence of quantum yield information we cannot determine if the specificity is due to a more efficient lumirearrangement or a less efficient side reaction. The hydrogen migration found in **23**, when compared with the rearrangment of the epimeric series **22a–c**, shows that lumirearrangement also has a geometrical requirement, but further work is needed to define the scope of this.

Lumiproduct yields based on total amount of starting enone vary from 5 to 30% (except for **24**) (Table II). Often the low yield of the lumiproduct is due to the formation of a 2-cyclopentenone product, as in ketones **15**, **18**, and **22b**, which arises either directly from

(22) H. Wehrli, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **46**, 678 (1963).

(23) See footnote *f*, Table I.

(24) T. Matsuura and K. Ogura, *J. Amer. Chem. Soc.*, **88**, 2602 (1966); *Bull. Chem. Soc. Jap.*, **40**, 945 (1967).

starting material or from the lumiproduct itself. In these latter cases, there is no difficulty in detecting the occurrence of both processes, and thus it seems unlikely that the absence of lumiproduct in the majority of enones can be ascribed to an extreme photolability of the lumiproducts themselves.

TABLE II
YIELDS OF LUMIPRODUCTS

Compound	% yield
15	16
18	5
19	33
22a	24
22b	9
22c	25
24	60

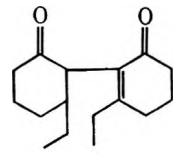
In the case of **15**, the rearrangement was found to be markedly dependent on solvent polarity and proceeded well in *t*-butyl alcohol. Irradiations in benzene and cyclohexane failed to yield the rearranged product. This result has been also noted by Chapman.[25] In the case of **21**, however, rearrangement is promoted with equal facility by irradiation in the nonpolar solvent benzene.[15]

No wavelength effect was noted in **15**, **19**, **20**, and **22a**, and the course of the reactions was unchanged by irradiation at shorter wavelengths than the n → π absorption band of each. This result is consistent with the concept of facile intersystem crossing in the excited-state manifold of ketones so as to yield the state of greatest stability.

Deconjugation.—This reaction appears to have a specific substitution requirement. Except for 10α-testosterone (**23**), those 2-cyclohexenones which undergo photochemical deconjugation (**3**, **4**, and **10**) all have a C-3 methyl group. Enones with C-3 ethyl or isopropyl groups fail in this reaction. A temperature effect has been noted by previous workers (high temperature induces reversal of the reactions).[17] The migration is apparently always into the peripheral substituent and not by deconjugation within the ring.

Hydrogen Abstraction.—Only a few of the cyclohexenones (**11**, **12a**, and **19**) underwent photoreduction to cyclohexanones. The reaction was studied in detail only in the case of **11** and was found to be solvent dependent. The order of ease of reduction found was cyclohexane > glyme = dioxane > *t*-butyl alcohol. No evidence for this reaction was found in **10** and **17**, the monocyclic analogs of **11** and **19**. The cause of this specificity is unknown at this time.

Dimerization.—Dimeric materials have been found from 2-cyclohexenones in each of the groups in Table I. Of all the enones studied, only those of group F do not give high yields of dimeric materials. Although dimers could be analyzed, quantitative yield data are not available from our results because of nonlinear glpc detector response to the dimer mixtures. Dilution of the irradiation solutions to 1×10^{-3} *M* did not stop dimerization/polymerization in the case of **11** and did not induce other reactions. No wavelength effect on the dimerization yield was found in **6**, **8**, **11**, and **25**. No solvent effect on this yield was found in **6**, **11**, **12a**, and **12b**. The dimers from the enones are thought to have the normal cyclobutane structure based on their cyclohexanone-type ir absorptions and lack of uv absorption. Only in the case of 3-ethyl-2-cyclohexenone (**5**) was there exception to this finding. Irradiation of this enone yielded a major dimer which possessed characteristic uv and ir absorptions of a cyclohexenone, as well as ir absorption for a saturated cyclohexanone ring; the structure is thought to be **34** or **35**. Dimers



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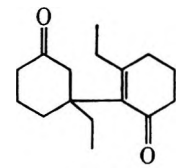

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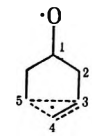
were found as mixtures in all groups, except H, where one crystalline cyclobutane-type compound was formed in high yield during the irradiation of **27**. The cause of this unique specificity for **27** is unknown.

From these results there is no doubt that dimerization is the most universal photoreaction of alkyl-substituted 2-cyclohexenones and that molecular rearrangement occurs only in a few compounds with very specific substitution patterns.

Mechanism.—In evaluating the mechanistic pathway of the lumirearrangement, Zimmerman[15] has invoked the intermediacy of bridged intermediates of the type **26**. In a similar manner, Chapman[5] has suggested a discrete dipolar form (**37**) for the intermediate. Such electron-deficient intermediates suggest



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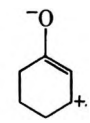

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that the substitution on the centers involved in the rearrangement of C-5 to C-3, *i.e.*, groups on C-3, C-4, C-5, should lower the energy of the intermediate and thus enhance the rearrangement. This expected result was not found since the substitution patterns of 4-alkyl-, 3,4-dialkyl-, and 5,5-dialkyl-2-cyclohexenones did not enhance the rearrangement. In view of the substitution effects found in the present work it appears likely that a highly developed positively charged intermediate does not occur in the reaction coordinate leading to the lumirearrangement.

It has recently been reported[26] that the dipole moment of the n → π* excited carbonyl system is decreased over that of the ground state, but, nonetheless, the charge displacement is still toward oxygen as it is in the ground state. Such charge displacement is the origin of the electron-deficient carbon centers, the deficiency of which should increase on going from the excited state to the ground state. Thus, a possible process for the lumirearrangement is that, as the molecule demotes from the excited state, positive charge on C-3 increases. This partial positive center at C-3 can

(25) See reference in footnote *i*, Table I.

(26) (a) D. E. Freeman and W. Klemperer, *J. Chem. Phys.*, **45**, 52 (1966); D. E. Freeman, J. R. Lombardi, and W. Klemperer, *ibid.*, **45**, 58 (1966); (b) For calculated π-electron densities which are in agreement with the dipole moment, see H. E. Zimmerman, R. W. Binkley, J. J. McCullough, and G. A. Zimmerman, *J. Amer. Chem. Soc.*, **89**, 6589 (1967).

induce the rearrangement of the C-4–C-5 bond only if the resulting charge at C-4 can be stabilized on a tertiary center and if this center in turn can be bridged with the resulting enolic center at C-2. This concept is in general agreement with the previously postulated mechanism but differs in that a role is indicated for C-4 in the process.

In line with the need for an interaction between C-3 and C-5 and C-2 and C-4 in the lumirearrangement the well-known tendency of enone triplet states to undergo twisting motion about the double bond[3] is an important feature. Such a twisting motion brings the lobes of charge at C-3 into close proximity with C-5, the atom to which C-3 is ultimately bonded during lumirearrangement. Such incorporation of twist provides a direct correlation between *cis–trans* isomerization reactions[3] and lumirearrangement. It also correlates ring-size effects and the variance between the photoreactions of cyclic and acyclic conjugated ketones.

The occurrence of an apparent steric effect in the nonreactivity of **16**, **17**, and **20** is unusual in a unimolecular process but can be rationalized by consideration of the steric environment of intermediates along the reaction coordinate. For example, this effect could be important if the lifetime of such intermediates were dependent on solvation. The solvent effect noted in irradiation of 4,4-dimethyl-2-cyclohexenone (**15**) where nonpolar solvents failed to yield lumiproducts (in contrast to polar solvents) is also indicative that solvation of intermediates may be important to lumirearrangement.

It is to be realized that, although partial positively charged intermediates have been suggested for the lumirearrangement, the photoreactions of dimerization, hydrogen abstraction, and *cis–trans* isomerization are distinctly radical processes. In both types of reaction, the intermediate triplets have long been considered to be of n,π^* type. However, the recent suggestion of π,π^* triplet in cyclohexenone dimerization[6] and solvent additions to acetylcyclohexene[8] makes the earlier generalization less secure.

Experimental Section

All irradiations were carried out using dilute solutions in purified solvents (see Table III). Except where noted, see Table III, a 450-W Hanovia lamp (Model 79-A36) in the standard Hanovia quartz probe was used. Glass tubing filters were cut to size and fitted around the lamp. The few experiments (see Experimental Section) using Nester–Faust low-pressure mercury lamp (Model NFUV-300) utilized a standard three-necked irradiation vessel and a quartz insert for lamp housing. Irradiation solutions were outgassed with argon for 30 min prior to irradiation. Progress of the reaction was followed by uv spectroscopy (except when benzene was used as solvent) and by gas–liquid partition chromatography (glpc) (except for the steroidal enones). The crude photomixtures were isolated by removal of solvent under vacuum on a warm water bath. Separation of monomeric materials was carried out by distillation under high vacuum. Monomeric photoproducts were isolated by standard glpc techniques (Carbowax 20M). Dimeric materials were isolated from the distillation residue by glpc on short (2 ft) columns having only 5% of the stationary phase. The products were characterized mainly by mass spectrometry. The results of the irradiations are summarized in Table III. Spectral data are described for those photoproducts not previously reported in the literature. Those irradiations which gave only a few per cent of several minor volatile photoproducts or complex mixtures of nonmonomeric material are not described in detail.

Combustion analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California. Mass spectral analyses were performed by Miss Sherri Firth, Mass Spectral Laboratory, University of California.

2-Methyl-2-cyclohexenone (**2**).—From 10.0 g (0.089 mol) of 2-methylcyclohexanone,[27] following the method of Warnhoff and Johnson,[28] there was obtained 4.86 g (49.5%) of **2**: bp 77–78° (23–24 mm) [lit.[28] bp 98–101° (27 mm)]; ν_{max} 1675 (s), 1357 (m), 1105 (m), 903 (m), and 882 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 235 mμ (ε 9400); nmr spectrum, τ 3.18–3.46 (1.0 H, broad singlet, vinylic H), 7.44–8.22 (6.0 H, multiplet) and 8.31 (2.8 H, doublet with further fine splitting, J = 1.5 cps, vinylic methyl H).

3-Ethyl-2-cyclohexenone (**5**).—From 10.0 g (0.071 mol) of 3-ethoxy-2-cyclohexenone,[29] following the method of Woods, *et al.*,[30] there was obtained 5.67 g (64.5%) of **5**: bp 75–76° (4 mm) [lit.[30] bp 56–57° (0.8 mm)]; ν_{max} 1672 (s), 1631 (m), and 893 (s) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 236 mμ (ε 14,100); $\lambda_{max}^{cyclohexane}$ 226 mμ (ε 14,700) and 340.5 (30); nmr spectrum, τ 4.32 (0.8 H, triplet, J = 1 cps, vinylic H), 7.52–8.30 (8.0 H, multiplet), and 8.92 ppm (3.2 H, triplet, J = 8 cps, methyl H).

3-Isopropyl-2-cyclohexenone (**6**).—From 12.7 g (0.102 mol) of a mixture of 1- and 3-isopropylcyclohexenes (obtained by dehydration of 2-isopropylcyclohexanol), following the method of Rao and Dev,[31] there was obtained 3.66 g (32%) of **6**: bp 66–69° (2.5 mm) [lit.[30] bp 83–84° (1–1.5 mm)]; 98% pure by glpc on a 20% DEGS column; mol wt, 138 (mass spectrum); ν_{max} 1669 (s), 1623 (m), and 893 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 236.5 mμ (ε 14,600); $\lambda_{max}^{cyclohexane}$ 227 mμ (ε 14,300); nmr spectrum, τ 4.30 (0.9 H, doublet, J = 1 cps, vinylic H), 7.35–8.30 (6.8 H, multiplet), and 8.92 ppm (6.3 H, doublet, J = 7 cps, *gem*-dimethyl H).

2-Carvenone (**7**).—From 16.7 g (0.110 mol) of dihydrocarvone, following the method of Büchi and Erickson,[32] there was obtained 11.6 g (69.5%) of **7**: bp 80–81° (3.5 mm) [lit.[32] bp 95–96° (8 mm)]; mol wt, 152 (mass spectrum); ν_{max} 1672 (s), 1631 (m), 1211 (s), and 885 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 235.5 mμ (ε 13,100); nmr spectrum, τ 4.30 (1.0 H, doublet, J = 1 cps, vinylic H), 7.33–8.73 (5.8 H, multilpet), 8.89 (strong doublet, J = 7 cps, *gem*-dimethyl H), 8.95 ppm (weaker doublet, J = 6.5 cps, methyl H), and combined methyl doublets integrated to 9.2 H.

3-*t*-Butyl-2-cyclohexenone (**8**).—From 14.1 g (0.102 mol) of 1-*t*-butylcyclohexene, using the above procedure for the synthesis of **6**, there was obtained 2.90 g (19%) of **8**: bp 80–81° (4 mm) [lit.[30] bp 70° (0.3 mm)]; ν_{max} 1666 (s), 1613 (m), and 893 (s) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 237 mμ (ε 13,750); nmr spectrum, τ 4.25 (1.1 H, triplet, J = 1 cps, vinylic H), 7.52–8.27 (6.2 H, multiplet), and 8.88 ppm (8.7 H, singlet, *t*-butyl H).

4-Methyl-2-cyclohexenone (**9**).—From 34.0 g (0.278 mol) of 4-methylanisole, following the reduction procedure of Wilds and Nelson,[33] there was obtained 13.8 g (45%) of **9**: bp 45.0–45.5° (4.5 mm) [lit.[23] bp 76° (24 mm)]; ν_{max} 1678 (s), 1626 (w), and 1248 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 225 mμ (ε 9100); nmr spectrum, τ 3.26 (0.9 H, two doublets of doublets, J = 10 cps, J' = 3 cps, J'' = 1 cps, vinylic H β to the carbonyl), 4.20 (0.9 H, doublet of doublets, J = 10 cps, J' = 2.5 cps, vinylic H α to the carbonyl), 7.22–8.61 (5.4 H, multiplet), and 8.85 ppm (2.8 H, doublet, J = 7 cps, methyl H).

3,4-Dimethyl-2-cyclohexenone (**10**).—From 38.0 g (0.279 mol) of 3,4-dimethylanisole, using the above procedure for the synthesis of **9**, there was obtained 17.8 g (52%) of **10**: bp 60–62° (4.5–5.0 mm); mol wt, 124 (mass spectrum); ν_{max} 1672 (s), 1629 (m), and 861 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 238 mμ (ε 13,230); nmr spectrum, τ 4.34 (0.8 H, quartet, J = 1 cps, vinylic H), 7.25–8.50 (8.3 H, multiplet with a strong doublet at 8.08 (vinylic methyl H), J = 1 cps), and 8.82 ppm (2.9 H, doublet, J = 6.5 cps, methyl H).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.58; H, 9.72.

3-Keto-Δ⁴-octalin (**11**).—From 134 g (0.80 mol) of 1-morpholino-1-cyclohexene in 750 ml of acetone and 59 g (0.84 mmol) of methyl vinyl ketone, there was obtained 75.2 g (65%) of **11**

(27) Aldrich Chemical Co., Milwaukee, Wis.

(28) E. W. Warnhoff and W. S. Johnson, *J. Amer. Chem. Soc.*, **75**, 494 (1953).

(29) R. L. Frank and H. K. Hall, Jr., *ibid.*, **72**, 1645 (1950).

(30) G. R. Woods, P. H. Griswold, Jr., B. H. Armbrecht, D. I. Blumenthal, and R. Plapinger, *ibid.*, **71**, 2028 (1949).

(31) G. S. K. Rao and S. Dev, *J. Indian Chem. Soc.*, **33**, 539 (1956).

(32) G. Büchi and R. E. Erickson, *J. Amer. Chem. Soc.*, **76**, 3493 (1954).

(33) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360 (1953).

TABLE III
REACTION CONDITIONS AND YIELD DATA FOR IRRADIATIONS

Group	Compound	Concn × 10³	Solvent	Filter	Irradn time, hr	% conversion	% monomeric products
B	2	51	*t*-BuOH	Vy[a]	25	50	6
C	5	34	C_6H_6	Py[b]	15	80	
	6	28	C_6H_6	Py	29	55	
	7	33	*t*-BuOH	Vy	4.5	78	8
			t-BuOH	Co[c]	10		
			C_6H_6	Co	17		
		30	Cyclohexane	Co	25	57	8
	8		Cyclohexane	Co	36		
			t-BuOH	Co	5		
		26	*t*-BuOH	Vy	23	58	8
D	9	31	*t*-BuOH	Co	7	63	
E	10	35	*t*-BuOH	Co	84	87	36
	11	24	*t*-BuOH	Py	7	37	2
		4	*t*-BuOH	*d*		98	5
		1	*t*-BuOH	Py		20	4
		10	*t*-BuOH	*d*		87	5
		12	Dioxane	Py		80	5
		15	Dioxane	Py		50	6
		8	Glyme	Py		66	6
		12	Cyclohexane	Py		56	42
	12a	5	Cyclohexane	*d*			
			t-BuOH	*d*			
	12b	48	*t*-BuOH	*d*	3.5	91	
		5	Dioxane	Quartz			
	13		*t*-BuOH	*d*	9.5	97	
	14		*t*-BuOH	Co	20	60	
F	15	28	*t*-BuOH	Co	5.5	74	38
		37	C_6H_6	Co	36	*e*	
		30	C_6H_6	Co	11.5	*e*	3
	17	28	*t*-BuOH	Co	22	80	
		26	*t*-BuOH	Co	4	85	
		28	*t*-BuOH	Py	24	5	
	18	53	*t*-BuOH	Co	11	55	13
		53	*t*-BuOH	Co	3	26	12
	19	85	*t*-BuOH	Co	60	40	28
	20	42	*t*-BuOH	Co	21		
		42	*t*-BuOH	Vy	6		
	22a		*t*-BuOH	Py	19	58	51
	24	39	*t*-BuOH	Co		60	60
G	25	8	*t*-BuOH	Co	19.5		
		8	*t*-BuOH	Vy	4	74	
	26a	1.3	*t*-BuOH	Vy	20	89	
H	27	35	*t*-BuOH	Co	8	49	4
I	28	30	C_6H_6	Co	7	68	

[a] Vy = Vycor filter. [b] Py = Pyrex filter. [c] Co = Corex filter. [d] Irradiation carried out with low-pressure mercury resonance lamp. [e] Amount of starting material converted not determined.

by the method of Augustine and Caputo:[34] bp 74° (0.1 mm)–103° (0.5 mm) [lit.[34] bp 143–145 (15 mm)]; $\nu_{max}^{CCl_4}$ 1675 (s) and 1621 (w) cm^{-1}; λ_{max}^{EtOH} 236 mμ (ε 17,000).

3,17-Diketo-Δ⁴-19-norandrostane (12a).—From 6.8 g (0.02 mol) of 3,17-diketo-19-aldehydo-Δ⁴-androstene in 300 ml of methanol and a solution of sodium methoxide (18 g of sodium in 150 ml of methanol), there was obtained[35] 5.86 g (95%) of **12a**: mp 166–169° (lit.[35] mp 172°); $\nu_{max}^{CS_2}$ 1745 (s), 1678 (s), and 1618 (w) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 234 mμ (ε 16,000).

19-Nortestosterone (12b).—Commercial material[36] was used, mp 120–124°.

Synthesis of 3-keto-1-methyl-Δ⁴-octalin (13).—From 1100 g (19 mol) of acetone, an ethanol solution of potassium hydroxide (4.25 g in 75 ml), and 182 g (3.0 mol) of acetaldehyde, there was obtained,[37] after dehydration with 0.3 g (0.024 mol) of iodine, 76.7 g (31%) of 3-penten-2-one: bp 118–124° (lit.[37] bp 122°); $\nu_{max}^{CCl_4}$ 1675 and 1631 cm^{-1}.

From 57 g of 3-penten-2-one, a solution of 16.5 g (0.42 g-atom) of potassium in 200 ml of anhydrous ethanol, and 150 g (0.88 mol) of 2-carbethoxycyclohexanone, there was obtained[38] 69 g (43%) of 3-keto-10-carbethoxy-1-methyl-Δ⁴-octalin (**38**): bp 160–170° (2 mm); mp 70.5–72° [petroleum ether (bp 30–60°)]; $\nu_{max}^{CCl_4}$ 1730 (s), 1276 (m), 1026 (m), 1672 (s), and 1629 (m) cm^{-1}; nmr, τ 10.03 (3 H, methyl doublet, J = 7 cps), 873 (3 H, methyl triplet J = 7.5 cps), 5.83 (2 H, methylene quartet, J = 7.5 cps), and 4.27 ppm (1 H, vinyl singlet); mol wt, 236 (mass spectrum).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.24; H, 8.64.

To a 2-l. flask fitted with stirrer was added 84 g of potassium hydroxide (1.5 mol), 1000 ml of 95% ethanol, and 69 g of **38** (0.29 mol). The mixture was refluxed for 24 hr, neutralized with glacial acetic acid, and concentrated at reduced pressure. Water was added, and the solution was extracted with ether. The combined ethereal extracts were washed with water, dried over magnesium sulfate, evaporated, and distilled through a Claisen head. The material distilling at 90–125° (2 mm) was fractionated to yield 11.6 g (24%) of **13**: $\nu_{max}^{CCl_4}$ 3040 (w), 1670 (s), and 1630

(34) R. L. Augustine and J. A. Caputo, "Organic Syntheses," Coll. Vol. XLV, John Wiley & Sons, Inc., New York, N. Y., 1965, p 80.

(35) H. Hagiwara, S. Hoguchi, and M. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **8**, 84 (1960).

(36) Mann Research Laboratories, Inc., New York, N. Y.

(37) J. E. Dubois, *Bull. Soc. Chim. Fr.*, 66 (1949).

(38) W. S. Rapson, *J. Chem. Soc.*, 1626 (1936).

(m) cm^{-1}; $\lambda_{max}^{t\text{-BuOH}}$ 237 mμ (ε 12,600); nmr, τ 8.95 (3 H, methyl doublet, J = 5 cps) and 4.40 ppm (1 H, vinyl singlet); mol wt, 164 (mass spectrum).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.62; H, 9.81.

3-Keto-4-methyl-Δ⁴-octalin (14).—To a 250-ml three-necked flask fitted with stirrer, reflux condenser, and addition funnel, and with provision for maintaining a dry nitrogen atmosphere, was added 150 ml of anhydrous ethanol and 5.4 g (0.14 g-atom) of potassium. To this solution was slowly introduced a mixture of freshly distilled ethyl vinyl ketone[39] (16 g, 0.19 mol) and 100 g (0.6 mol) of 2-carbethoxycyclohexanone. The addition was carried out during 2 hr with vigorous stirring and in the dry nitrogen atmosphere. When the addition was complete, the mixture was allowed to stir for 15 hr. To the thick, red reaction product was added 100 ml of water containing 8 ml of glacial acetic acid, and the neutral solution was extracted with three 150-ml portions of ether. The combined ethereal extracts were washed with two 100-ml portions of water, dried over magnesium sulfate, and evaporated. The crude product resisted attempts at recrystallization and was distilled to remove starting materials. The crude distillation residue (20 g, 0.079 mol) was dissolved in 100 ml of ethanol in a 250-ml flask fitted with stirrer and with provision for maintaining a nitrogen atmosphere. To the solution was added 100 ml of 10% hydrochloric acid. The acidic solution was refluxed for 24 hr, neutralized with sodium bicarbonate solution, and dried over magnesium sulfate; the solvent was evaporated. The product was distilled in a short-path still to remove high-boiling material and gave 16.5 g of 10-carbethoxy-3-keto-4-methyl-Δ⁴-octalin (**39**) (89% yield from the acid dehydration, 36% over-all yield from ethyl vinyl ketone). The keto ester **39** exhibited $\nu_{max}^{CCl_4}$ 1729 (s), 1670 (s), and 1180 (s, broad) cm^{-1}; mol wt, 236 (mass spectrum).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.34; H, 8.40.

To a 100-ml flask fitted with magnetic stirrer and reflux condenser, and with provision for maintaining a dry nitrogen atmosphere, was added 5 g (0.02 mol) of the keto ester **39** and 50 ml of 10% ethanolic sodium hydroxide. The reaction mixture was refluxed for 24 hr, neutralized with dilute hydrochloric acid, concentrated at reduced pressure, diluted with 100 ml of water, and extracted with three 100-ml portions of ether. The combined ethereal extracts were dried over magnesium sulfate and evaporated. The product was distilled to remove high-boiling material and gave 1.6 g (30% yield) of **14**: $\nu_{max}^{CCl_4}$ 1670 (s) and 1625 (w) cm^{-1}; λ_{max}^{EtOH} 244 mμ (ε 15,500); nmr, τ 8.29 ppm (3 H, vinyl methyl doublet, J = 1 cps) and no vinyl hydrogens were visible; mol wt, 164 (mass spectrum).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.17; H, 9.67.

4,4-Dimethyl-2-cyclohexenone (15).—A solution of 46.7 g (0.667 mol) of freshly distilled methyl vinyl ketone, 48.0 g (0.667 mol) of freshly distilled isobutyraldehyde, 70 ml of water, and sufficient methanol to ensure homogeneity was slowly added to a stirred solution of 2.5 g of potassium hydroxide in 15 ml of methanol. Heating with an oil bath was started at the same time as addition. After about one-fifth of the solution had been added, the reaction mixture changed immediately from clear yellow to light orange, and two layers began to separate. The addition was completed in 70 min, at which time the oil-bath temperature was 75–80°. The mixture was allowed to cool, diluted with 100 ml of water, and extracted with ether (seven 75-ml portions). The ethereal extract was washed with water, dried over magnesium sulfate, filtered, and concentrated. Spinning-band distillation of the crude oil (78.6 g) gave a colorless distillate (52.0 g), the major fraction of which was 4,4-dimethyl-2-cyclohexenone (**15**): 39.3 g (47.5% yield); bp 42–43° (3 mm) [lit.[23] bp 76° (21 mm)]; mol wt, 124 (mass spectrum); ν_{max} 1678 (s), 1626 (w), and 1116 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 226 mμ (ε 11,130); $\lambda_{max}^{cyclohexane}$ 340 mμ (ε 24); $\lambda_{max}^{benzene}$ 339 mμ; nmr spectrum, τ 3.38 (1.0 H, doublet of doublets, J = 10 cps, J = 0.5 cps, vinylic H β to the carbonyl), 4.32 (0.9 H, doublet, J = 10 cps, vinylic H α to the carbonyl), 7.49–7.81 (2.1 H, multiplet, methylene H α to the carbonyl), 7.99–8.33 (2.0 H, multiplet, methylene H), and 8.85 ppm (6.2 H, singlet, *gem*-dimethyl H).

3,4,4-Trimethyl-2-cyclohexenone (17).—From 46.7 g (0.667 mol) of methyl vinyl ketone and 57.3 g (0.667 mol) of methyl isopropyl ketone, following the procedure of Eliel and Lukach,[40] there was obtained 9.2 g (10%) of **17**: bp 42–43° (1.0–2.0 mm); mol wt, 138 (mass spectrum); ν_{max} 1678 (s) and 1626 (w) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 234 mμ (ε 13,700); nmr spectum, τ 4.4 (1.0 H, multiplet, vinylic H α to the carbonyl), 7.7 (2.3 H, triplet, methylene H α to the carbonyl), 8.1 (3.8 H, singlet, methyl H), 8.3 (1.3 H, multiplet, methylene H), and 9.0 ppm (6.2 H, singlet, *gem*-dimethyl H).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.42; H, 10.29.

4,4,6-Trimethyl-2-cyclohexenone (18).—From 25.9 g (0.308 mol) of isopropenyl methyl ketone[41] and 27.5 g (0.382 mol) of isobutyraldehyde, following the procedure of Eliel and Lukach,[40] there was obtained 18.1 g (42.5%) of **18**: bp 44.5–45.5° (2.5–3.0 mm); mol wt, 138 (mass spectrum); ν_{max} 1678 (s), 1621 (w), and 1370 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 227 mμ (ε 9500); nmr spectrum, τ 3.46 (0.9 H, doublet of doublets, J = 10 cps, J' = 1.5 cps, vinylic H β to the carbonyl), 4.32 (0.9 H, doublet, J = 10 cps, vinylic H α to the carbonyl), 7.25–7.85 (1.2 H, multiplet, H α to the carbonyl), 8.01–8.52 (2.5 H, multiplet, methylene H), 8.80 and 8.86 ppm (two singlets, *gem*-dimethyl H), 8.96 (doublet, J = 6.5 cps, methyl H), and integration from 8.80–9.01 ppm totaled 8.5 H.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.51; H, 10.06.

3-Keto-10-methyl-Δ⁴-octalin (19).—The material used had been synthesized by a previously described method:[42] bp 97–98° (2 mm) [lit.[32] bp 97–98° (2 mm)]; $\nu_{max}^{CCl_4}$ 1672 (s) and 1616 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 238 mμ (ε 16,400).

3-Keto-6,6,10-trimethyl-Δ⁴-octalin (20).—From 38.3 g (0.22 mol) of 6,6,10-trimethyl-Δ⁴-octalin,[42] 225 ml of acetic anhydride, and 38 g (0.23 mol) of anhydrous potassium chromate, there was obtained 21 g (52%) of **20**: bp 85–86° (0.4 mm) [lit.[42] bp 129–130° (10 mm)]; $\nu_{max}^{CCl_4}$ 1669 (s) and 1600 (m) cm^{-1}; $\lambda_{max}^{t\text{-BuOH}}$ 242 mμ (ε 13,700).

Testosterone Acetate (22a).—From 1.20 g (4.17 mmol) of testosterone, 10 ml of acetic anhydride, and 5 ml of anhydrous pyridine, following recrystallization from aqueous ethanol, there was obtained 1.16 (84.5%) of testosterone acetate (**22a**): mp 139.5–141.0 (lit.[43] mp 140–141°); mol wt, 330 (mass spectrum); $\nu_{max}^{CHCl_3}$ 1727 (s), 1667 (s), and 1613 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ε 16,350); nmr spectrum, τ 4.30 (0.9 H, singlet, vinylic H), 5.40 (0.9 H, triplet, J = 7.0–7.5 cps, H geminal to acetyl group), 7.45–9.32 (28.2 H, multiplet with sharp singlet at 7.99, acetyl methyl H), 8.80 (C-19 methyl H), and 9.16 ppm (C-18 methyl H).

5-Keto-8-methyl-Δ⁴⁽⁹⁾-tetrahydroindan (24).—From 71.52 g (0.73 mol) of 2-methylcyclopentanone, 4.55 ml of 3 N sodium ethoxide, and 49.2 g (0.73 mol) of methyl vinyl ketone,[27] there was obtained[44] 35.05 g (32% yield) of **24**: bp 65° (0.3 mm); $n^{20}D$ 1.5155; λ_{max}^{EtOH} 239.3 mμ (ε 13,850); ν_{max} 3230, 1669, 887, and 861 cm^{-1}; nmr, τ 8.83 (3 H, singlet; angular CH_3), 7.68–7.88 (2 H, multiplet; allylic), 7.2–7.6 (2 H, multiplet; H α to carbonyl), and 4.38 ppm (1 H, triplet, J = 2.0 cps; vinyl H split by C-3 H); 2,4-dinitrophenylhydrazone, red platelets from ethanol, mp 151.5–153°.

3-Keto-Δ¹-10-methyloctalone (25).—Synthesis of the sample of **25** used in this study was previously described.[45]

3-Keto-Δ¹-cholestene (26a).—From 48.8 g (0.105 mol) of 3-keto-2α-bromocholestane, 40 g of calcium carbonate, and 500 ml of N,N-dimethylformamide, there was obtained 21.7 g (54%) of **26a**: mp 97.5–99.5° (hexene) (lit.[46] mp 98°); λ_{max}^{hexane} 225 mμ (ε 9800).

5,5-Dimethyl-2-cyclohexenone (27).—Lithium aluminum hydride reduction of 84.3 g (0.479 mol) of 3-ethoxy-5,5-dimethyl-2-cyclohexenone (monoethyl ether of dimedone), followed by stirring over 3 N sulfuric acid, yielded 52.5 g (89%) of 5,5-dimethyl-2-cyclohexenone (**27**): bp 77–78° (18 mm) [lit.[29] bp 75° (15 mm)]; mol wt, 124 (mass spectrum); ν_{max} 1681 (s), 1631 (w), 1385 (m), 1366 (m), and 905 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 226 mμ (ε 9100); nmr spectrum, τ 3.03–3.38 (1.0 H, doublet

(39) Araphoe Chemicals Inc., Boulder, Colo.

(40) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

(41) E. F. Landon and E. P. Chang, *J. Org. Chem.*, **12**, 422 (1947).

(42) W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963).

(43) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(44) F. T. Bond, Ph.D. Dissertation, University of California at Berkeley, 1961.

(45) W. G. Dauben and P. Oberhänsli, *J. Org. Chem.*, **30**, 3947 (1965).

(46) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

of triplets, J_d = 10 cps, J_t = 4 cps, vinylic H β to the carbonyl), 4.10 (0.8 H, doublet of triplets, J_d = 10 cps, J_t = 2 cps, vinylic H α to the carbonyl), 7.66–7.83 (4.1 H, 4-peak multiplet), and 8.95 ppm (6.2 H, singlet, *gem*-dimethyl H).

6-Methyl-2-cyclohexenone (28).—From 40.0 g (0.374 mol) of *o*-toluidine, following the reduction procedure of Stork and White,[47] there was obtained 12.2 g (30%) of **28**: ν_{max} 1684 (s), 1626 (m), 1215 (s), and 890 (m) cm^{-1}; $\lambda_{max}^{95\% \text{ EtOH}}$ 224.5 mμ (ϵ 9400); nmr spectrum, τ 2.92–3.28 (1.0 H, multiplet, vinylic H β to the carbonyl), 4.15 (1.0 H, doulet of triplets, J_d = 10 cps, J_t = 1.5 cps, vinylic H α to the carbonyl), 7.41–8.71 (5.0 H, multiplet), and 8.93 ppm (2.9 H, doublet, J = 6.5 cps, methyl H).

Data Obtained for Isolated Photoproducts. 3-Ethyl-3- (or -2-) [1′-(6-keto-2-ethyl-Δ′-cyclohexenyl)]cyclohexanone from Irradiation of 5.—The solvent was removed from the irradiation mixture of **5**. Glpc of the yellow oil (577 mg) on a 20% DEGS column (5 ft × 0.25 in.) gave no peaks other than starting material. Glpc on a 10% Carbowax 6000 column (2.5 ft × 0.25 in.) showed four major photoproducts, all of which had mass spectral molecular ions at *m/e* 248 (*i.e.*, dimers). The major dimer had $\lambda_{max}^{cyclohexane}$ 239 mμ (ϵ 11,500) and ν_{max} 1715 (s), 1667 (s), and 1629 (m) cm^{-1}, and on the basis of this spectral evidence it was identified as 3-ethyl-3- (or -2-) [1′-(6-keto-2-ethyl-Δ^1-cyclohexenyl)]cyclohexanone.

***t*-Butyl 4,5-Dimethyl-Δ^5-hexenoate from Irradiation of 10.**—The solvent was removed from the irradiation mixture of **10**; the residue was distilled to obtain volatile products; and the photoproduct (26%) was isolated by glpc. This product was identified as *t*-butyl 3,4-dimethyl-Δ^5-hexenoate (**29**) by comparison with authentic *t*-butyl 3,4-dimethyl-Δ^5-hexenoate (see below).

***t*-Butyl 4,5-Dimethyl-Δ^5-hexenoate (29).**[48]—Hydrogen peroxide (9.90 g of 30%, 0.0874 mol) was added rapidly, but dropwise, to 22.6 g (0.179 mol) of 3,4-dimethylcyclohexanone (prepared by Jones oxidation[49] of 3,4-dimethylcyclohexanol)[27] in a 300-ml, three-necked flask, equipped with mechanical stirrer, dropping funnel, and thermometer. The mixture was rapidly stirred for 45 min; 0.5 ml of 6 *N* sulfuric acid was added; and stirring was continued for 15 min. The suspension, cooled in an ice bath to 20°, was swept with nitrogen, and a cupric–ferrous sulfate solution (45 g of $CuSO_4 \cdot 5H_2O$, 50 g of $FeSO_4 \cdot 7H_2O$, 10 ml of concentrated H_2SO_4, and 180 ml of H_2O) was added as rapidly as temperature control (30°) would permit. Rapid stirring was continued at room temperature for 2 hr, and the mixture was then diluted with 100 ml of 10% sulfuric acid. The mixture was extracted with chloroform (three 100-ml portions), and the combined chloroform extract was washed with saturated salt solution (one 25-ml portion) and extracted with 5% sodium hydroxide solution (two 50-ml portions). The basic extract was acidified with 10% sulfuric acid and extracted with ether (three 75-ml portions). The combined ethereal extract was dried and concentrated.

Oxalyl chloride (4.0 g) was added dropwise to the unpurified acid (1.33 g), and the brown solution was stirred for 24 hr at room temperature. Most of the excess oxalyl chloride was removed under reduced pressure, and then a solution of 5.0 g of *t*-butyl alcohol and 5.0 g of pyridine was added dropwise. The mixture was stirred for several minutes and diluted with 75 ml of water and 75 ml of ether, and the layers were separated. The aqueous layer was washed with ether (two 25-ml portions), and the combined ethereal extract was washed with 10% sulfuric acid (one 25-ml portion), washed with saturated sodium bicarbonate solution (one 25-ml portion), dried, and concentrated.

The residual oil (2.34 g), which contained crystalline di-*t*-butyloxalate, was analyzed on a 20% Carbowax 20M column (5 ft × 0.25 in.). The glpc trace showed one minor product and two major products, as well as a large peak for di-*t*-butyl oxalate. Two major products (61 and 39%) were found.

The 61% compound was collected from glpc and was identified as *t*-butyl 3,4-dimethyl-Δ^5-hexenoate on the basis of the following data: mass spectrum, last peak at 142 (M − 56); ν_{max} 1727 (s), 1642 (w), 1151 (s, broad), 1000 (m), 958 (m), 917 (s), and 848 (m) cm^{-1}; nmr, τ 4.01–4.66 (0.9 H, multiplet, vinylic H), 4.90–5.30 (1.7 H, multiplet, terminal vinylic H), 7.50–8.71 [13.9 H, multiplet with a very strong singlet at 8.59 (*t*-butyl H)], and 9.03 and 9.13 ppm (5.5 H, two overlying doublets that appeared as a broad triplet, J_1 = 7 cps, J_2 = 5 cps).

The 39% compound was collected from glpc and was identified as *t*-butyl 4,5-dimethyl-Δ^5-hexenoate (**29**) on the basis of the following data: mass spectrum, last peak at 142 (M − 56); ν_{max} 1730 (s), 1642 (w), 1149 (s, broad), 896 (m), and 852 (m) cm^{-1}; nmr, τ 5.36 (1.4 H, broad singlet, vinylic H), 7.74–8.68 [17.0 H, multiplet with a broad singlet at 8.36 (vinylic methyl H) and a very strong singlet at 8.60 (*t*-butyl H)], and 8.98 ppm (3.6 H, doublet, J = 6.5 cps, methyl H).

An analysis was obtained on a sample of both esters, collected together from glpc.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.65; H, 11.24.

Irradiation of 3-Keto-Δ^4-octalin (11).—In every irradiation of **11** the disappearance of the starting material could be followed by examination of the vpc tracings and the uv spectrum. No equal increase in photoproducts was observed. The starting material gave rise mainly to products of higher molecular weight which were not detectable under the vpc conditions nor by uv spectroscopy. The photoproduct mixtures were isolated by evaporating the solvent, and the thick oily product was analyzed, by utilizing vpc conditions with low stationary-phase concentrations, short columns, and high temperatures. Three peaks were collected separately and subjected to mass spectral analysis. In each case they demonstrated molecular ions for dimers of **11** at 300 mass units. Analysis of the dimers using high-efficiency analytical vpc columns showed the presence of at least 13 dimeric products; none occurred in greater proportion than 10% of the mixture. The close similarity in retention times of these left little doubt that all of them were dimeric in nature. Attempts at recrystallization failed to resolve this dimer mixture as did alumina chromatography and analytical thin layer chromatography. The formation of dimeric photoproducts was unchanged between irradiation of the n → π^* or π → π^* absorption bands (high-pressure arc lamp or low-pressure resonance lamp), but in the second case the reaction was more rapid because of the higher uv absorption of the π → π^* band. During irradiation in *t*-butyl alcohol two monomers could be seen forming slowly, but after 90% of the octalone (**11**) had been converted into photoproducts the two monomers were only present in 2 and 3% of the amount of starting material, respectively. These photoproducts were collected, and their ir spectra were identical with those of *cis*- and *trans*-3-decalones. *trans*-3-Decalone was the major (3%) monomeric photoproduct.

A summary of the irradiations with different solvents appears in Table IV. The only solvent that gave a respectable yield of monomeric photoproducts was cyclohexane where 75% of the 3-keto-Δ^4-octalin which had been converted into photoproduct appeared as *cis*- and *trans*-3-decalone. All of the solvents gave hydrogen abstraction to some extent. Enone dimers were isolated from irradiation in each solvent. Unfiltered photolyses in benzene, acetone, and glacial acetic acid yielded thick, dark, immobile irradiation mixtures which were not further investigated.

TABLE IV

SUMMARY OF RESULTS FROM IRRADIATION OF 11

Solvent	Procedure[a]	Filter	Concn × 10^{-3} *M*	% conversion	% decalones[b]
t-Butyl alcohol	A	Pyrex	24	37	2
t-Butyl alcohol	B		4	98	5
t-Butyl alcohol	A	Pyrex	1	20	4
t-Butyl alcohol	B		10	87	5
Dioxane	A	Pyrex	12	80	5
Dioxane	A	Pyrex	15	50	6
Glyme	A	Pyrex	8	66	6
Cyclohexane	A	Pyrex	12	56	42

[a] Procedure A, 450-W mercury arc lamp; procedure B, low-pressure mercury resonance lamp. [b] Based on total amount of starting material and not on amount of starting material converted.

The photomixtures from all the irradiations demonstrated a weight increase over the amount of enone used, and, in each ir-

(47) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4604 (1956).

(48) H. E. De La Mare, J. K. Kochi, and F. F. Rust, *ibid.*, **83**, 2013 (1961); U. S. Patent 3,013,068 (1961).

(49) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

radiation, products that are attributed to reaction of the solvent could be isolated. When glyme was used as solvent, higher molecular weight ethers were isolated from the photomixture (by vpc), and from *t*-butyl alcohol the "dimer" 2,5-dihydroxy-2,5-dimethylhexane (**40**) was isolated and compared with an authentic[50] sample.

The length of time needed for reaction varied among the solvents. Concise comparisons are not possible, as the age of lamp and transmission properties of the probes were not identical in all cases; however, irradiations in cyclohexane which caused mainly reduction to the decalones proceeded approximately three times more rapidly than did irradiation in the other solvents which caused dimerization to predominate. It was found that a tenfold dilution reduced the reaction time even more and yet no new monomeric photoproducts formed.

3,6,6-Trimethylbicyclo[3.1.0]hexan-2-one and 3-Isopropyl-5-methyl-2-cyclopentenone from Irradiation of 18.—The solvent was removed from the irradiation mixture which was distilled, and two photoproducts were isolated by glpc. The first eluted product (5% yield) was identified as 3,6,6-trimethylbicyclo-[3.1.0]hexane-2-one on the basis of the following data: mol wt, 138 (mass spectrum); ν_{max} 1724 (s), 1374 (m), 1192 (m), 1117 (m), 996 (m), 893 (w), and 868 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 208 mμ (ϵ 3690); nmr, τ 7.3–8.53 (5.6 H, multiplet) and 8.54–9.10 (8.4 H, multiplet with a strong singlet at 8.84 ppm (*gem*-dimethyl H)). The structural assignment was verified by comparison with authentic 3,6,6-trimethylbicyclo[3.1.0]hexan-2-one. Both samples had identical ir spectra and glpc retention times and almost identical nmr spectra.

The second product (8%) was identified as 3-isopropyl-5-methyl-2-cyclopentenone on the basis of the following data: mol wt, 138 (mass spectrum); ν_{max} 1706 (s), 1616 (m), and 867 (m) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 227 mμ (ϵ 14,000); nmr, τ 4.21 (0.9 H, broad singlet, vinylic H), 6.84–8.09 (4.1 H, multiplet), 8.82 (doublet, J = 7 cps, *gem*-dimethyl H), 8.91 ppm (doublet, J = 6.5 cps, methyl H), and both doublets combined integrated to 9.0 H.

Anal. Calcd for $C_9H_{14}O$: mol wt, 138.10446. Found: mol wt, 138.10623 (high-resolution mass spectrum).

The low absolute yields of the photoproducts are probably due to secondary photochemical reactions as 3,6,6-trimethylbicyclo-[3.1.0]hexan-2-one was shown to be unstable to the irradiation conditions.

Photoproducts from 19.—The crude photoproduct (11.5 g) was isolated by evaporation of the solvent and was chromatographed on neutral activity III alumina. Petroleum ether eluted 9.7 g (89% of total product) of a mobile yellow oil. Further elution with ether, ethyl acetate, and methanol yielded small amounts of material that were later characterized as dimers of **19** and as the solvent "dimer" **40**. The first chromatographic fraction was distilled [bp 53–55° (0.1 mm)] to give a clear oil which was shown to contain 60% **19** and 12% lumiproduct **41** (25% converted **19**) and 16% a saturated ketone (33% converted **19**). The photoproduct **41** possessed the following properties: λ_{max}^{EtOH} 208 mμ (ϵ 4200); $\nu_{max}^{CCl_4}$ 3020 and 1715 cm^{-1}; nmr, τ 8.80 ppm (3 H, methyl singlet, no absorption for vinyl or allyl protons). The material was identical with that previously described.[15] The saturated ketone was identical with *trans*-10-methyl-2-decalone when compared by infrared and vpc retention times on two different columns.

This reaction was reproducible, and smaller samples were irradiated to greater conversion and followed by analytical vpc. No new major photoproducts could be observed upon extended irradiation; the lumiproduct **41** could be gained in 33% yield after about 70% irradiation. Extended irradiation led to a decrease in the amount of **41**. Large vpc injections and high attenuations revealed the presence of five minor materials (11%) with retention times similar to those of **19**; these were not investigated.

Two major dimers exhibiting mass spectral molecular ions of twice the weight of **19** were detected by analysis of the chromatography fractions using the short (2 ft), low stationary-phase (5%) vpc column.

Photoproduct from 24.—Aliquots removed from the irradiation solution at regular intervals were analyzed by uv spectroscopy and vpc and demonstrated the formation of a photoproduct that possessed only weak uv end absorption and a vpc retention time approximately half that of the starting material. This photoproduct was formed exclusively and did not react further. The irradiation was ceased when 60% of the starting material had been converted and the solution contained 60% photoproduct which was shown to be the lumiproduct: $\nu_{max}^{CCl_4}$ 3021 (w) and 1721 (s) cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 205 mμ (ϵ 5700); nmr spectrum, τ 9.13 (3 H, methyl singlet) and 8.5–8.8 ppm (11 H, methylene hump, no vinyl hydrogens).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39; mol wt, 152. Found: C, 80.11; H, 9.40; mol wt, 152 (mass spectrum).

3-*t*-Butoxy-5,5-dimethylcyclohexanone and Crystalline Dimer from Irradiation of 27.—The solvent was removed from the irradiation mixture of **27**, and the volatile photoproduct was isolated by glpc, after the mixture was distilled, on a 20% Carbowax 20M column (5 ft × 0.25 in.). This product (4% yield) was identified as 3-*t*-butoxy-5,5-dimethylcyclohexanone on the basis of the following data: mol wt, 198 (mass spectrum); ν_{max} 1718 (s), 1389 (m), 1362 (m), 1196 (m), and 1063 (s) cm^{-1}; $\lambda^{95\%\ EtOH}$ only end absorption; nmr, τ 6.09–6.50 (1.0 H, multiplet, H geminal to oxygen), 7.43–8.10 (4.0 H, multiplet, methylene H α to carbonyl), and 8.24–8.58 ppm (2.5 H, multiplet, methylene H).

The residual oily crystals (43%), remaining after distillation, were a mixture of dimers. The major dimer, which recrystallized as white plates from 95% ethanol, was identified as 5,5,10,-10- or 11,11-tetramethyltricyclo[6.4.0.$0^{2,7}$]-3,12- or 9-dodecadione on the basis of the following data: mp 114–115°; mol wt, 248 (mass spectrum); ν_{max} 1706 (s) cm^{-1}; $\lambda^{95\%\ EtOH}$ only end absorption; nmr, τ 6.63–7.21 and 7.32–7.69 (4.4 H, two multiplets, cyclobutyl H), 7.90 (4.0 H, singlet, methylene H α to carbonyl), 8.07–8.77 (4.1 H, multiplet, methylene H), and 8.94 and 9.04 ppm (11.5 H, two singlets, *gem*-dimethyl H).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.64; H, 9.80.

Registry No.—**2**, 1121-18-2; **5**, 17299-34-2; **6**, 6328-22-9; **7**, 499-74-1; **8**, 17299-35-3; **9**, 5515-76-4; **10**, 10463-42-0; **11**, 1196-55-0; **12a**, 734-32-7; **12b**, 434-22-0; **13**, 17299-39-7; **14**, 5164-37-4; **15**, 1073-13-8; **17**, 17299-41-1; **18**, 13395-73-8; **19**, 826-56-2; **20**, 17299-44-4; **22a**, 1425-10-1; **24**, 17299-55-7; **24** dinitrophenylhydrazone, 17299-45-5; **25**, 17299-46-6; **26a**, 601-55-8; **27**, 4694-17-1; **28**, 6610-21-5; **29**, 17299-49-9; 3,6,6-trimethylbicyclo[3.1.0]hexan-2-one, 2198-79-0; 5-methyl-3-isopropyl-2-cyclopentenone, 17299-51-3; 3-*t*-butoxy-5,5-dimethylcyclohexanone, 17299-52-4; **38**, 17299-53-5; **39**, 723-05-7; *t*-butyl 3,4-dimethyl-Δ^5-hexenoate, 17299-09-1.

Acknowledgment.—We are grateful to W. T. Wipke and P. Oberhänsli for the synthesis of **24** and **25**, respectively, and to G. Miles and R. G. Williams for the synthesis and irradiation of **17** and **22a**, respectively.

(50) H. A. Bruson and J. W. Kroeger, *J. Amer. Chem. Soc.*, **62**, 36 (1940).

Mass Spectra of Saturated and Unsaturated Derivatives of Thiacyclohexane and 4-Thiacyclohexanone

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In the series 4-thiacyclohexanone, its oxide, and its dioxide, the fragmention patterns indicate that less and less ionization takes place at sulfur upon electron impact as its oxidation state increases. The primary processes in the mass spectral decomposition of 4-thiapyrone 4,4-dioxide appear to be sulfone–sulfinate rearrangement, loss of O_2, and ring-cleavage reactions analogous to those found for 4-thiapyrone. 3-Phenyl-2H-thiapyran 1,1-dioxide decomposes principally to stabilized hydrocarbon ions. The behavior of these and similar compounds is discussed in terms of charge localization upon electron impact.

The concept of charge localization has proven very useful in the interpretation of the mass spectra of heteroatomic organic molecules.[1] It holds, essentially, that ionization can be represented as the net removal of an electron of low ionization potential; these are frequently localized in the nonbonding orbitals associated with the heteroatoms. Recent studies of the ionization potentials of polyheteroatomic molecules support this view.[2] Much attention has been devoted of late to mass spectrometric rearrangements,[3] and many of these may be rationalized by invoking charge localization. We cite as examples the rearrangement of aromatic nitro compounds to nitrite molecular ions;[4] the rearrangement of aromatic sulfoxides[5] and sulfones[5,6] to sulfenate and sulfinate ester molecular ions; and the loss of C_6F_5O from $(C_6F_5)_3PO$,[7] presumably by way of the phosphinite ester, all upon electron impact. Each of these rearrangements involves a reduction in oxidation state of the least electronegative heteroatom (N, S, or P), making that atom a better site for charge localization. A change from higher to lower metal valence states has been shown to be an important determinant of the mass spectral cracking patterns of organometallic compounds.[8]

With these concepts in mind we undertook a study of various cyclic sulfones and some related compounds. The fragmentation patterns of aromatic and acyclic aliphatic sulfones and sulfoxides are well documented. The aromatic derivatives tend to lose SO_2[5,6] and SO,[5] respectively, as well as undergoing the rearrangements noted above. There is no evidence of appreciable rearrangement of aliphatic sulfoxides[5] or sulfones[5,9] upon electron impact. Carbon–sulfur bond cleavage seems to be the dominant process, accompanied by hydrogen transfer from the alkyl group to the sulfur oxide portion of the molecule. Most of the ion current arises from hydrocarbon fragments. Alkyl alkanesulfonates behave very similarly to sulfones upon electron impact,[10] and their spectral patterns are compatible with those predicted from charge localization considerations.

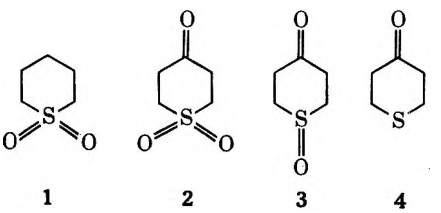
Saturated Compounds.—Our reference compound was pentamethylene sulfone (1). Its mass spectrum (Table I)[11] was unexceptional, consisting in the main

TABLE I

PARTIAL MASS SPECTRUM OF PENTAMETHYLENE SULFONE

m/e	Probable composition	% Σ_{28}
134	M	4.3
106	M − C_2H_4	0.70
70	M − SO_2	3.2
69	M − SO_2H	11.
55	$C_4H_7^+$	8.3
43	$C_3H_7^+$	4.1
42	$C_3H_6^+$	15.
41	$C_3H_5^+$	12.
39	$C_3H_3^+$	5.4

of peaks due to hydrocarbon ions. Loss of SO_2 and HSO_2 are important processes, with the latter predominating. In fact, the spectrum strongly resembled that of cyclopentane and/or 1-pentene,[12] except for the unusually intense peaks at *m/e* 69, 43, and 28. A small peak at M − 28 indicates that loss of C_2H_4 is a minor process.



1 2 3 4

Introduction of a carbonyl group at C-4 of the sulfone (4-thiacyclohexanone 4,4-dioxide, 2) radically alters the fragmentation pattern (Figure 1). Peaks corresponding to M − SO_2 and M − SO_2H are no longer discernible. The relative abundance of M − 28 rises sharply, reflecting the ease of α cleavage at both the carbonyl and sulfonyl groups. Sulfur dioxide is apparently lost next, giving rise to the base peak at *m/e* 56. A large peak is also found at *m/e* 55, which may arise by expulsion of SO_2H from the M − 28

(1) (a) F. W. McLafferty, *Chem. Commun.*, 78 (1966); (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Molecules," Holden-Day, Inc., San Francisco, Calif., 1967, p 9.

(2) M. Baldwin, A. Kirkien-Konasiewicz, A. G. Loudon, A. Maccoll, and D. Smith, *Chem. Commun.*, 574 (1966); H. J. Svec and G. A. Junk, *J. Amer. Chem. Soc.*, **89**, 790 (1967).

(3) P. Brown and C. Djerassi, *Angew. Chem. Intern. Ed. Engl.*, **6**, 477 (1967).

(4) J. H. Beynon, R. A. Saunders, and A. E. Williams, *Ind. Chim. Belge*, **29**, 311 (1964); S. Meyerson, I. Puskas, and E. K. Fields, *J. Amer. Chem. Soc.*, **88**, 4974 (1966).

(5) J. H. Bowie, D. H. Williams, S.-O. Lawesson, J. Ø. Madsen, C. Nolde, and G. Schroll, *Tetrahedron*, **22**, 3515 (1966).

(6) S. Meyerson, H. Drews, and E. K. Fields, *Anal. Chem.*, **36**, 1294 (1964).

(7) H. J. Emeléus and J. M. Miller, *J. Inorg. Nucl. Chem.*, **28**, 662 (1966); J. M. Miller, *J. Chem. Soc., A*, 828 (1967).

(8) J. S. Shannon and J. M. Swann, *Chem. Commun.*, 33 (1965).

(9) R. T. Aplin and K. Baily, *J. Chem. Soc., B*, 513 (1967).

(10) W. E. Truce, R. W. Campbell, and G. D. Manning, *J. Org. Chem.*, **32**, 308 (1967).

(11) Mass spectrum was determined with a Varian M-66 mass spectrometer.

(12) B. J. Millard and D. F. Shaw, *J. Chem. Soc., B*, 664 (1966).

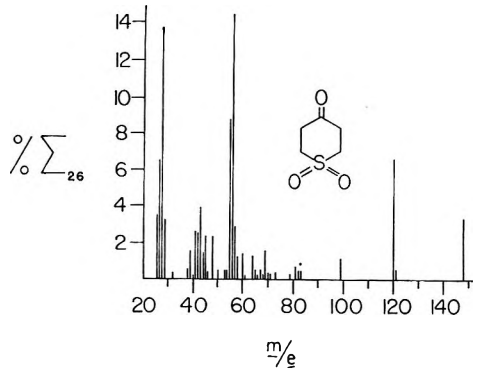
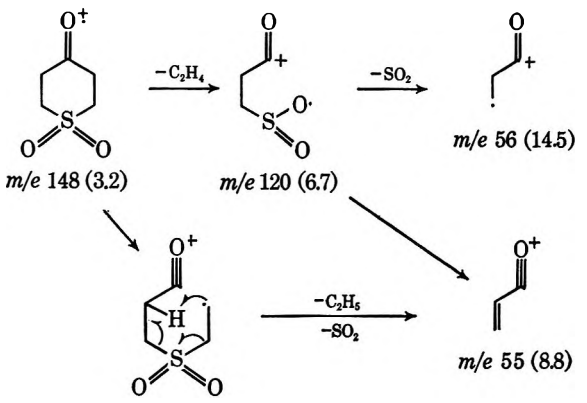


Figure 1.—Mass spectrum of 4-thiacyclohexanone 4,4-dioxide, Varian M-66.

species; alternatively, the molecular ion may lose C_2H_5 and SO_2. The latter pathway is similar to one found for cyclohexanone, in the spectrum of which *m/e* 55 is the base peak.[13]

Scheme I indicates the proposed fragmentation paths for 2[14] (asterisks denote processes for which metastables were observed). They may be adequately accounted for by assuming initial ionization at the carbonyl group. A small peak at *m/e* 99 gives the only indication that some ionization may take place at the sulfone group. This peak most likely corresponds to M − HSO, which would be in line with our detection of a peak at *m/e* 48 (SO^+). The occurrence of these peaks implies some C–O bond formation.

SCHEME I



4-Thiacyclohexanone 4-oxide (**3**) decomposes somewhat similarly to the corresponding sulfone,[11,15] but significant differences are observed (Figure 2). The M − 28 peak is now the second most intense one, its stability possibly reflecting the lower valence state of sulfur. A greater over-all percentage of the ion current in the sulfoxide spectrum is carried by sulfur-containing ions.

The base peak of the spectrum is located at *m/e* 55, indicating that the sulfur is lost as HSO (Scheme II); sulfoxide groups are known to abstract hydrogen pyrolytically[16] and under electron impact.[5,16] An

(13) Reference 1b, p 143.

(14) In our discussion of the mass spectra of **2**–**4**, it is assumed that M − 28 corresponds mainly to M − C_2H_4, rather than M − CO. Retention of the carbonyl group would most reasonably rationalize the fragmentation patterns, and it is to be expected from the behavior of related compounds.

(15) Mass spectrum was obtained with an AEI MS9 mass spectrometer.

(16) I. D. Entwistle, R. A. W. Johnstone, and B. J. Millard, *J. Chem. Soc., C*, 302 (1967).

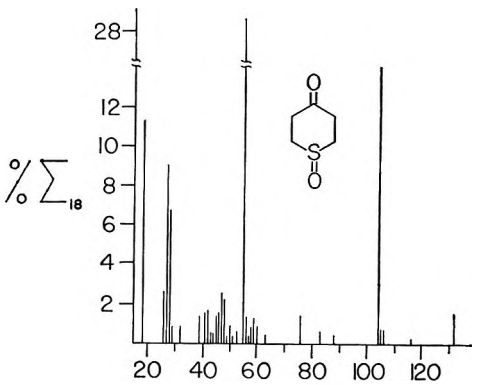
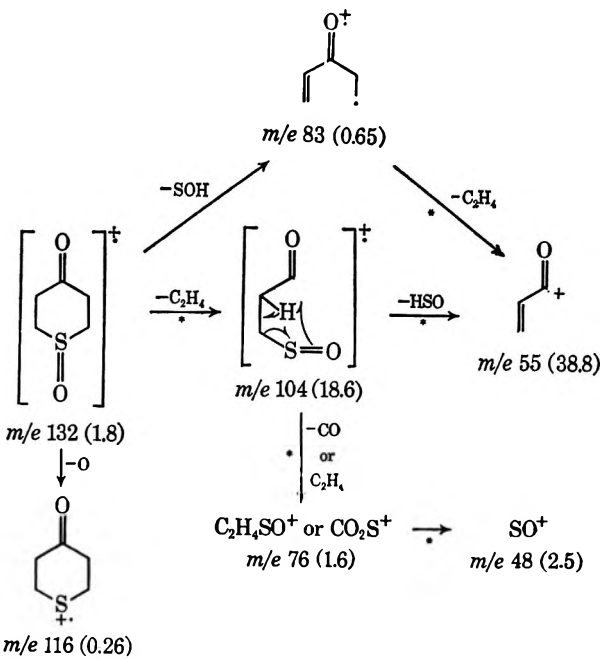


Figure 2.—Mass spectrum of 4-thiacyclohexanone 4-oxide, AEI MS9.

SCHEME II



alternative route to *m/e* 55 involves loss of HSO first and subsequent loss of C_2H_4; the low abundance of *m/e* 83 ions (M − HSO) might indicate that this path is less favorable.

A very weak peak at *m/e* 116 corresponds to the molecular ion of 4-thiacyclohexanone (**4**). Loss of O and OH radicals from aromatic and aliphatic sulfoxide molecular ions has been observed;[5] the same fragments are also expelled by the molecular ions of aromatic N oxides.[17] Interestingly, loss of O or OH from sulfones upon electron impact has rarely been reported.

The mass spectrum (Table II)[11] of **4** itself might readily have been predicted from the spectra of **2** and **3**. While M − 28 is still prominent, *m/e* 55 is relatively weak and *m/e* 56 barely discernable. Groups of intense peaks are found at *m/e* 45, 46, 58, 59, and 60, a pattern characteristic of the mass spectra of cyclic sulfides.[18] Most of the ion current from fragmentation of **4** is carried by sulfur-containing ions, and it seems

(17) T. A. Bryce and J. R. Maxwell, *Chem. Commun.*, 206 (1965); A. Tatematsu, H. Yoshizumi, E. Hayashi, and H. Nakata, *Tetrahedron Lett.*, 2985 (1967).

(18) Reference 1b, p 284.

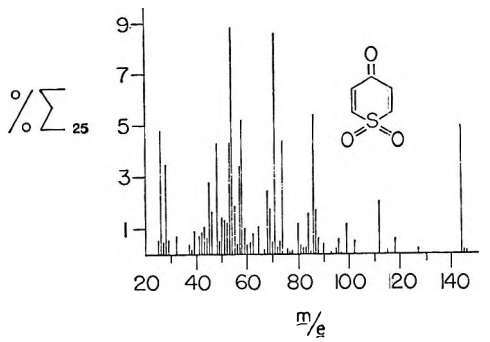


Figure 3.—Mass spectrum of 4-thiapyrone 4,4-dioxide, Varian M-66.

clear from the fragmentation patterns that a larger portion of the ionization takes place at sulfur as one goes from **2** to **3** to **4** (see Schemes I and II, and Table II).

TABLE II
PARTIAL MASS SPECTRUM OF 4-THIACYCLOHEXANONE

m/e	Probable composition	%Σ26
116	M	17.1
88	M − C_2H_4	10.5
60	$C_2H_4S^+$	12.4
59	$C_2H_3S^+$	5.8
58	$C_2H_2S^+$	3.3
55	M − C_2H_5S	2.4
47	CH_3S^+	0.92
46	CH_2S^+	12.0
45	CHS^+	9.2

Very recently a report on some cage keto sulfones has appeared in the literature, including their mass spectra.[19] These molecules tend to lose SO_2 and CO readily upon electron impact; as the authors observe, however, there are very strong compressional forces present.

Unsaturated Compounds.—Marked changes occur in the mass spectra of cyclic sulfones upon introduction of unsaturation into the ring. Sulfone–sulfinate rearrangement might be expected, by analogy with the aryl sulfones, and evidence for such rearrangements has been uncovered. The mass spectrum[11,20] of 4-thiapyrone 4,4-dioxide (**5**) exhibits its second most intense peak at *m/e* 71, which can only correspond to the ions $C_3H_3O_2^+$ and/or $C_3H_3S^+$. The former, which seems more likely on mechanistic grounds (*vide infra*), requires a rearrangement involving C–O bond formation. Noteworthy in this regard is a substantial peak corresponding to SO^+.

Loss of acetylene from the molecular ion by a "retro Diels–Alder" process (*m/e* 118) was to be expected on the basis of the mass spectrometric behavior of 4-pyrone[21] (**6**) and 4-thiapyrone[22] (**7**). Most remarkable, however, and perhaps not to be expected by analogy with other systems, is a peak at *m/e* 112, M − 32 (Figure 3),[23] corresponding most probably to $C_5H_4OS^+$ or $C_5H_4O_3^+$. Close examination of an MS12 spectrum revealed that *m/e* 112 consisted of an unresolved doublet, in which the component of smaller mass predominated. This would tend to eliminate $C_5H_4O_3^+$, since the low intensity of *m/e* 110 and 111 precludes any substantial contribution to *m/e* 112 from ions containing heavy isotopes. The molecular ion thus loses O_2,[24] the driving force no doubt being the formation of an aromatic cation having a large fraction of the charge localized on sulfur. We infer that the oxygen atoms are lost as molecular oxygen, since M − 16 or M − 17 peaks are not observed.

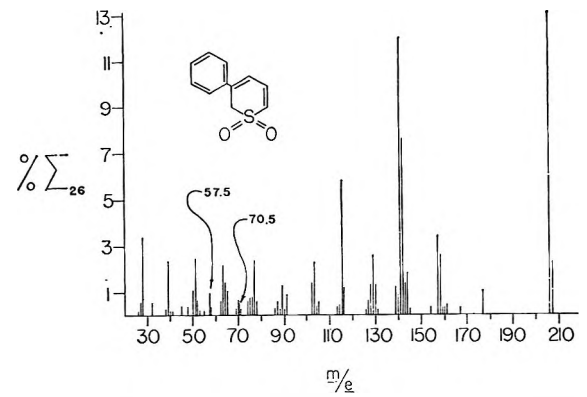
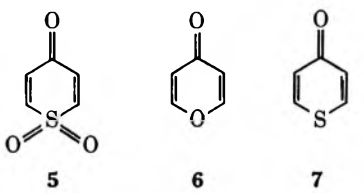


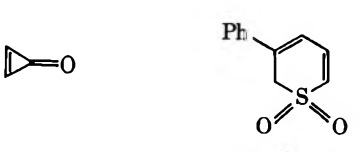
Figure 4.—Mass spectrum of 3-phenyl-2H-thiapyran 1,1-dioxide, AEI MS12.



5 **6** **7**

The M − O_2 ion from **5** is the molecular ion of **7**. Decomposition of **7** by a "retro Diels–Alder" cleavage is well established,[22] and the spectrum of **5** contains an intense peak at *m/e* 86 identical with this fragment ion. Furthermore, metastable peaks establish the conversion of *m/e* 86 into 58 and 54, ions which are prominent in the spectrum of **7**.

The low intensity peak at *m/e* 96 may be formulated as the molecular ion of **6**. Loss of CO from this ion, which is a prominent decomposition mode of **6**,[21] is suggested by a metastable at *m/e* 48.2; the fact that other transitions could give rise to a metastable in this region prevents our making this assignment with certainty. The odd-electron ions at *m/e* 112 (**7**), 96 (**6**), and 54 [cyclopropenone (**8**), base peak] are similar in that they may be depicted with the positive charge delocalized in an aromatic ring, and the odd spin localized on an exocyclic oxygen.



8 **9**

(19) L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **89**, 6659 (1967).

(20) Mass spectrum was obtained with an AEI MS12 mass spectrometer.

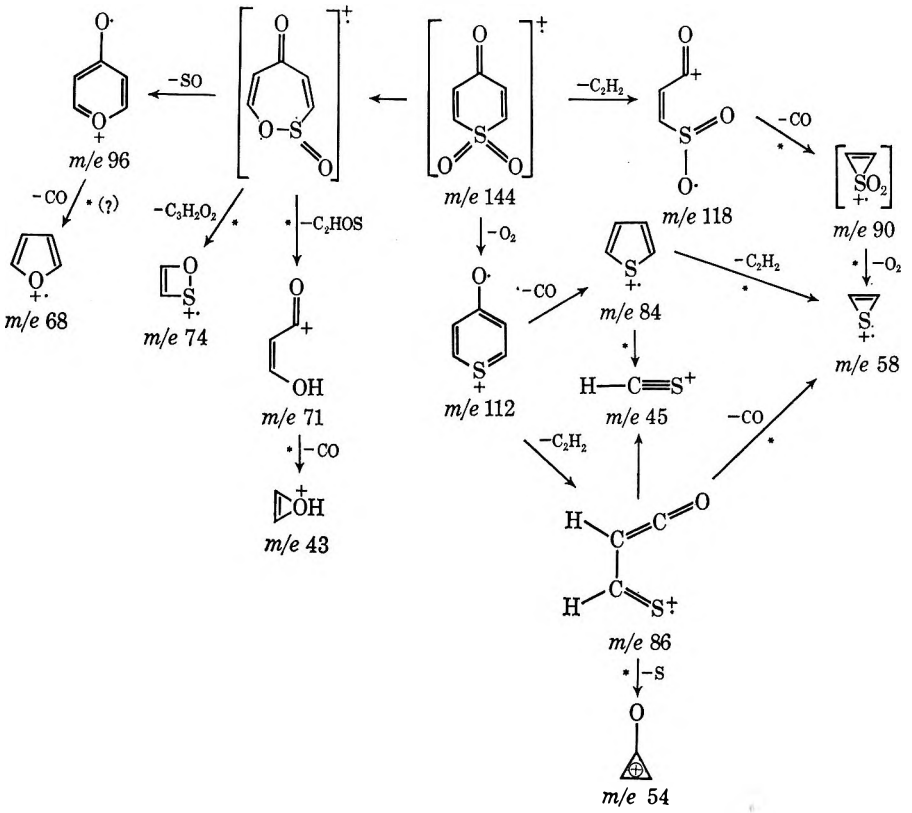
(21) P. Beak, T. H. Kinstle, and G. Carls, *J. Amer. Chem. Soc.*, **86**, 3833 (1964).

(22) J. Bonham, E. McLeister, and P. Beak, *J. Org. Chem.*, **32**, 639 (1967).

(23) This peak, which had an intensity about 23% that of the base peak on the M − 66 spectrum, was very weak on the MS12 spectrum (1% relative intensity). In general, peaks at *m/e* > 54 were much less intense in the MS12 spectra. The dependence of cracking pattern on instrument design has been noted many times before; for an opposite example, see ref 1b, p 8. Further discussion may be found in the Experimental Section.

(24) Dibenzothiophene 5,5-dioxide loses O_2 upon pyrolysis or electron impact [E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 2836 (1966)]; in the mass spectrum, M − O_2 has a relative intensity of 4%. This seems to be the only other reported case of O_2 loss from a sulfone.

SCHEME III



There may be one more instance of O_2 loss in the fragmentation of **5**. A weak metastable at *m/e* 37.4 could correspond to the transition $90^+ \rightarrow 58^+ + 32$ (calculated m* 37.5). Once again, a sulfone would be reduced to a sulfide in the process. Also of interest is the presence of an M − SO_2 peak, in view of the absence of an M − CO peak; CO loss from **6** and **7** was very prominent. The highly electronegative sulfone unit may be a better "leaving group" than carbon monoxide. Scheme III depicts the proposed fragmentation scheme for 4-thiapyrone 4,4-dioxide.

Loss of oxygen from the molecular ion of **5** is presumably favored by the relative stability of the product. We sought to ascertain the effect of a keto group on the various decomposition modes by measuring the mass spectrum of 3-phenyl-2H-thiapyran 1,1-dioxide (**9**).[20] While our own work was in progress we learned that Molenaar and Strating had prepared the parent compound, 2H-thiapyran 1,1-dioxide.[25] Their results and ours are in qualitative agreement as far as the mass spectrometric behavior of these compounds is concerned. We will amplify a bit more on their similarities and differences below.

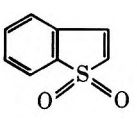
Loss of HO_2 from the molecular ion of **9** would be necessary to achieve a thiapyrylium structure; a low intensity peak at *m/e* 173 (M − 33) would seem to indicate that this is not a major process. A metastable peak corresponding to the loss of S from the fragment ion has been detected, but that assignment would not be unique. The expected sulfone–sulfinate rearrangement apparently also occurs, as evidenced by the peaks at *m/e* 144 (M − CH_2SO), 157 (M − HSO), 158 (M − SO), and 177 (M − CHO). The dominant fragmentation pathways involve loss of SO_2 and SO_2H.

We have deduced a fairly detailed decomposition scheme for the molecular ion of **9**, aided by the abundance of metastable peaks in the mass spectrum (Figure 4 and Scheme IV).

Many product ions are depicted as phenyl-substituted stable cyclic cations. The presence of peaks corresponding to the ions at *m/e* 173^{2+}, 167^{2+}, 157^{2+}, 144^{2+}, 142^{2+}, 141^{2+}, 129^{2+}, and 115^{2+} is certainly compatible with these formulations. The peaks arising from 141^{2+} and 115^{2+} are particularly intense, and a metastable peak at *m/e* 46.9 may correspond to the transition $141^{2+} \rightarrow 115^{2+} + 26$ (calculated m* 46.9).

Unsubstituted 2H-thiapyran 1,1-dioxide[25] has the base peak of its mass spectrum at *m/e* 66 (M − SO_2), while the molecular ion is the base peak in the spectrum of the phenyl derivative. Peaks corresponding to the unsubstituted thiapyrylium (*m/e* 97) and pyrylium (*m/e* 81) ions are observed, with intensities relative to the base peak of 3.5 and 26%, respectively.

In light of the analyses presented it might be expected that loss of O_2 from the cyclic unsaturated sulfones would show a dependency on ring size; there is some evidence in favor of this interpretation. The mass spectrum of benzo[*b*]thiophen 1,1-dioxide[26] (**10**)



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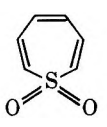
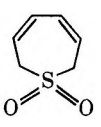


11



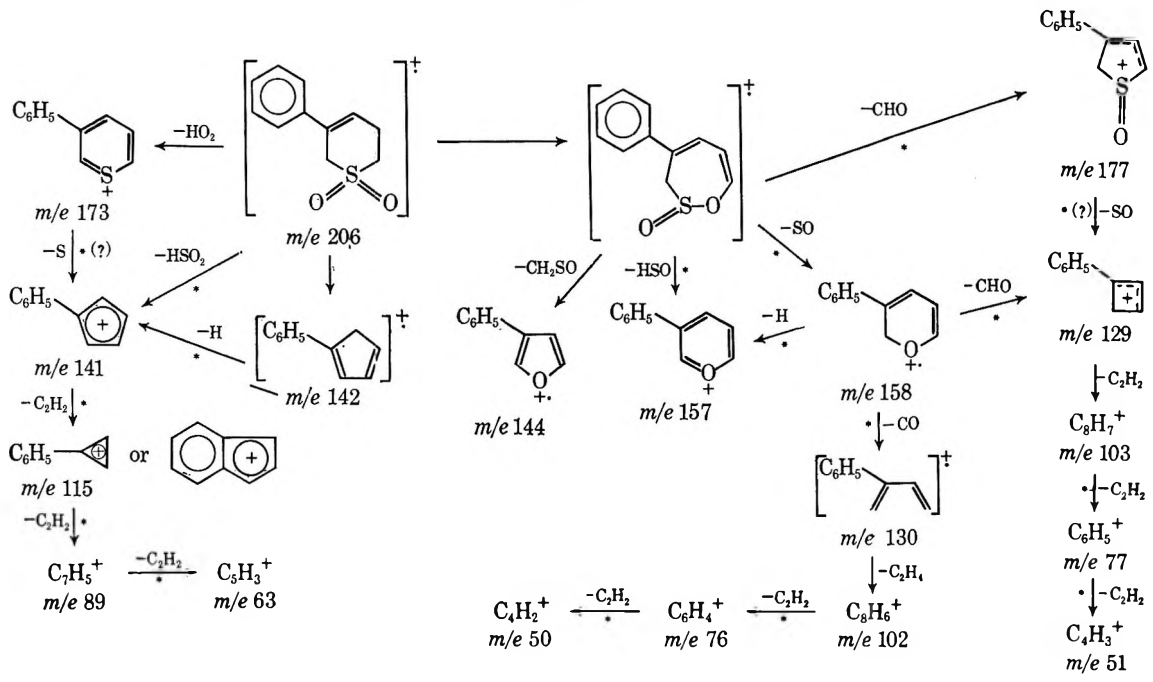
12

contains no M − O_2 peak, although a low intensity M − O peak was observed. No indication of O_2 expulsion was obtained either from the mass spectrum of

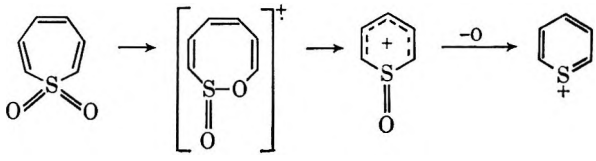
(25) Professor J. Strating, personal communication; E. Molenaar and J. Strating, *Rec. Trav. Chim.*, **86**, 1047 (1967).

(26) Q. N. Porter, *Aust. J. Chem.*, **20**, 103 (1967).

SCHEME IV



thiepin 1,1-dioxide (**11**).[27] A characteristic M − CHO peak signaled the occurrence of the sulfone–sulfinate rearrangement. The formation of thiapyrylium ion may be inferred from the presence in the spectrum of a low intensity peak at *m/e* 97. Its formation is easily rationalized on the basis of the preceding discussions. 2,7-Dihydrothiepin 1,1-dioxide (**12**) loses neither O_2 nor HO_2 upon electron impact. In common with **11**, its principal modes of decomposition involve loss of SO_2 and HSO_2.



Experimental Section[28]

Pentamethylene Sulfone (1).—Pentamethylene sulfide was prepared by the reaction of 1,5-dibromopentane with excess sodium sulfide.[29] The corresponding sulfone was obtained by oxidation of the sulfide with 35% hydrogen peroxide in acetic acid. The sulfone was best recrystallized from carbon tetrachloride, mp 98.5–99.5° (lit.[30] mp 97–98°). Its mass spectra were obtained with the probe at 30° and the analyzer at 100°.

4-Thiacyclohexanone (4).—This compound was prepared essentially by the method of Fehnel and Carmack.[31] Condensation of 2 mol of methyl acrylate with 1 mol of hydrogen sulfide in the presence of a catalytic amount of Triton B led to methyl-β-thiodipropionate. The diester underwent cyclic Claisen condensation when treated with 1 mol of sodium hydride (mineral oil suspension, Metal Hydrides, Inc.) and a small quantity of dry methanol in absolute ether. We found this method to be superior to that employing 1 mol of sodium methoxide. Hydrolysis of the keto ester in refluxing 10% sulfuric acid gave 4-thiacyclohexanone, recrystallized from hexane, mp 59–60° (lit.[31] mp 59–60°). Its mass spectrum was determined with the probe at room temperature and the analyzer at 120°.

4-Thiacyclohexanone 4-Oxide (3).—The sulfoxide was prepared by oxidation of **4** with 35% hydrogen peroxide in acetic acid. It was recrystallized from hexane, mp 111–112° (lit.[32] mp 109–110°).

The mass spectrum of **3** seemed to be critically dependent in certain ways on the operating conditions. In the M-66 (probe 45°, analyzer 110°) the sulfoxide yielded no molecular ion; in addition, peaks of low–medium intensity were present at *m/e* 76, 77, and 78, with the latter the most intense. Spectra obtained with the MS9 (ion source 90°) contained a molecular ion of 26% relative intensity and no peaks at *m/e* 77 and 78. The spectrum of this compound obtained at 100° was essentially identical, but a spectrum obtained at 140° was substantially different, with no observable molecular ion. Spectra obtained with both spectrometers had reasonably intense peaks at *m/e* 18.

4-Thiacyclohexanone 4,4-Dioxide (2).—This sulfone was obtained by oxidation of **4** with excess 35% hydrogen peroxide in acetic acid, mp 173–174° (lit.[31] mp 170°). Its mass spectrum was measured with the probe at 75° and the analyzer at 100°.

4-Thiapyrone 4,4-Dioxide (5).—Bromination of **2** with 2 mol of bromine in acetic acid, followed by dehydrobromination of the product with sodium acetate in acetone, led to **5**.[31] The crude product was recrystallized from acetic acid and further purified by sublimation *in vacuo*, mp 176–177.5° (lit.[31] mp 173–174°). Its ir spectrum agreed with one published in the literature.[33]

The M-66 mass spectra were obtained with the probe at 50° and the analyzer at 110°; the MS12 spectra were obtained with a source temperature of 50–60° and a slightly warmer probe.

The mass spectrum of **5** not only varies from instrument to instrument, it is also dependent on the length of time that the sample spends in the spectrometer. If a moderate amount of time elapses after sample introduction, before the scan is started, the resultant M-66 spectrum resembles the MS12 spectra. As time increases, *m/e* 26 increases in intensity at the expense of other peaks. The material used for this study was a mixture of freshly prepared compound and original compound, purified together. The likelihood that *m/e* 112 arises from an impurity of 4-thiapyrone in the sample is rendered unlikely because (1) there is no evidence of any **4** in the sample of **2** used to prepare 4-thiapyrone 4,4-dioxide and (2) there are profound changes in

(27) Dr. W. L. Mock, private communication of data to be published; *J. Amer. Chem. Soc.*, **89**, 1281 (1967).

(28) Melting points are uncorrected. All samples were introduced directly into the ionizing regions of the various mass spectrometers by means of probes, and all spectra were obtained with a nominal ionizing voltage of 70 V. The complete mass spectra will be submitted to the Mass Spectrometry Data Centre, Atomic Weapons Research Establishment, Aldermaston, Berks, England. They are also tabulated in the M.S. thesis of A. A. Kutz, Worcester Polytechnic Institute, 1968.

(29) W. E. Haines, R. V. Helm, G. L. Cook, and J. S. Ball, *J. Phys. Chem.*, **60**, 550 (1956).

(30) L. Bateman, J. I. Cunneen, and J. Ford, *J. Chem. Soc.*, 1539 (1957).

(31) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **70**, 1813 (1948).

(32) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(33) D. S. Tarbell and P. Hoffman, *J. Amer. Chem. Soc.*, **76**, 2451 (1954).

the entire spectrum, such as the great variation in intensity of *m/e* 71, which could not possibly be laid to this source.

3-Phenyl-2H-thiapyran 1,1-Dioxide (9).—The preparation of this compound has recently been reported.[34] Mercapotacetone, prepared from chloroacetone, was treated with phenacyl bromide in the presence of triethylamine. The diketo sulfide was oxidized to the corresponding sulfone with acidic potassium permanganate, and the sulfone underwent internal aldol condensation in the presence of acetic acid–sodium acetate.

The cyclic keto sulfone was reduced to an alcohol with sodium borohydride, and the alcohol dehydrated with 85% phosphoric acid to yield the desired product. The latter material was taken up in a small volume of methanol, and approximately twice the volume of water was added. After standing overnight in the refrigerator the mixture deposited clear needles, mp 99–101.5° (lit.[34] mp 99–100°). The mass spectrum of this compound was obtained with an ion source temperature of approximately 100° and a slightly warmer probe.

(34) S. Rossi and G. Pagani, *Tetrahedron Lett.*, 2129 (1966).

Registry No.—**1**, 4988-33-4; **2**, 17396-35-9; **3**, 17396-36-0; **4**, 1072-72-6; **5**, 17396-38-2; **9**, 6581-28-8.

Acknowledgments.—This study was made possible through the generosity and goodwill of Dr. Gerald Dudek (Harvard Univesity, MS9), Mr. David Quarton (Worcester Foundation for Experimental Biology, M-66), and Dr. Thomas Shannon (Dow Research Laboratory, Wayland, MS12), who obtained the mass spectra. We are also grateful to Dr. E. Molenaar and Professor J. Strating (Groningen) and to Dr. W. L. Mock (Carnegie-Mellon) for information made available prior to publication.

Addition of Bromotrichloromethane and Carbon Tetrachloride to Dibenzobicyclo[2.2.2]octatriene

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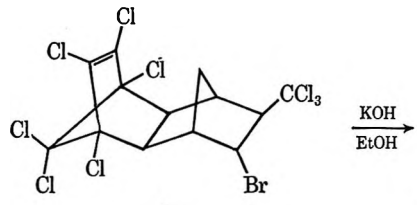
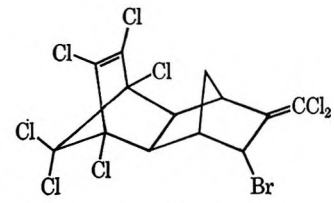
Bromotrichloromethane reacts with dibenzobicyclo[2.2.2]octatriene (**5**) at 105° to give a 1:1 adduct in high yield, whereas the reaction between carbon tetrachloride and **5** at 125–130° (sealed tube) gives a 1:1 adduct in low yield (*ca.* 5%). Both additions occur stereospecifically *trans* and are not accompanied by rearrangement. Upon treatment with base, the 1:1 adduct of bromotrichloromethane and **5** loses both hydrogen chloride (75%) and hydrogen bromide (25%). The 1:1 adduct of **5** and carbon tetrachloride upon treatment with base gives only the exocyclic olefin **8**. Some free-radical and solvolytic reactions of these olefins are discussed.

Additions of carbon tetrahalides to bridged cyclic compounds have been investigated by a number of workers.[1] Bromotrichloromethane reacts readily under free-radical conditions to give 1:1 adducts with norborene,[2,3] bicyclo[2.2.2]octene,[2] norbornadiene,[4,5] aldrin,[6] and hexachloronorbornadiene.[7] The reaction of these compounds with carbon tetrachloride was significantly slower, and in one case[7] the addition reaction failed to take place. Strong evidence has been presented to indicate that these additions to norbornene[3] and aldrin[6] were the result of stereospecific *trans* additions.

The resulting adducts of bromotrichloromethane with norbornene and bicyclo[2.2.2]octene were inert to 0.7 *N* potassium hydroxide in ethanol at 50° for 6 hr.[2] However, later it was shown that the 1:1 adducts of both carbon tetrachloride and bromotrichloromethane with norbornene lost hydrogen chloride in alcoholic potassium hydroxide to give 2-dichloromethylene-*endo*-3-chloro(bromo)norbornane. Also, the 1:1 adduct (**1**) of bromotrichloromethane and aldrin underwent dehydrohalogenation under similar conditions to give as the only observable product the exocyclic olefin **2**, the result of dehydrochlorination.[6]

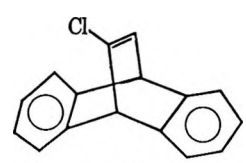


1

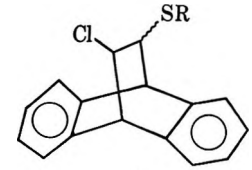


2

In the free-radical addition of thiols to 7-chlorodibenzobicyclo[2.2.2]octatriene (**3**) the stereochemistry of the products depended on the mercaptans used. Both *p*-thiocresol[8] and methyl mercaptan[9] gave mixtures of *cis* and *trans* adducts **4**.



3



4

Results and Discussion

The addition of bromotrichloromethane to dibenzobicyclo[2.2.2]octatriene (**5**) went smoothly in neat

(1) For reviews in this area, see (a) D. I. Davies and S. J. Cristol in "Advances in Free-Radical Chemistry," Vol. 1, G. H. Williams, Ed., Logas Press, London, 1965, p 155; (b) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The Macmillan Co., New York, N. Y., 1964, Chapter 2.

(2) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.*, **14**, 239 (1949).

(3) E. Tobler and D. J. Foster, *ibid.*, **29**, 2839 (1964).

(4) D. J. Trecker and J. P. Henry, *J. Amer. Chem. Soc.*, **85**, 3204 (1963).

(5) D. I. Davies, *J. Chem. Soc., C*, 2691 (1967).

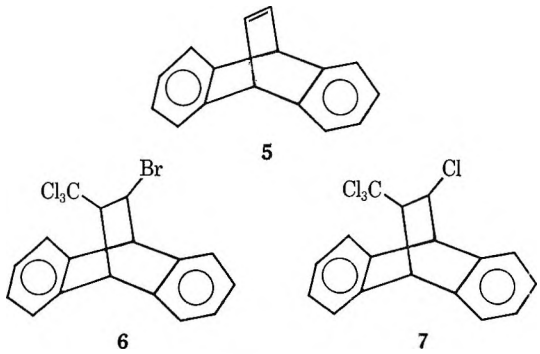
(6) D. I. Davies, *ibid.*, 3669 (1960).

(7) J. A. Clasisse, D. I. Davies, and C. K. Alden, *ibid.*, 1498 (1966).

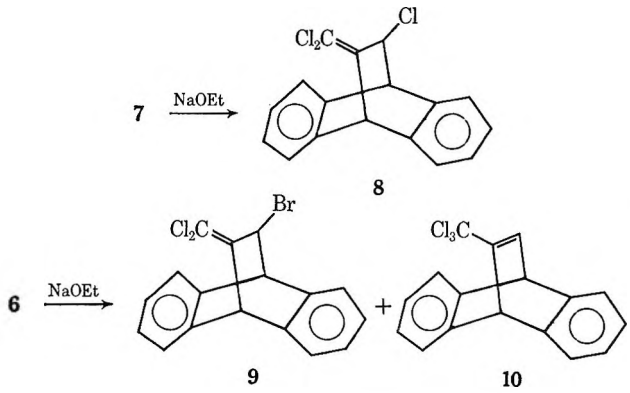
(8) S. J. Cristol and R. P. Arganbright, *J. Amer. Chem. Soc.*, **79**, 6039 (1957).

(9) S. J. Cristol, R. Caple, R. M. Sequeira, and L. O. Smith, Jr., *ibid.*, **87**, 5679 (1965).

bromotrichloromethane at the boiling point (105°) with a catalytic amount of benzoyl peroxide present. The adduct (**6**) obtained in essentially quantitative yield was shown by nmr analysis to be the *trans* adduct. An nmr spectrum of the reaction mixture showed only **6** present with none of the corresponding *cis* isomer observable. The reaction of **5** with carbon tetrachloride at elevated temperature (125–130°) in the presence of benzoyl peroxide gave the *trans* compound **7** as the only observable 1:1 adduct, albeit in low yield.

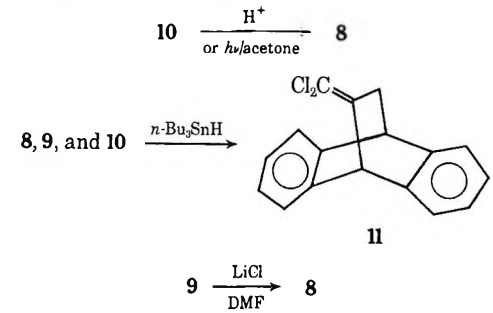


Treatment of **7** with sodium ethoxide in ethanol gave the exocyclic olefin **8** while under similar conditions **6** gave a 3:1 mixture of the exocyclic olefin **9** and the endocyclic olefin **10**, respectively. The olefins **9** and **10** were separated by fractional crystallization from hexane.

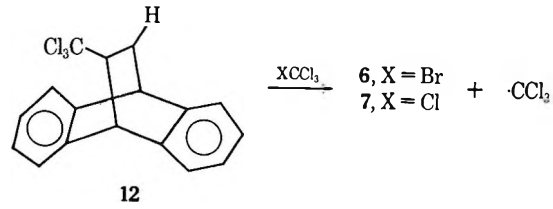


The endocyclic olefin **10** underwent isomerization to the exocyclic olefin **8** under mild conditions [chromatography over silica gel, treatment with anhydrous hydrogen chloride in ether, heating at the melting point (*ca.* 165°), or standing in methanol solvent at room temperature, the latter being accompanied by methanolysis]. Furthermore, an attempt to isomerize **10** to the dibenzotricyclo[3.3.0.0^{2,8}]octadiene system by irradiation in acetone solution (Pyrex filter), conditions known[10] to bring about similar rearrangements of dibenzobicyclo[2.2.2]octatrienes, gave the allylic isomer **8**. With direct irradiation in ether or hexane, **10** disappeared but gave unidentifiable material. Under these conditions, **8** was stable toward irradiation.

Both **9** and **10** were treated with 1 equiv of tributyltin hydride at 80° in benzene to give the exocyclic olefin **11**. Under these conditions, the trichloromethyl olefin **10** reacted about twice as fast as the allylic bromide **9**. Since the allylic chloride **8** was far less reactive toward tributyltin hydride than was **9** or **10**, it was necessary to use higher temperatures (132°) in order for the reaction **8** → **11** to take place at an appreciable rate. The relationship between the allylic halides **8** and **9** was illustrated by the conversion of **9** into **8** with lithium chloride in N,N-dimethylformamide (DMF).



The assignment of the *trans* configurations to **6** and **7** rests on the observed coupling constants (J values) between the C-7 and C-8 protons. For **6**, J_{78} = 4.4 Hz, and for **7** J_{78} = 4.2 Hz, which agree well with the $J_{7,8}$ values reported[11] for analogous *trans*-substituted dibenzobicyclo[2.2.2]octadienes but are not within the range ($J_{cis\text{-}78}$ = 8.8 ± 0.8 Hz) reported[11] for the corresponding *cis* compounds. The assignment of the chemical shifts (see Experimental Section) to the aliphatic protons in **6** and **7** is based on the observed coupling constants and the observation that the chemical shift of the proton α to the trichloromethyl group occurs *ca.* 1 ppm upfield[3] from the proton α to the halogen atom; the position of the latter is based on assignments made on closely related compounds.[11] As in the case of previous free-radical additions to dibenzobicyclo[2.2.2]octatrienes,[8,9] no products of Wagner–Meerwein rearrangement were observed, although such rearrangements were observed in bicyclo[2.2.1]-heptadiene systems.[7,12,13] The stereochemistry of these additions to **5** can be attributed to the steric requirement of the bulky trichloromethyl group which, in the chain-transfer step to the intermediate radical **12**,[3] hinders the approach of the carbon tetrahalide molecule from the *cis* side.



The base-catalyzed elimination of hydrogen halide from **6** gave a 3:1 mixture of **9** (loss of hydrogen chloride) and **10** (loss of hydrogen bromide), respectively, while, under these same conditions, **7** gave only the exocyclic olefin **8**. The assignment of the structures of **8**, **9**, and **10** follows from their mode of synthesis and the patterns of the nmr spectra. In deuteriochloroform **8** gives three absorptions (1 H each) outside the aromatic region: a singlet at τ 4.68 and a pair of doublets at 5.20 and 5.42 (J_{48} = 3.5 Hz). For **9**, the

(10) E. Ciganek, *J. Amer. Chem. Soc.*, **88**, 2882 (1966).

(11) S. J. Cristol, T. W. Russell, J. R. Morig, and D. E. Plorde, *J. Org. Chem.*, **31**, 581 (1966).

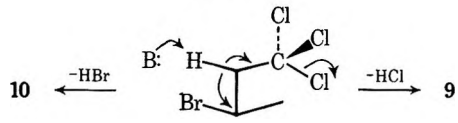
(12) C. K. Alden, J. A. Claisse, and D. I. Davies, *J. Chem. Soc.*, 1540 (1966).

(13) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3727 (1967).

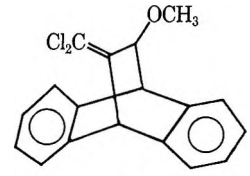
corresponding protons appear at τ 4.73 (singlet), 5.18, and 5.42 (J_{48} = 3.4 Hz). In carbon tetrachloride solvent, the chemical shift for the C-4 and C-8 protons in the allylic chloride **8** appears *ca.* 6–10 Hz upfield from the allylic bromide **9**. This small upfield shift in going from bromides to chlorides is typical of secondary halides.[14] The nmr spectrum of **10** shows a complex pattern of protons from τ 2.5 to 3.2 (9 H) and two doublets (1 H each) located at 4.53 (J_{18} = 2.2 Hz) and 4.85 (J_{48} = 6.4 Hz). The allylic coupling J_{18} is not observable in 7-chlorodibenzobicyclo[2.2.2]octatriene (**3**), but the vicinal coupling (J_{48} = 6.0 Hz) in **3** is on the same order as that observed in **10**.[11] Also, the carbon–carbon double-bond stretching ($\nu_{C=C}$) in **8** and **9** is very strong, typical of the dichloromethylene group,[15] whereas $\nu_{C=C}$ for **10** is relatively weak.

Because of the rigidity of the system in **6**, the loss of hydrogen bromide must be *cis* and coplanar while loss of hydrogen chloride presumably will occur in a *trans* coplanar (antiperiplanar) manner in the E2 elimination[16] (Scheme I). The inherent propensity for loss of hydrogen bromide over loss of hydrogen chloride (*ca.* a factor of 50 in favor of loss of hydrogen bromide[17]) appears to compete with the *trans* elimination of hydrogen chloride.[18–20] However, several factors tend to complicate simple interpretation of the data. First, it is clear from earlier work[21] that the relative reactivity of chlorine as a leaving group from trichloromethyl compounds is not expected to have the same relative reactivity as the typical alkyl chloride. From the product distribution observed in the base-catalyzed loss of hydrogen chloride from 1,1,1,3-tetrachloropropane (about a 2:1 mixture of 3,3,3-trichloropropene and 1,1,3-trichloropropene, respectively),[22] it appears that the ability of chlorine to act as a leaving group in E2 eliminations diminishes when it becomes the member of a trichloromethyl group. Treatment of the 1:1 adducts of bromotrichloromethane and typical acyclic olefins with base most often gives rise only to loss of hydrogen bromide.[1b,22] However, analogous adducts of bicyclic olefins react with base to give only the exocyclic olefins, the result of loss of hydrogen chloride.[1,3–7] Another difficulty in interpreting the product distribution in the reaction of **6** with base is the obvious difference in the stabilities of the resulting olefins **9** and **10** (*vide infra*). The higher the double-bond character in the transition state of these E2 reactions, the correspondingly more favorable will be the formation of the more stable olefin (**9**).

SCHEME I



Attempts to separate **9** and **10** by chromatography over silica gel led to the isomerization of **10** to its allylic isomer **8**. Subsequently, it was shown that **10** isomerizes to **8** under mild conditions (*vide supra*). Compounds resembling **10**, in that they possess a trichloromethyl group bound to a carbon–carbon double bond, are known to undergo analogous rearrangements under acidic[15,23–25] and free-radical conditions.[26] It is clear from thermodynamic studies on 3,3,3-trichloropropenes[26] that the allylic isomers, 1,1,3-trichloropropenes, are far more stable. The high reactivity of **10** toward solvolysis is illustrated by its behavior in absolute methanol. After standing at room temperature for 15 hr, **10** gave 30% recovered starting material, 14% allylic isomer **8**, and 56% methyl ether **13**. The presence of 0.15 *M* potassium hydroxide had no appreciable effect on either the rate or product distribution of this reaction, clearly indicting that in methanol **10** solvolyzes by a unimolecular process (SN1). Under these same conditions, neither the allylic chloride **8** nor the allylic bromide **9** showed any signs of solvolyzing.[27] When treated with silver perchlorate in methanol, **8**, **9**, and **10** all gave the methyl ether **13**.



13

In the methanolysis of **10**, the only observed products are the rearranged chloride **8** (which slowly gives **13**) and the methyl ether **13**. The fact that no unrearranged methyl ether **14** was detected should be noted in view of the previous observations that under kinetic conditions the more unstable allylic isomer often is found to predominate in SN1 solvolysis of allylic halides.[28] However, solvolysis of 3-bromo-2-methylenenorborane[29] under SN1 conditions gives a 2:1 mixture

(14) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p 54.

(15) J. R. Shelton and L. Lee, *J. Org. Chem.*, **23**, 1876 (1958).

(16) D. Banthrope, "Elimination Reactions," Elsevier Publishing Co., New York, N. Y., 1963.

(17) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **90**, 408 (1968).

(18) The implication that the *trans* elimination of HX should be more favored than *cis* elimination of HX in this system may not be true. It was pointed out recently[19,20] that the difference in rate between *cis* and *trans* eliminations may be due primarily to steric effects (*e.g.*, eclipsing effects) rather than to stereoelectronic control. However, since the base presumably approaches **6** in the same manner for *cis* and *trans* elimination, the steric factors are essentially the same no matter which pathway is taken (Scheme I). Unfortunately, nothing can be said about the relative ease of *cis vs. trans* eliminations in this system since the products depend on the mode of elimination adapted.

(19) C. H. Depuy, G. F. Morris, J. S. Smith, and R. J. Smat, *ibid.*, **87**, 2421 (1965).

(20) D. J. McLennan, *Quart. Rev.* (London), **21**, 490 (1967). See, however, E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York N. Y., 1965, pp 483, 484.

(21) S. J. Cristol, N. L. Hause, A. J. Quant, H. W. Miller, K. R. Eilar, and J. S. Meek, *J. Amer. Chem. Soc.*, **74**, 3333 (1952).

(22) W. Reeve and L. W. Fine, *Can. J. Chem.*, **41**, 2231 (1963).

(23) D. G. Kundiger and H. N. Haney, *J. Amer. Chem. Soc.*, **76**, 615 (1954).

(24) C. H. Shuford, Jr., D. L. West, and H. W. Davies, *ibid.*, **76**, 5803 (1954).

(25) F. Boberg, H. Khalaf, and K. Kirchhoff, *Tetrahedron Lett.*, 5181 (1967).

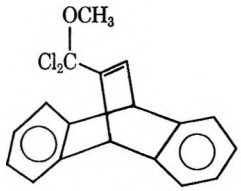
(26) A. N. Nesmeyanov, R. Kh. Freidlina, and V. I. Firstov, *Dokl. Akad. Nauk SSSR*, **78**, 717 (1951).

(27) The kinetics of these and related reactions will be reported at a later date. Preliminary data indicate that the high reactivity of **10** toward SN1 solvolyss compared with that of **8** can be ascribed to the relatively high ground-state energy of **10**. The literature gives little information on the relative reactivities of analogous compounds toward SN1 solvolysis. However, under SN2 (or SN2′) reaction conditions, 1,1,3-trichloropropene appears to be *ca.* six times more reactive than 3,3,3-trichloropropene.[22]

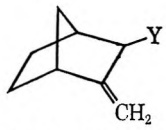
(28) R. H. DeWolfe and W. G. Young in "Chemistry of Alkenes" S. Patai, Ed., Interscience Publishers, New York, N. Y., 1964, p 705.

(29) C. W. Jefford and W. Wajnarowski, *Chem. Commun.*, 129 (1968).

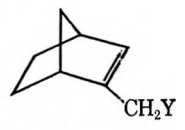
of more stable[30] unrearranged **15** and the less stable endocyclic olefin **16**, respectively. If **14** had formed initially in the reaction of **10** with methanol, it seems likely that **14** might have reacted under the conditions of the reaction to give methyl ketals (acetals) or a methyl ortho ester (or derivatives of these species), but none of these was observed.



14



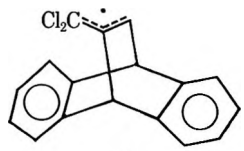
15, Y = OAc, OH



16, Y = OAc, OH

From the data it is obvious that the equilibrium between **8** and **10** lies far toward the side of **8**. Thermodynamic data from the 2-methylbicyclo[2.2.2]octene–2-methylenebicyclo[2.2.2]octane system show the preference for the double bond to be endocyclic in that system.[30] However, the bicyclo[2.2.2]octene system may not be a good model for the dibenzobicyclo[2.2.2]-octatriene system as indicated by the observation that acid-catalyzed dehydration of 7-hydroxy-7-methyldibenzobicyclo[2.2.2]octadiene gave as the only observable product 7-methylenedibenzobicyclo[2.2.2]octadiene.[31] Substitution by the chlorine atom also no doubt affects the position of equilibrium in favor of **8**.[26,32]

The reactions of **8**, **9**, and **10** with tributyltin hydride presumably all lead to the same intermediate allylic radical **17**.[33] The product-determining step occurs in the hydrogen-atom transfer from the tributyltin hydride to **17** which takes place exclusively at one end (C-8) of the allyl system so as to give the more stable product.[34]



17

Experimental Section[35]

8-Bromo-7-trichloromethyldibenzobicyclo[2.2.2]octadiene (6).—A mixture of 3.0 g (14.7 mmol) of dibenzobicyclo[2.2.2]-octatriene (**5**),[8] 8 ml of freshly distilled bromotrichloromethane, and 60 mg of benzoyl peroxide were held at reflux (105°) under 1 atm of nitrogen for 2 hr. An nmr spectrum of the crude reaction mixture showed only **6** present. The excess bromotrichloromethane was removed by rotary evaporation, and the resulting light yellow oil was crystallized from methanol to give 5.5 g (92%) of **6**, mp 134–135°.

The nmr spectrum in carbon tetrachloride shows two doublets (1 H each) at τ 5.27 (J_{17} = 2.0 Hz) and 5.58 (J_{48} = 2.8 Hz), two doublet of doublets (1 H each) at 5.73 (J_{48} = 2.8 Hz, J_{78} = 4.4 Hz) and 6.72 (J_{17} = 2.0 Hz, J_{78} = 4.4 Hz), and a complex multiplet (8 H) for the aromatic protons from 2.6 to 3.1.

Anal. Calcd for $C_{17}H_{12}BrCl_3$: C, 50.72; H, 3.01. Found: C, 50.97; H, 3.04.

8-Chloro-7-trichloromethyldibenzobicyclo[2.2.2]octadiene (7).—A mixture of 3.0 g (14.7 mmol) of **5** and 100 mg of benzoyl peroxide dissolved in 25 ml of carbon tetrachloride was sealed in a Carius tube under nitrogen and heated at 125–130° for 15 hr. The tube was allowed to cool to room temperature and opened; the excess carbon tetrachloride was removed by rotary evaporation. The resulting yellow oil was chromatographed over 150 g of silica gel packed in Skellysolve B. Elution with Skellysolve B gave 1.5 g of an unidentifiable oil whose nmr spectrum (carbon tetrachloride) showed broad absorptions in the aromatic region and in the higher field region of τ 8–9. Elution with 5% benzene in Skellysolve B gave 260 mg (5%) of **7**, recrystallized from ethanol, mp 118–119°.

The nmr spectrum in carbon tetrachloride shows a doublet (1 H) at τ 5.21 (J_{17} = 2.0 Hz) and a doublet of doublets at 6.81 (J_{17} = 2.0 Hz, J_{78} = 4.2 Hz). The doublet (1 H) at 5.60 (J_{48} = 2.9 Hz) and doublet of doublets (1 H) at 5.68 (J_{48} = 2.9 Hz, J_{78} = 4.2 Hz) were overlapping. The aromatic protons (8 H) appeared as a complex multiplet from 2.5 to 3.0.

Anal. Calcd for $C_{17}H_{12}Cl_4$: C, 57.02; H, 3.38. Found: C, 56.93; H, 3.37.

8-Chloro-7-dichloromethylenedibenzobicyclo[2.2.2]octadiene (8).—To a solution of 200 mg (0.56 mmol) of **7** dissolved in 5 ml of ethanol was added 5 ml of 1.3 *M* sodium ethoxide solution. This mixture was held at reflux for 10 min and worked up by pouring it into water and extracting the resulting mixture well with ether. The ether was dried over anhydrous magnesium sulfate and was removed by rotary evaporation. An nmr spectrum of the resulting oil showed only the presence of **8**. The oil was crystallized from methanol to give 150 mg (84%) of **8** ($\nu_{C=C}$ at 1624 cm^{-1}, strong), mp 137–138°.

The nmr spectrum of **8** in deuteriochloroform shows a singlet (1 H) at τ 4.68, a pair of doublets (1 H each, J = 3.5 Hz) at 5.20 and 5.42, and a complex multiplet for the aromatic protons (8 H) from 2.5 to 3.0.

Anal. Calcd for $C_{17}H_{11}Cl_3$: C, 63.48; H, 3.45. Found: C, 63.67; H, 3.47.

Dehydrohalogenation of 6.—To a solution of 8.0 g (19.8 mmol) of **6** dissolved in 10 ml of dioxane was added 40 ml of ethanol in which 0.6 g of sodium metal had been dissolved. The resulting solution was heated at reflux for 1 min, cooled, and poured into water. Work-up with ether gave an oil whose nmr spectrum showed a mixture of 8-bromo-7-dichloromethylenedibenzobicyclo-[2.2.2]octadiene (**9**) (75%) and 7-trichloromethyldibenzobicyclo-[2.2.2]octatriene (**10**) (25%). The oil was dissolved in 30 ml of hexane, and after 2 days 3.3 g of **9** was collected by filtration. The mother liquor yielded 0.90 g of **10**, and successive fractional crystallizations of the mother liquor gave a total of 4.0 g (55%) of **9** ($\nu_{C=C}$ at 1613 and 1622 cm^{-1}, strong), mp 126–127°, and 1.25 g (20%) of **10** ($\nu_{C=C}$ at 1630 cm^{-1}, weak), mp 165–167°.[36]

The nmr spectrum of **9** in deuteriochloroform shows a singlet (1 H) at τ 4.73, two doublets (1 H each, J = 3.4 Hz) at 5.18 and 5.42, and a complex multiplet for the aromatic protons (8 H) from 2.6 to 3.1.

Anal. Calcd for $C_{17}H_{11}BrCl_2$: C, 55.77; H, 3.03. Found: C, 55.48; H, 3.13.

The nmr spectrum of **10** in deuteriochloroform shows two doublets (1 H each) at τ 4.53 (J = 2.2 Hz) and 4.85 (J = 6.4 Hz) and a complex multiplet (9 H) from 2.5 to 3.2.

Anal. Calcd for $C_{17}H_{11}Cl_3$: C, 63.48; H, 3.45. Found: C, 63.30; H, 3.53.

Irradiation of 10.—A solution of 200 mg of **10** in 20 ml of acetone was irradiated with a 450-W Hanovia type L lamp (Pyrex

(30) In this system, equilibria data show that 2-methylenenorbornane is considerably more stable than 2-methylnorbornene: calculated from the data given in Table III by S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Amer. Chem. Soc.*, **89**, 6897 (1967); see also G. Van Binst and Y. Merck, *Tetrahedron Lett.*, 3897 (1967).

(31) V. J. Shiner and J. S. Humphrey, Jr., *J. Amer. Chem. Soc.*, **85**, 2416 (1963).

(32) Reference 28, p 723.

(33) H. G. Kuivila, *Advan. Organometal. Chem.*, **1**, 73 (1964).

(34) J. Mantecón, L. Cortés, E. Payo, and C. Piemonti, *J. Org. Chem.*, **33**, 1235 (1968).

(35) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nuclear magnetic resonance spectra were measured with a Varian A-60A nmr spectrometer with tetramethylsilane (τ 10.00) as the internal standard. J values reported are "observed" ones. Infrared spectra were measured in carbon tetrachloride solution on a Beckman IR-5 infrared spectrometer. The ultraviolet spectrum of **10** was measured in hexane solution, using a Cary 14 uv spectrometer. Elemental analyses were performed by Dr. Franz J. Kasler, University of Maryland.

(36) If the melting point of **10** is taken slowly, the melting point range is large (*viz.* 148–160°). This is due no doubt to the isomerization of **10** to **8**; when **10** was heated neat at 165–170° for 1 hr, the resulting material had mp 125–127°, undepressed on admixture with **8**. The melting point given for **10** was determined by dropping a crystal of **10** on the melting point block which was heated to a temperature near the melting point.

filter) for 2 days. An nmr spectrum of the resulting orange-brown reaction solution showed a mixture of **8** and **10** in the ratio of *ca.* 95:5, respectively, and a small amount of material whose absorptions in the nmr spectrum were very broad high field (τ 8–9) signals. This same contaminant was observed when **8** was irradiated under these same conditions.

Irradiation of **10** for 2 days in ether or hexane (in the presence or absence of benzophenone) gave no readily identifiable material (again, only broad signals were observed in the nmr spectrum). Under these conditions, **8** showed <10% decomposition.

The uv spectrum of **10** in hexane [λ 256 mμ (ϵ 2400), 267 (2550), 272 (3200), and 278 (3570)] agrees well with those published for similarly substituted dibenzobicyclo[2.2.2]octatrienes.[37,38]

7-Dichloromethylenedibenzobicyclo[2.2.2]octadiene (11).—A mixture of 1.5 g (4.1 mmol) of the allylic bromide **9** and 1.2 g (4.1 mmol) of tributyltin hydride[39] was heated at reflux in 20 ml of dry benzene under nitrogen for 20 hr (an nmr spectrum of the reaction mixture after 3 hr showed that the reaction was about 50% complete). The benzene was removed by rotary evaporation, and the resulting oil was chromatographed over 100 g of silica gel packed in Skellysolve B. Tributyltin bromide was eluted with Skellysolve B, and elution with 5% benzene in Skellysolve B gave 1.0 g (85%) of **11** ($\nu_{C=C}$ at 1625 cm^{-1}, strong), mp 123–124° (from methanol).

The nmr spectrum in carbon tetrachloride shows a singlet (1 H) at τ 4.76, a triplet (1 H, J_{48} = 2.9 Hz) at 5.67, a doublet (1 H) at 7.55, and a complex multiplet (8 H) from 2.6 to 3.1.

Anal. Calcd for $C_{17}H_{12}Cl_2$: C, 71.10; H, 4.21. Found: C, 71.31; H, 4.28.

Under these same conditions, **10** had a half-life of *ca.* 1.5 hr and gave **11** as the only observable (nmr analysis) product (isolated in 85% yield). The allylic chloride **8** under these conditions showed <5% reaction after 10 hr. Use of refluxing chlorobenzene (132°) as the solvent (0.30 g of **8**, 0.29 g of tributyltin hydride, and 10 ml of chlorobenzene under nitrogen) gave complete conversion of **8** into **11** after 1 day.

Reaction of 9 with Lithium Chloride in N,N-Dimethylformamide (DMF).—A solution of 2.0 g (5.5 mmol) of **9** and 5.0 g of anhydrous lithium chloride dissolved in 25 ml of dry DMF was held at 90–95° for 1 day. The mixture was poured into water and extracted well with ether. The ether was dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation, and the resulting oil was crystallized from ethanol to give 1.7 g (96%) of **8**, mp and mmp 137–138°.

Isomerization of 10 to 8.—An attempt to separate a mixture of **9** and **10** (3:1, respectively) by passing the mixture over silica gel gave a mixture of **9** and **8** (3:1, respectively.). The nmr and ir spectra of this resulting mixture were identical with the ir and nmr spectra of a synthetic mixture of **9** and **8** (3:1, respectively). When pure **10** was eluted through a column of silica gel (20:1, silica gel/**10** by weight) with 5% benzene in Shellysolve B, a quantitative conversion into **8** was realized.

Treatment of 200 mg of **10** in 20 ml of 2% anhydrous hydrogen chloride in ether solution at room temperature for 6 hr gave complete conversion into the allylic isomer **8**.

Methanolysis of 10.—A solution of 100 mg of **10** in 20 ml of methanol stood at room temperature for 15 hr. The methanol was removed at 0° under reduced pressure, and an nmr spectrum of the resulting oil showed a mixture of 30% **10**, 14% allylic isomer **8**, and 56% methyl ether **13**. Under these same conditions in 0.15 *M* potassium hydroxide in methanol, **10** gave 28% **10**, 12% **8**, and 60% **13** (nmr analysis). Under identical conditions, in the presence or absence of base, the allylic halides **8** and **9** gave no reaction.

Heating 200 mg (0.62 mmol) of **10** in methanol at reflux for 1 hr gave *ca.* 4:1 mixture of **13**/**8**, respectively. From this mixture was crystallized 110 mg (56%) of 8-methoxy-7-dichloromethylenedibenzobicyclo[2.2.2]octadiene (**13**) ($\nu_{C=C}$ at 1630 cm^{-1}, strong), mp 137–139°.

A mixture of 200 mg (0.62 mmol) of the allylic chloride **8** and 200 mg of anhydrous silver perchlorate was heated at reflux in 15 ml of methanol for 1 hr. Work-up gave 180 mg (91%) of **13**. Under these same conditions, **9** and **10** gave essentially identical results.

The nmr spectrum of **13** in deuteriochloroform shows two singlets at τ 4.81 (1 H) and 6.67 (3 H), two doublets (1 H each, J = 3.6 Hz) at 5.40 and 5.96, and a complex multiplet for the aromatic protons (8 H) from 2.6 to 3.2.

Anal. Calcd for $C_{18}H_{14}Cl_2O$: C, 68.15; H, 4.45. Found: C, 68.17; H, 4.48.

Registry No.—Bromotrichloromethane, 75-62-7; carbon tetrachloride, 56-23-5; **5**, 2734-13-6; **6**, 17519-19-6; **7**, 17497-39-1; **8**, 17497-43-7; **9**, 17497-40-4; **10**, 17497-41-5; **11**, 17497-42-6; **13**, 17519-20-9.

Acknowledgment.—Financial support from the donors of the Petroleum Research Fund of the American Chemical Society (Grant No. 1050-G1) is gratefully acknowledged.

(37) W. E. Noland and R. Libers, *Tetrahedron Suppl. 1*, **19**, 23 (1963).

(38) M. Yamakawa and T. Kubota, *Shionogi Kenkyusho Nempo*, **15**, 109 (1965); *Chem. Abstr.*, **64**, 12053*b* (1966).

(39) H. G. Kuivila and O. F. Beumel, Jr., *J. Amer. Chem. Soc.*, **83**, 1246 (1961).

Chlorination Studies of Unsaturated Materials in Nonpolar Media. VIII. Ionic Chlorination of Some Simple Allenes[1]

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Chlorinations of tetramethylallene (**3**), 1,1-dimethylallene (**8**), and allene have been carried out in nonpolar media in the presence of oxgen as a radical inhibitor. The only chlorination product of **3** at 25° in $C_2F_3Cl_3$ solution is 3-chloro-2,4-dimethyl-1,3-pentadiene (**4**). However, the hydrogen chloride coproduct leads to extensive isomerization of **3** to form 2,4-dimethyl-1,3-pentadiene (**5**) and subsequent telomerization of **5** in large part to 1,3,3,5,5-pentamethyl-4-isopropenylcyclohexene (**6**). Dimer **6** can also be prepared from **5** by boron trifluoride catalysis. Similar chlorination of **8** gave 2-chloro-3-methyl-1,3-butadiene (**9**), 2,3-dichloro-3-methyl-1-butene (**10**), and 1,2-dichloro-3-methyl-2-butene (**11**) in a ratio of *ca.* 85:2:13, the exact ratio being slightly dependent on the nonpolar solvent used. Chlorination of neat allene at −30° gave, in addition to the expected 2,3-dichloropropene (**1**) and propargyl chloride (**2**), a large number of other products. Two of these have been identified as compounds containing two allene units, namely, 2-chloro-1-hexen-5-yne (**15**) and 2,5-dichloro-1,5-hexadiene (**16**). Possible ionic mechanisms are discussed for formation of these products. Relative rate measurements show that **3** and **8** are as reactive as or even more so than the correspondingly substituted olefins, tetramethylethylene and isobutylene. Chlorination of **8** under nitrogen leads to significant initiation of radical reactions.

In spite of recent interest in the chemistry of allenes[2] few reports have appeared concerning chlorination of simple alkylated allenes in nonreactive solvents. We herein report studies of chlorination of allene, 1,1-dimethylallene, and tetramethylallene in nonpolar solvents in the presence of oxygen to inhibit potential radical reactions.[3a] While not so extensive as our previous studies of olefin chlorination,[3] they reveal some significant synthetic aspects of allene chlorination; namely, the high tendency for allenes with chain branching at a double bond to give substitution products (chloro-1,3-dienes) and the tendency for allene itself to undergo condensation reactions. Thus, in apparent contrast to bromination,[2a] uncatalyzed chlorination of simple allenes does not seem to be a particularly efficient route to 2,3-dichloropropenes.

Peer[4] reported that treatment of allene itself in methylene chloride or tetrachloroethane solution at −30° with chlorine in the dark under nitrogen gave 2,3-dichloropropene (**1**) and propargyl chloride (**2**) in yields of 20–25% and 30–35%, respectively; it was noted that reaction did not occur in carbon tetrachloride solution in the absence of light. An electrophilic attack of chlorine was proposed to give an intermediate "propadiene–Cl^+ complex" which stabilized itself by chloride ion addition to give **1** or proton loss to give **2**.

$$CH_2{=}C{=}CH_2 + Cl_2 \xrightarrow[-30°]{CH_2Cl_2} \underset{\displaystyle Cl}{CH_2{=}CCH_2Cl} + \underset{\displaystyle 2}{HC{\equiv}CCH_2Cl}$$

1

More recently, allene chlorination at *ca.* −60° in the presence of boron trifluoride catalyst was reported[5] also to give similar amounts of **1** (30%) and **2** (45%) along with minor amounts of 1,2,2,3-tetrachloropropane, 1,2,2-trichloropropane, 1,2,3-trichloropropene, and 1,3-dichloropropene. These by-products which all retained the C_3 skeleton were postulated to result from chlorination–hydrochlorination–dehydrochlorination sequences subsequent to the primary reaction. In particular, no evidence was obtained for cyclodimerization products (cyclobutanes) such as have been observed from hydrobromination and hydrochlorination of allene.[6] Formation of dichloride **1** did occur in much better yield (60–73%) when chlorination was conducted at 140° in a $NaAlCl_4$–$KAlCl_4$ eutectic melt.[5] Dichloride **1** has been produced in good yield by vapor phase chlorination at 420° with a N_2–allene–Cl_2 ratio of 15:2:1.[7]

Treatment of tetramethylallene (**3**) in 1,1,2-trichlorotrifluoroethane solution with a limited amount of chlorine under an oxygen atomosphere at 25° gives a single chlorine-containing product in essentially quantitative yield based on chlorine as determined by glpc analysis with an internal standard. Spectral characteristics and Diels–Alder condensation with tetracyanoethylene indicate its structure to be 3-chloro-2,4-dimethyl-1,3-pentadiene (**4**); the same compound has been prepared from thermal rearrangement of 1,1-dichloro-2,2,3,3-tetramethylcyclopropane.[8] However, more than 1 mol of allene **3** is consumed/mol of chlorine introduced. Considerable isomerization to 2,4-dimethyl-1,3-pentadiene (**5**) occurs, and a fraction of this diene is telomerized. A single predominant dimer was detected in all chlorination runs although higher telomers were probably present. These isomerization and dimerization side reactions can be significantly suppressed by the presence of solid sodium carbonate during chlorination; on the other hand, they can be effected by treatment of allene **3** with hydrogen chloride alone in the absence of chlorine. Therefore it seems likely that the hydrogen chloride coproduct from formation of chlorodiene **4** is responsible for the complications observed. (See Scheme I.) Some typical runs are summarized in Table I.

(1) For previous paper, see M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1966).

(2) For recent reviews, see (a) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967); (b) M. V. Mavrov and V. F. Kucheroy, *Russ. Chem. Rev.* (English Transl.), **36**, 233 (1967); (c) K. Griesbaum, *Angew. Chem. Intern. Ed. Engl.*, **5**, 933 (1966).

(3) (a) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 2161, 2172 (1965); (b) M. L. Poutsma, *ibid.*, **87**, 4285 (1965); (c) M. L. Poutsma, *Science*, **157**, 3792 (1967).

(4) H. G. Peer, *Rec. Trav. Chim.*, **81**, 113 (1962). See also H. G. Peer, German Patent 1,132,121; *Chem. Abstr.*, **58**, 3313 (1963).

(5) W. H. Mueller, P. E. Butler, and K. Griesbaum, *J. Org. Chem.*, **32**, 2651 (1967).

(6) K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Amer. Chem. Soc.*, **87**, 3151 (1965).

(7) J. Van Leeuwen, British Patent 908,219; *Chem. Abstr.*, **58**, 6693 (1963).

(8) (a) L. Skattebøl, private communication; (b) G. C. Robinson, *J. Org. Chem.*, **33**, 607 (1968).

SCHEME I

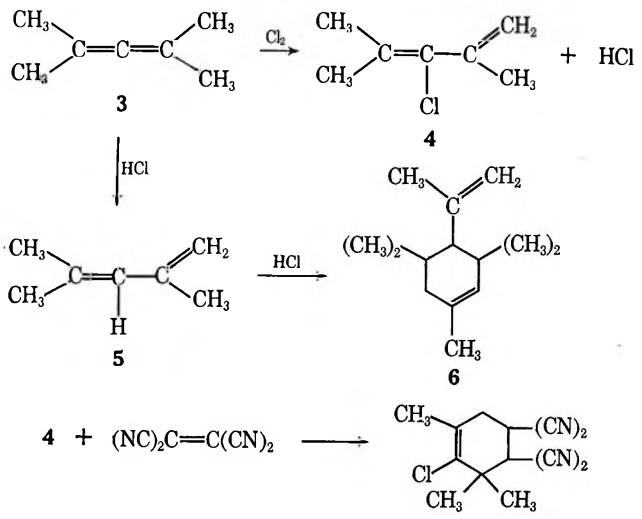


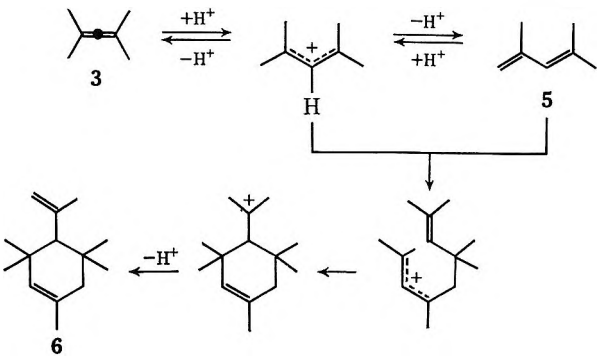
TABLE I

CHLORINATION OF TETRAMETHYLALLENE UNDER OXYGEN AT 25.0°

Reactants, mmol				Products, mmol	
Allene	$C_2F_3Cl_3$	Cl_2	Conditions	4	6
36.4	41.7	1.4	*a, b*	1.35	0.75
36.4	41.7	1.4	*c, d*	1.39	0.06
7.3	75.1	1.2	*a, e*	1.24	0.46
7.3	75.1	1.4	*f, g*	1.45	2.13

[a] Chlorine introduced in an oxygen stream; product yields determined by glpc analysis with an internal standard added after reaction. [b] Final C-7 fraction is 16% diene **5**. [c] Solid sodium carbonate added. [d] Final C-7 fraction is 7% diene **5**. [e] Final C-7 fraction is 30% diene **5**. [f] Oxygen sweep rate slower than other runs. [g] No allene remaining after reaction; only ~5% of original C-7 fraction present as diene **5**.

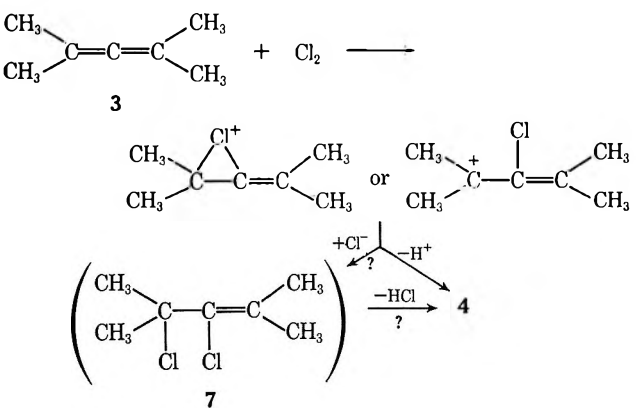
A number of reports of dimers of diene **5** have appeared[9] without definitive structural assignment. Several of these prepared by treatment of the diene or diene precursors with acidic catalysts[9a,b,d,f,h,i,j] may well be the same compound. We have prepared a product in >40% yield, identical with the by-product formed during chlorination of allene **3**, by treatment of diene **5** with boron trifluoride etherate. Hydrogenation indicates two dissimiliar double bonds (and hence one ring based on $C_{14}H_{24}$) while ir analysis indicates that at least one of them is of the $R_2C{=}CH_2$ type. The nmr spectrum shows three distinct olefinic protons in rather narrow multiplets, nine protons in the allylic hydrogen region six of which seem to be in only slightly split $-CH_3$ groups, and twelve protons ascribable to saturated unsplit $-CH_3$ groups. These data coupled with a reasonable mode of acid-catalyzed formation of a cyclic dimer support the assignment 1,3,3,5,5-pentamethyl-4-isopropenylcyclohexene (**6**).[10] This assignment is also consistent with earlier reports that the compound absorbed 1.86 mol of iodine[9d] and gave on ozonization formic acid and a nonvolatile acid whose silver salt contained 31.16% silver[9i] (calculated 30.9% if **6** gives the expected diketo acid by ozonization of both double bonds). This structure was suggested



earlier by Merezhkovskii[9c] for a dimer from thermal polymerization of diene **5**. In our hands simple thermal treatment (Diels–Alder conditions) in the presence of a radical inhibitor (hydroquinone) and an acid acceptor (sodium carbonate) gave at least three significant dimers, of which the major seemed to be **6**.

In competition experiments with added trimethylethylene under oxygen,[3b] allene **3** reacted at a rate comparable with that of its similarly substituted olefin, tetramethylethylene ($k_3/k_{\text{trimethylethylene}} \simeq 60$).

The production of chlorodiene **4** proceeded smoothly under an oxygen atmosphere under conditions where added cyclohexane was not attacked[3a] and hence is ascribed to an ionic rather than radical pathway.[3b] The most probable mechanism involves direct loss of a proton from an intermediate chlorocarbonium ion in analogy to the behavior of branched olefins.[3b] Although the possible intermediacy of 3,4-dichloro-2,4-dimethyl-2-pentene (**7**) with rapid thermal dehydrochlorination cannot be completely ruled out, no evidence for **7** was ever obtained from a chlorination run. The intermediacy of **7** seems unlikely in light of the considerable thermal stability of the corresponding



analog with a terminal methylene rather than isopropylidene group (see **10** below); analog **10** was

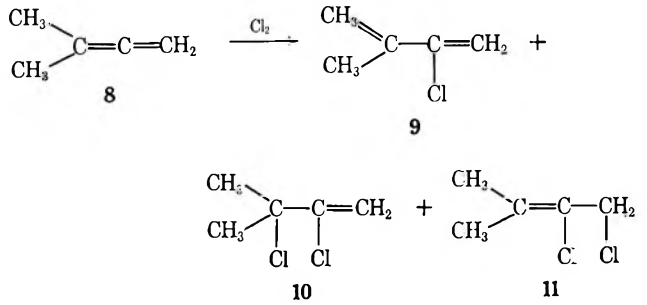
(9) (a) V. Grignard, *Ann. Chim. Phys.*, **24**, 477 (1901); (b) T. von Fellenberg, *Ber.*, **37**, 3579 (1904); (c) B. K. Merezhkovskii, *J. Russ. Phys. Chem. Soc.*, **45**, 1940; *Chem. Abstr.*, **8**, 1420 (1914); (d) G. S. Whitby and W. Gallay, *Can. J. Res.*, **6**, 280 (1932); (e) Ya. M. Slobodin, *J. Gen. Chem. USSR*, **6**, 1806 (1936); *Chem. Abstr.*, **31**, 4264 (1937); (f) R. Ya. Levina, A. M. Panyushkina, N. A. Shcheglova, N. A. Smirnova, K. D. Shcherbakova, and N. I. Shor, *J. Gen. Chem. USSR*, **11**, 411 (1941); *Chem. Abstr.*, **35**, 5862 (1941); (g) R. Jacquemain, *Compt. Rend.*, **215**, 200 (1942); (h) R. Ya. Levina, N. P. Shusherina, N. I. Volchinskaya, and M. Yu. Lure, *Zh. Obshch. Khim.*, **23**, 400 (1953); *Chem. Abstr.*, **48**, 3885 (1954); (i) M. A. Chel'tsova, E. A. Chernyshev, and A. D. Petrov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* (English Transl.), 459 (1955); *Chem. Abstr.*, **50**, 6288 (1956); (j) R. Ia. Levina, Iu. S. Shabarov, and V. K. Daukshas, *J. Gen. Chem. USSR* (English Transl.), **28**, 2089 (1958).

(10) A referee has pointed out that our data do not totally eliminate 1,3,3,4,4-pentamethyl-5-isopropenylcyclohexene as a possible structure. However, its formation would require an unlikely addition of tetramethylallyl cation at the more crowded terminus of **5** to give the less stable product ion rather than that proposed.

distilled at 120°, whereas the chlorination of **3** occurred at 25°.

Under a nitrogen atomosphere, compound **4** remained the only detectable chlorination product, and added cyclohexane was not attacked to a significant extent; hence the reaction remains ionic, and potential spontaneous initiation of radical chains[3a] cannot compete effectively for this tetraalkylallene.

Chlorination of 1,1-dimethylallene (**8**) under oxygen gives three products which account for all the chlorine introduced. These were shown by comparison with authentic materials (see Experimental Section) to be 2-chloro-3-methyl-1,3-butadiene (**9**), 2,3-dichloro-3-methyl-1-butene (**10**), and 1,2-dichloro-3-methyl-2-butene (**11**) in a ratio of ~85:2:13; exact values depended slightly on the solvent as shown in Table II.



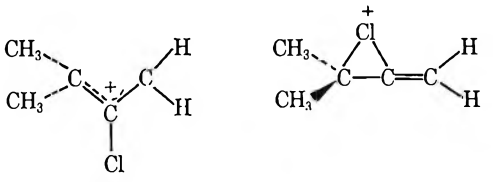
In this case the dichloride **10** showed no tendency to dehydrochlorinate, and hence diene **9** is definitely a primary chlorination product. In contrast to tetramethylallene, allene **8** did not isomerize to isoprene under the reaction conditions. In competitive experiments with trimethylethylene,[3b] allene **8** reacted at a rate some 20 times faster than that of its similarly substituted olefinic analog, isobutylene ($k_{\text{trimethylethylene}}/k_{\mathbf{8}} \simeq 10$).

TABLE II
CHLORINATION OF 1,1-DIMETHYLALLENE UNDER OXYGEN AT 25.0°

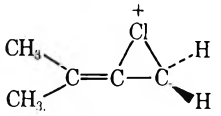
Reactants, mmol			Products,	Product composition, %[a]		
Allene	Solvent	Cl_2	mmol[a]	**9**	**10**	**11**
80.1	None	2.0	1.55	82.0	2.8	15.2
20.0	$C_2F_3Cl_3$, 66.8	1.2	1.25	83.1	1.8	15.2
10.0	$C_2F_3Cl_3$, 75.1	1.3	1.25	83.6	1.3	15.1
50.1	*c*-C_6H_{12}, 46.3	1.65	1.65[b]	82.0	2.2	15.6
10.0	*c*-C_6H_{12}, 83.3	1.4	1.45[b]	88.6	1.9	9.5
7.5	*c*-C_6H_{12}, 85.6	1.5	1.45[b]	87.6	2.3	10.0
3.0	*c*-C_6H_{12}, 89.8	0.5		90.6	1.5	7.9

[a] Determined by glpc analysis with an internal standard added after reaction. [b] <0.005 mmol of cyclohexyl chloride.

Again the failure of added cyclohexane to be chlorinated demonstrates an ionic pathway. However, the details of the mechanism cannot be specified because, whereas products **9**–**11** could all arise from a single 1,1-dimethyl-2-chloroallyl cation (**12**) formed by electrophilic attack at the central carbon and rotation of the carbon skeleton to attain a planar resonance-stabilized structure, one can equally well imagine two separate bridged chloronium ions (**13** and **14**), which maintain the unique perpendicular allenic geometry, with **13** being the precursor of products **9** and **10** and **14** being the precursor of **11**.



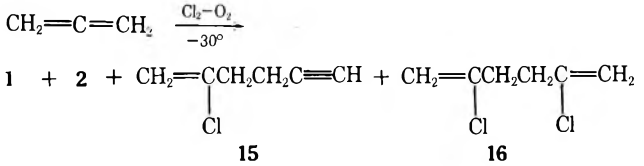
12 **13**



14

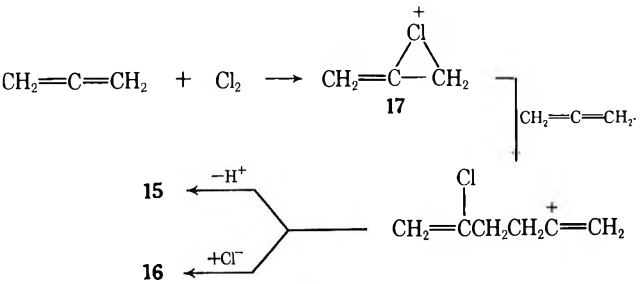
Replacement of oxygen with nitrogen does lead to radical-initiation reactions[3a] for allene **8**. Added cyclohexane is chlorinated to a significant extent, and the addition products of **8** (**10** and **11**) become more important. However, the radical pathway has not been explored in detail and will not be considered further here.

Neat refluxing allene (~−30°) was treated with 0.5 equiv of chlorine under oxygen. Glpc analysis revealed a multitude of products, four of which have been isolated. Dichloride **1** (23%) and propargyl chloride (**2**, 20%) were produced as expected. A third product, isolated in 4.3% yield, was found to have the empirical formula C_6H_7Cl. Since exhaustive catalytic hydrogenation gave *n*-hexane, a linear chain is indicated. Spectral properties accord with the structure of 2-chloro-1-hexen-5-yne (**15**). The final isolated product (1.5%) was shown in similar fashion to be 2,5-dichloro-1,-



15 **16**

5-hexadiene (**16**). A reasonable pathway for formation of these dimeric products would involve addition of an (allene–Cl)$^+$ species (**17**) (whether bridged or open is again a question) to another allene molecule. Such



a process is reminiscent of the initial steps postulated for the cyclodimerization of allene and hydrogen bromide,[6] although in this latter case the initial proton addition must be terminal rather than central. Such a dichotomy is not unreasonable if the species **17** is a bridged ion and the (allene–H)$^+$ complex is not. The chlorination in our hands gave even higher molecular weight products not explored further; however they suggest that products **15** and **16** are representative of a family of products containing more than one allene unit and that condensation reactions play a significant

role in polar chlorination of neat allene. Although our conditions were not identical with either of those previously reported,[4,5] these condensation reactions may explain the only moderate amounts of **1** and **2** obtained, particularly by Peer.[4]

The occurrence of what seemed to be slight inhibition periods even under oxygen caused us to consider the possibility of radical reactions.[3] Thus, product **15** could be formulated as the result of terminal addition of propargyl radical to allene followed by chain transfer with chlorine molecule. However, it seems highly likely that the propargyl radical would be much more effectively trapped by either chlorine or oxygen. An alternative possibility is that the hydrogen chloride produced along with products such as **2** and **15** serves as a catalyst for the polar chlorination.

Experimental Section

Infrared spectra were determined as 10% carbon disulfide and carbon tetrachloride solutions on a Beckman IR-10 instrument. Nmr spectra were determined as 20% carbon tetrachloride solutions on a Varian A-60A instrument, and the results are expressed in parts per million downfield from internal tetramethylsilane. Boiling points are uncorrected.

Materials.—Tetramethylallene (Columbia Organic Chemicals) was distilled through an all-glass helix-packed column and showed single glpc and nmr (δ 1.63 ppm) bands; distillation through a platinum spinning-band column led to extensive isomerization apparently to diene **5**. 1,1-Dimethylallene was prepared by reduction of 3-chloro-3-methyl-1-butyne with a zinc–copper couple in ethanol by the general procedure of Hennion and Sheehan[11] and purified by repeated distillation, bp 41°. Allene was purchased from the Matheson Co., minimum purity 99%.

Chlorination of Tetramethylallene (3). Product Isolation.—To 50 ml (36.3 g) of tetramethylallene at 0° was added 0.14 mol of gaseous chlorine (measured as a liquid at −78°) in a flowing nitrogen stream over a 30-min period. Glpc analysis revealed two major products. Distillation through an 18-in. spinning-band column gave, after removal of some unreacted starting material, the following fractions: (1) 1.9 g, bp 32–54° (60 mm); (2) 11.0 g, bp 53–55° (50 mm), n^{23}D 1.4608; (3) 2.0 g, bp 32° (13 mm)–52° (5 mm); and (4) 10.0 g, bp 55–61° (3 mm), n^{23}D 1.4766; 5.0 g of pot residue remained.

Glpc analysis of fraction 2 showed it to be the more volatile product in good purity. The ir spectrum agreed with that of a sample of 3-chloro-2,4-dimethyl-1,3-pentadiene (**4**) prepared by Skattebøl[8a] [lit.[8b] bp 58° (65 mm)]. The nmr and uv spectra were consistent with those reported.[8b] A mixture of 0.50 g of fraction 2 and 0.45 g of sublimed tetracyanoethylene in 10 ml of benzene was heated at reflux for 1 hr. The benzene was evaporated and the semisolid residue was suspended in pentane and recovered by filtration to give 0.90 g of crude product, mp 103–109°. Recrystallization from benzene–hexane gave 0.65 g, mp 113–114°. The nmr spectrum showed the expected singlets for 2-chloro-4,4,5,5-tetracyano-1,3,3-trimethylcyclohexene at 3.20, 2.00, and 1.75 ppm in a ratio of 2:3:6.

Anal. Calcd for $C_{13}H_{11}ClN_4$: C, 60.35; H, 4.29; N, 21.66; Cl, 13.71. Found: C, 60.45; H, 4.21; N, 21.70; Cl, 13.54.

Glpc analysis of fraction (4) showed ~10% each of two impurities of similar volatility to the major component. Preparative glpc gave a "best" sample still containing 5–10% of the more volatile impurity. Spectra of this sample showed it to correspond to diene dimer **6** described below.

Chlorination of Tetramethylallene (3). Quantitative Runs.—The general apparatus has been described previously.[3a] In all cases the reaction mixture was purged with the carrier gas used for 15 min after chlorine introduction ceased to remove hydrogen chloride. Glpc analyses were then carried out on a Microtek 2500R instrument equipped with a flame ionization detector and 2-m Perkin-Elmer "O" columns (silicone grease) operated at a helium flow rate of *ca.* 200 ml/min with the following temperature program: isothermal operation for 7 min at 52°, linear temperature increase to 120° in 8 min, and isothermal operation at 120° for another 25 min. In a typical run a major band appeared at 14 min, four minor bands appeared at 16–18 min (<10% of the 14-min band), and a second major band appeared at 32 min flanked by at least two minor bands. The major products were assigned structures **4** and **6** as shown above. Yields were determined by addition of toluene as an internal standard after chlorination was complete. Areas were converted into molar quantities by use of calibration factors determined from mixtures of authentic materials. The amount of **3** remaining could be semiquantitatively estimated by comparison of glpc spectra of aliquots of constant size before and after chlorination. In a typical case considerably more than 1 mol of **3** disappeared for each mole of chlorine introduced, and a new peak appeared which had the same retention time as rearranged diene **5**. The minor peaks at 16–18 min were simulated by chlorination of diene **5** alone. If solid sodium carbonate was added to the reaction flask, the loss of **3** was much closer to stoichiometric, the formation of diene was reduced, the formation of dimer was practically eliminated, and the peaks at 16–18 min disappeared. Treatment of **3** with gaseous hydrogen chloride instead of chlorine gave extensive conversion into diene **5** and dimer **6**. Inclusion of cyclohexane in the medium under either oxygen or nitrogen did not lead to production of significant quantities of chlorocyclohexane. Some individual runs are summarized in Table I.

To compare the relative rates of ionic chlorination, competitive chlorinations of **3** and trimethylethylene were carried out under oxygen as described previously;[3b] sodium carbonate was added to suppress isomerization of **3**. The amount of chlorodiene **4** produced was compared to the amount of 3-chloro-2-methyl-1-butene formed with the assumption that trimethylethylene produces 85% of the latter.[3b] From three runs which covered a sixfold variation in ratio of hydrocarbons the allene was found to be 58 ± 7 times more reactive than the olefin; to the extent that allene **3** is isomerized to diene **5** during the run, this is a minimum value.

Condensations of 2,4-Dimethyl-1,3-pentadiene (5).—To 25 g of 2,4-dimethyl-1,3-pentadiene (Aldrich) was added three small drops of boron trifluoride etherate. The mixture became very warm and required external cooling to prevent boiling. A second similar addition of catalyst gave no further heating. After 15 min, the mixture was partitioned between carbon tetrachloride and water, and the organic layer was dried and evaporated to give 25 g of residue. Glpc analysis showed a major band in the region expected for dimers along with a significant minor band and several very small bands. Distillation through an 18-in. spinning-band column gave the following fractions: (1) 2.7 g, bp 96–99° (16 mm), 93.5% the major product by glpc; (2) 5.7 g, bp 99° (16 mm), 96.5% the major product; (3) 2.3 g, bp 99° (16 mm), n^{24}D 1.4785, >98% pure; (4) 4.0 g, bp 57–120° (1 mm); and (5) 6.0 g of residue which did not distil at 200° (1 mm). The ir spectrum of fraction 3 showed bands at 1645 and 1635 cm^{-1} (m) (C=C), 1405 and 1392 cm^{-1} (s) [$(CH_3)_2C<$], and 895 cm^{-1} (s) (>C=CH_2). The nmr spectrum showed three multiplets at 5.03, 4.92, and 4.70 ppm of equal size, complex absorption from 1.90–1.60 ppm consisting of two rather narrow multiplets superimposed on a broader background, and three singlets at 1.03, 0.98, and 0.93 ppm in the ratio ~1:1:2; the relative areas of the three regions were 2.9:9.4:11.7. Hydrogenation of fraction 3 in acetic acid over 5% Pd–C catalyst at atmospheric pressure consumed 1.88 mol of hydrogen/mol of starting material, the first mole being consumed more rapidly than the second. The most reasonable structure based on spectral data and mode of formation is 1,3,3,5,5-pentamethyl-4-isopropenylcyclohexene (**6**).[10]

The same peak was observed in the glpc spectrum when a solution of diene (20 g) in 1,1,2-trichlorotrifluoroethane (50 ml) was treated with anhydrous hydrogen chloride. Work-up in the usual fashion after washing with sodium bicarbonate solution gave on distillation 1.0 g of product, bp 68° (3 mm), with an nmr spectrum the same as that observed above.

Diene **5** (25 g) was heated in an autoclave at 195° for 30 hr in the presence of solid sodium carbonate and hydroquinone; the maximum autogeneous pressure was 70 psi. Distillation gave 14.5 g of recovered diene and 1.8 g of liquid, bp 78–85° (5 mm), the last portions of which tended to crystallize in the distillation head. The nmr spectrum was more complex than that observed above and suggested additional types of olefinic protons and saturated methyl groups. The glpc spectrum showed

(11) G. F. Hennion and J. J. Sheehan, *J. Amer. Chem. Soc.*, **71**, 1964 (1949).

three major components in the ratio of ~60:10:30, the first of which had the same retention time as that of 6, plus several minor components.

Chlorination of 1,1-Dimethylallene (8). Product Isolation.—1,1-Dimethylallene (6.54 g, 96 mmol) was treated at 0° with gaseous chlorine (40 mmol) introduced in a flowing oxygen stream over a 15-min period. Glpc analysis showed three products in a ratio of ~68:4:28 in order of increasing retention time. Distillation gave two major fractions: (1) 0.8 g, bp 46° (140 mm), n^{23}D 1.4630; and (2) 0.5 g, bp 50–60° (40 mm). Fraction 1 was mainly the most volatile product contaminated by a small amount of starting allene determined by glpc analysis, and its ir spectrum agreed with that of authentic 2-chloro-3-methyl-1,3-butadiene (9). Fraction 2 contained both of the less volatile materials by glpc analysis and was separated into its components by preparative glpc. These were identified by spectral comparison to authentic materials as 2,3-dichloro-3-methyl-1-butene (10) and 1,2-dichloro-3-methyl-2-butene (11). The poor recovery of the chlorodiene apparently results from its polymerization during distillation as evidenced by a considerable pot residue which also contained residual higher boiling dichloroolefin 11 by glpc analysis.

Chlorination of 1,1-Dimethylallene (8). Quantitative Runs.—The chlorination procedure and analysis was identical with that used for tetramethylallene above. No evidence was obtained for greater than stoichiometric losses of allene, and no isoprene was ever detected by glpc analysis. Deliberate chlorination of isoprene gave a set of glpc peaks which were never observed during chlorination of 8. Typical runs are summarized in Table II, p 4082.

The relative reaction rate was compared with that of trimethylethylene as described above. In four runs which covered a twofold variation in ratio of starting hydrocarbons, trimethylethylene was found to be 10 ± 1 times more reactive than allene 8.

Authentic Products from 1,1-Dimethylallene Chlorination.—Dehydration of 2-methyl-3-butyn-2-ol (Farchan Research Laboratories) with *p*-toluenesulfonic acid by the method of Carothers and Coffman[12] gave 2-methyl-1-buten-3-yne. Hydrochlorination of the latter in the presence of concentrated hydrochloric acid, ammonium chloride, and cuprous chloride[12] gave 2-chloro-3-methyl-1,3-butadiene (9), bp 42° (120 mm), n^{23}D 1.4672 [lit.[12] bp 41° (113 mm), n^{20}D 1.4689]. The nmr spectrum showed three multiplets at 5.57, 5.38, and 5.13 ppm (~1:2:1) and a slightly split band at 1.97 ppm in the ratio 4.0:3.0. This material polymerized slowly on standing, and the samples required for glpc calibration were distilled bulb to bulb at room temperature (20 mm) immediatedly before use. Chlorination of 1-chloro-3-methyl-2-butene (Eastman Organic Chemicals) in refluxing carbon tetrachloride with sulfuryl chloride by the method of Ultée[13] gave 1,2,3-trichloro-3-methylbutane, bp 76–78° (22 mm), n^{23}D 1.4746 [lit.[13] bp 76.5–77° (20 mm), n^{20}D 1.4748]. This trichloride was dehydrochlorinated over solid potassium hydroxide,[13] and fractional distillation gave samples (>95% pure) of the two dichloro olefins in ~15% yield each. The nmr spectrum of 2,3-dichloro-3-methyl-1-butene (10), bp 120–123°, $n^{23.5}$D 1.4560 [lit.[13] bp 50° (60 mm), n^{20}D 1.4618] showed an AB pattern with the doublets centered at 5.60 and 5.28 ppm (J = 1.9 cps) and a singlet at 1.78 ppm in the ratio 2.0:6.0. The nmr spectrum of 1,2-dichloro-3-methyl-2-butene (11), bp 154–156°, $n^{23.5}$D 1.4808 [lit.[13] bp 58.5–60° (15 mm), n^{20}D 1.4812], showed a singlet at 4.23 ppm and a singlet at 1.88 ppm in the ratio 2.0:6.0.

Chlorination of Allene.—Into 120 ml (~2 mol) of liquid allene held under a Dry Ice filled condenser was passed 1 mol (43 ml liquid) of chlorine diluted in an oxygen stream at the boiling point of the mixture (allene bp −32°) in a 1-hr priod. A yellow color built up early in the reaction but seemed to dissipate in the later stages. After reaction was completed, excess allene was allowed to escape through a water-cooled condenser set for reflux. Glpc analysis at 125° (Perkin-Elmer column "O") showed four rather volatile components, A–D, in a ratio of *ca.* 6:8.5:3:1. Analysis at 150° showed these same peaks plus several others of longer retention time. Distillation on an 18-in. spinning-band column gave the following fractions: (1) 12.5 g, bp 55–60°, n^{23}D 1.4309; (2) 4.0 g, bp 60–90°; (3) 18.8 g, bp 90–93°, n^{23}D 1.4565; (4) 3.0 g, bp 93° (760 mm)–40° (90 mm); (5) 4.9 g, bp 40–60° (90 mm); (6) 1.3 g, bp 45–47° (55 mm), n^{23}D 1.4576; (7) 3.2 g, bp 50–68° (45 mm); (8) 4.9 g, bp 44–70° (18 mm); (9) 8.3 g, bp 55–90° (2 mm); and (10) 7.5 g, bp 70–110° (0.2 mm). Considerable tarry residue remained. While this distillation is not claimed to have been particularly efficient, it does show the complexity of the reaction mixture. Fraction 1, almost completely A by glpc analysis, was shown to be propargyl chloride (2) by comparison with an authentic sample. Fraction 3, almost completely B, was similarly shown to be 2,3-dichloropropene (1). Component C was most cleanly found in fraction 6 and component D in fraction 7. Fractions 8–10 contained mainly higher boiling materials than D by glpc analysis. By combination of the weights of fractions 1–7 corrected for their composition as determined by glpc analysis, the isolated yields were 14.5 g of A (20% propargyl chloride), 25.2 g of B (23% 2,3-dichloropropene), 4.9 g of C (4.3% based on C_6H_7Cl, see below), and 2.3 g of D (1.5% based on $C_6H_8Cl_2$, see below). Pure samples of C and D were obtained by preparative glpc.

Compound C showed infrared absorption at 3320 (s) (C≡CH), 2120 (w) (C≡C), 1635 (s) (unsymmetrical C=C), and 890 cm^{-1} (s) (R_2C=CH_2). The nmr spectrum showed a singlet at 5.20, a multiplet at 2.47, and a triplet (J = 2.5 cps) at 1.88 ppm in the ratio 2.2:3.9:0.9. Hydrogenation in acetic acid over Adams catalyst followed by dilution with water and extraction with carbon tetrachloride gave an organic solution containing *n*-hexane as determined by glpc retention time and nmr analysis (spectrum identical with that of a known sample; in particular the correct $-CH_2-/-CH_3$ area ratio was observed). These data allow assignment of the structure of 2-chloro-1-hexen-5-yne (15) to C.

Anal. Calcd for C_6H_7Cl: C, 62.89; H, 6.16; Cl, 30.95. Found: C, 62.07; H, 6.24; Cl, 31.21.

Compound D, n^{24}D 1.4700, had ir bands at 1635 (s) (unsymmetrical C=C) and 885 cm^{-1} (s) (R_2C=CH_2) and nmr singlets at 5.20 and 2.58 ppm of equal area. Hydrogenation as above again gave *n*-hexane. The structure of 2,5-dichloro-1,5-hexadiene (16) is assigned to D.

Anal. Calcd for $C_6H_8Cl_2$: C, 47.71; H, 5.34; Cl, 46.95. Found: C, 47.35; H, 5.38; Cl, 46.72.

Registry No.—**3**, 1000-87-9; **5**, 1000-86-8; **8**, 598-25-4; **15**, 17396-43-9; **16**, 14225-24-2; allene, 463-49-0; 2-chloro-4,4,5,5-tetracyano-1,3,3-trimethylcyclohexene, 17414-31-2.

Acknowledgment.—The author wishes to acknowledge several constructive discussions of this work with Dr. Lars Skattebøl.

(12) W. H. Carothers and D. D. Coffman, *J. Amer. Chem. Soc.*, **54**, 4071 (1932).

(13) A. J. Ultée, *Rec. Trav. Chim.*, **68**, 125 (1949).

The Acid-Catalyzed Isomerization of Tricyclics

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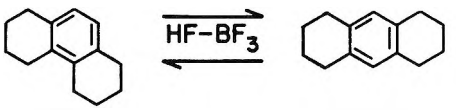
The isomerization of 1,2,3,4,5,6,7,8-octahydroanthracene (OHA) and 1,2,3,4,5,6,7,8-octahydrophenanthrene (OHP) was carried out at 0, 30, and 50° with an HF–BF_3 catalyst system. At 0 and 30°, with an excess of anhydrous hydrofluoric acid and a boron trifluoride to substrate mole ratio of 0.6 and 0.7 to 1, equilibrium was reached when ~70% of the OHP was isomerized to OHA. The OHA:OHP ratio in the hydrocarbon and acid layers was also established under conditions that provided information regarding the position of the thermodynamic equilibrium of the hydrocarbons and carbonium ions involved. Isomerization with less than equivalent amounts of HF and BF_3 was shown to have a pronounced effect on the OHA:OHP ratio. A comparison of the HF- and HF–BF_3-catalyzed isomerization of OHP was made. Competition experiments have shown the following relative order of basicity: OHA > OHP ≃ prehnitene > durene.

Some years ago Schroeter[1] showed that 1,2,3,4,5,6,7,-8-octahydroanthracene and 1,2,3,4,5,6,7,8-octahydrophenanthrene were among the products obtained from the action of aluminum chloride on tetralin. He also demonstrated that the interconversion of these compounds, in the presence of additional aluminum chloride, was possible and that very small amounts of dodecahydrotriphenylene and a viscous high-boiling yellow hydrocarbon were also obtained. Grove[2a] repeated this work and, aside from the yield of products, confirmed Schroeter's results. An equilibrium constant of one was obtained. Based upon spectroscopic evidence, the yellow compound was postulated to be 1″,2″,3″,4″,5′,6′,7′,8′-octahydro-8,9-benzonaphtho-[2′,3′:3,4]pyrene, which upon dehydrogenation gave 8,9-benzonaphtho[2′,3′:3,4]pyrene. The presence of these same two compounds was established in a subsequent investigation of "Schroeter Tar."[2b] The conversion of 1,2,3,4,5,6,7,8-octahydroanthracene-9-sulfonic acid into 1,2,3,4,5,6,7,8-octahydrophenanthrene-9-sulfonic acid by means of sulfuric acid was demonstrated by Schroeter and Götzky.[3] On the other hand, neither 1,2,3,4,5,6,7,8-octahydroanthracene nor its 9-carboxylic acid, 9-methyl, 9-ethyl, or 9-acetic acid derivatives underwent isomerization in the presence of anhydrous hydrogen fluoride at room temperature.[4,5]

Furthermore, neither 1,2,3,4,5,6,7,8-octahydrophenanthrene nor its 9-methyl derivative could be isomerized under the above conditions. This seemed to exclude an equilibrium in which 1,2,3,4,5,6,7,8-octahydroanthracene or its derivatives would be highly favored. A British patent[6] describes the conversion of phenanthrene into anthracene *via* the isomerization of octahydrophenanthrene to octahydroanthracene. The isomerization step was carried out at 30° with aluminum chloride as the catalyst, and the total contact time was 15 hr.

We previously reported[7] on the disproportionation of tetralin in the presence of HF–BF_3 and showed that a high yield of 1,2,3,4,5,6,7,8-octahydroanthracene and 1,2,3,4,5,6,7,8-octahydrophenanthrene could be obtained. This paper will deal with the isomerization of these tricyclic products (eq 1) using HF–BF_3 as the catalyst system.



(1)

In addition, two major by-products have also been noted to form, depending upon the severity of the experimental conditions. These compounds are *trans,syn,-trans*-tetradecahydroanthracene, mp 90° (lit.[8] mp 90°), and dodecahydrotriphenylene, mp 231.5–232.5° (lit.[1] mp 232–233°). Small amounts of other high molecular weight compounds are also formed. Among these trace products is the yellow hydrocarbon discussed by Grove[2a] and Kimber.[2b]

Experimental Section

The experimental procedure for the isomerization has been adequately described elsewhere.[7] All isomerization studies at 0, 30, and 50° (Tables I–III) were run under heterogeneous conditions. The OHA:OHP ratio obtained by this method was based upon quenching the entire reaction mixture and, therefore, reflects the total OHA and OHP distribution in both the hydrocarbon and acid layers.

TABLE I

ISOMERIZATION OF OHP AT 0°

Run no.	1	2	2*[a]	3	4	5
Time (min)	5	15	15	30	60	120
Product distribution (wt %)[b]						
Tetralin		1.1		1.2		1.1
OHA	54.5	64.5	71.1	71.6	64.3	68.6
OHP	44.0	28.4	28.6	24.6	34.7	27.4
Other[c]	1.5	6.0	0.3	2.6	1.0	2.9
OHA/OHP[d]	1.2	2.3	2.5	2.9	1.8	2.5
Conversion of OHP	56.0	71.6	28.9	75.4	65.3	72.6
Yield, OHA (%)	97.4	90.1	99.0	95.3	98.5	94.5

[a] Run 2* shows, for comparison, the isomerization of OHA → OHP at 0°. The conversion and yield refer to OHA and OHP, respectively. [b] The mole ratio of HF:OHP and BF_3:OHP was 10:1 and 0.6–0.7:1 in all experiments. [c] This fraction consists of high molecular weight condensation products, some of which have resulted from hydrogen disproportionation reactions. [d] OHA:OHP = ($[OHA]_{acid}$ + $[OHA]_{HC}$):($[OHP]_{acid}$ + $[OHP]_{HC}$).

The thermodynamic equilibrium of the hydrocarbons and carbonium ions was determined in separate experiments, under

(1) G. Schroeter, *Ber.*, **57**, 1990 (1924).

(2) (a) J. F. Grove, *J. Chem. Soc.*, 483 (1953); (b) R. W. L. Kimber, *Chem. Ind.* (London), 657 (1960).

(3) G. Schroeter and A. Götzky, *Ber.*, **60**, 2035 (1927).

(4) G. M. Badger, W. Carruthers, J. W. Cook, and R. Schoental, *J. Chem. Soc.*, 169 (1949).

(5) G. M. Badger, W. Carruthers, and J. W. Cook, *ibid.*, 2044 (1949).

(6) E. T. Borrows, H. M. E. Steiner, and I. Goodman, British Patent 694,961 (July 29, 1953).

(7) R. D. Bushick, *Ind. Eng. Chem., Prod. Res. Develop.*, **6**, 172 (1967).

(8) R. K. Hill, J. G. Martin, and W. H. Stouch, *J. Amer. Chem. Soc.*, **83**, 4006 (1961).

TABLE II

ISOMERIZATION OF OHA AND OHP AT 30°[a]

	OHA					OHP			
Run no.	6	7	8	9	10	11	12	13	14
Time (min)	15	30	60	120	240	15	30	60	120
Product distribution (wt %)									
Tetralin				1.2	4.2	1.6	3.5	4.4	3.7
trans,syn,trans-Tetradecahydroanthracene	0.7	1.0	1.1	2.5	6.7			1.3	2.9
OHA	70.0	71.0	69.6	60.7	42.9	61.5	57.5	56.0	57.0
OHP	29.3	26.0	28.6	30.6	29.0	34.3	29.6	27.5	30.7
Dodecahydrotriphenylene	1.0	1.0	0.2	5.0	17.2		5.2	6.4	5.8
Others		2.0				2.6	4.2	4.4	
OHA/OHP[b]	2.4	2.7	2.4	2.0	1.5	1.8	1.9	2.0	1.9
Conversion of OHA	30	29	30.4	39.3	57.1				
Yield, OHP (%)	97.5	90	94.1	77.8	50.7				
Conversion of OHP						65.7	70.4	72.5	69.3
Yield, OHA (%)						93.5	82.0	77.3	82.4

[a] In all experiments, the BF_3:OHP mole ratio was 0.6–0.7:1 and the HF:OHP mole ratio was 10:1. [b] OHA:OHP = ($[OHA]_{acid}$ + $[OHA]_{HC}$):($[OHP]_{acid}$ + $[OHP]_{HC}$).

TABLE III

COMPARISON OF HF- AND HF–BF_3-CATALYZED ISOMERIZATION OF OHP

Run no.	15	16	17[a]	18[a]	19	20	21	22
OHP (g)	18.6	18.6	18.8	18.9	18.6	19.2	19.0	18.6
HF (g)	20.0	20.0	20.0	21.0	20.0	20.0	20.0	20.0
BF_3 (g)	4.4		4.7		4.4		4.1	
Time (min)	30	90	15	30	90	90	90	90
Temp (°C)	0	0	0	0	30	30	50	50
Product composition (wt %)								
Tetralin	1.2				6.2		13.2	
OHA	71.6		71.1	99+	52.5	5.6	28.1	48.5
OHP	24.6	99+	28.6		30.8	88.0	18.7	42.0
By-products[b]	2.6		0.3		10.5	6.4	40.0	9.5
Conversion of OHP	75.4		28.9[c]		69.2	12.0	81.3	58.0
% yield OHA	95.3		99.0[c]		76.0	45.0	34.6	83.5
OHA/OHP[d]	2.9		2.5		1.7	0.1	1.5	1.2

[a] For comparison, runs 17 and 18 at 0° show the isomerization of OHA. [b] The by-product fraction at 30 and 50° contains dodecahydrotriphenylene, *trans,syn,trans*-tetradecahydroanthracene, and small amounts of condensed cyclics, some of which have resulted from hydrogen disproportionation reactions. [c] Refers to the conversion of OHA and yield of OHP, respectively. [d] OHA:OHP = ($[OHA]_{acid}$ + $[OHA]_{HC}$):($[OHP]_{acid}$ + $[OHP]_{HC}$).

different reaction conditions, by sampling the hydrocarbon and acid layers, respectively.

Distribution studies were carried out in a 75-ml Hoke pressure vessel. An excess of anhydrous hydrofluoric acid (10:1 HF:hydrocarbon) was used in all experiments. The boron trifluoride molar concentration was one-half that of the hydrocarbon. An amount of *n*-heptane equal in volume to the amount of anhydrous hydrofluoric acid was used in all of the experiments. The reaction vessel and its contents were shaken for about 5–10 min at 0°, whereupon the hydrocarbon layer was separated from the acid layer by means of a conductivity valve. The hydrocarbon distribution was established by vpc analysis of the raffinate and extract layers.

Results and Discussion

The isomerization of 1,2,3,4,5,6,7,8-octahydrophenanthrene (OHP) was carried out at 0 and 30° with an excess of anhydrous hydrofluoric acid and a boron trifluoride:OHP mole ratio of 0.6–0.7:1. The reaction time was varied, and the effect on the product distribution was noted. Table I illustrates that after only 5 min 56% of the OHP was converted into products and of these almost 55% was OHA. As the reaction was allowed to proceed the conversion increased, with equilibrium being achieved when approximately 71% (average of 15 to 120 min runs) of the OHP was converted into products. For comparison, run 2* indicates that within 15 min octahydroanthracene was isomerized to octahydrophenanthrene to the extent of 29%. Table II illustrates the data obtained for the isomerization of octahydrophenanthrene and octahydroanthracene, respectively, at 30°. Again, equilibrium was reached when *ca.* 70% of the OHP was converted into products. Approaching from the opposite direction, equilibrium was reached when *ca.* 32% of the octahydroanthracene was converted into products in close agreement with the expected value. If a longer reaction time was permitted, such as in run 10, side reactions began to occur leading to by-products.

A synthetic mixture of OHA (70%) and OHP (30%) was subjected to experimental conditions identical with those cited previously to obtain additional information with respect to the position of equilibrium. After 60 min at 30° the reaction was terminated and the product was found to contain OHA and OHP in a ratio that was essentially unchanged (70.6% OHA:29.4% OHP).

In separate experiments at 50°, the hydrocarbon (HC) and acid layers were each examined to obtain information regarding the thermodynamic equilibrium of both the hydrocarbons and carbonium ions, respectively (Figure 1). With a catalytic amount of BF_3 present (0.015 mol/mol of substrate), little hydrocarbon would be expected to be present in the acid layer, either in the protonated form or physically dissolved. The OHA:OHP ratio in the hydrocarbon layer was found to be 1.1. Under similar reaction conditions, but with an excess of BF_3 (1.3 mol/mol of substrate), the OHA:OHP ratio in the acid layer was determined to be 1.6.

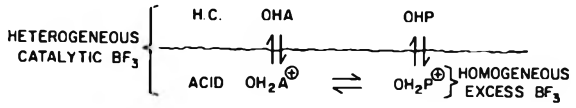


Figure 1.—OHA and OHP equilibria.

At 50°, the isomerization of OHP did not appear to be extremely sensitive to changes in BF_3 concentration over the range studied. Figure 2 illustrates the data obtained over the range of BF_3:OHP mole ratios of between 0.3 and about 0.75. The line drawn through these points could be extrapolated close to a point obtained from an independent experiment in which no BF_3 was used.

It was undesirable to use HF alone for the isomerization experiments, since reactions of this type proved to be too sluggish. An example of this effect is borne out by the data shown in Table III, which compares runs made in both the presence and absence of BF_3. At 0°, in the absence of BF_3, no isomerization of octahydrophenanthrene to octahydroanthracene occurred; however, when BF_3 was present (run 15) about 75% of the octahydrophenanthrene was converted into products in only one-third the time, and of the products formed 95% was octahydroanthracene. Comparing runs at 30°, it again becomes apparent that little isomerization of octahydrophenanthrene occurred within 90 min of reaction in the absence of BF_3, but in the presence of BF_3 (run 19) the conversion of octahydrophenanthrene rose from 12 to 69% and approximately 53% of the product mixture was octahydroanthracene. At 50°, with no BF_3 present, about 49% of the product consisted of octahydroanthracene. The conversion, however, was somewhat lower than was obtained in experiments, in the presence of BF_3, at other temperatures. Experiments carried out at 50° in the presence of BF_3 (run 21) led to a much higher conversion of OHP into products (~81%); however, by-products made up 40% of the total products. About 13% tetralin was also formed under the severe reactions conditions. At 30 and 50°, regardless of the presence or absence of BF_3, a substantially greater amount of by-products were formed. Dodecahydrotriphenylene was identified as the major component of the by-product fraction. Some *trans,syn,trans*-tetradecahydroanthracene also occurred at the higher temperatures, as already mentioned. The other components which make up the by-product fraction are thought to be cyclic structures which have undergone condensation reactions accompanied by various degrees of hydrogen disproportionation.

For comparison, the isomerization of octahydroanthracene is shown in the presence and absence of BF_3 (runs 17 and 18). As might be expected, no isomerization of octahydroanthracene to octahydrophenanthrene occurred in the absence of BF_3. However, when BF_3 was added, 29% of the octahydroanthracene was converted into products, giving a 99% yield of octahydrophenanthrene. The highest OHA:OHP ratio occurred at 0° and decreased as the temperature was raised. The high OHA content at the lower temperature is presumably due to the shift in the OHP–OHA equilibrium toward OHA, since this component solidifies at the lower temperature and would separate out of solution, thus causing an over-all shift in the equilibrium.

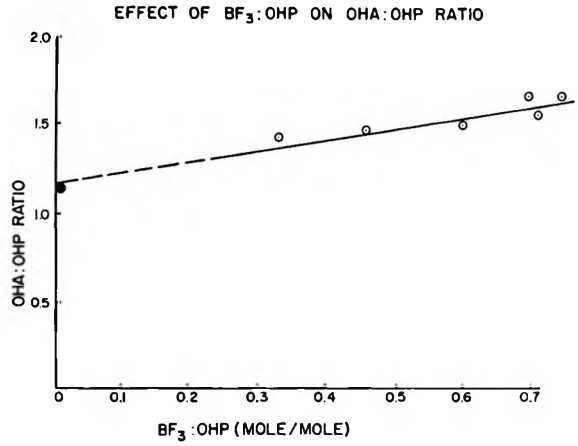


Figure 2.—The effect of BF_3:OHP on the OHA:OHP ratio: temperature 30°; HF:OHP (mole/mole) 10:1; reaction time 90 min.

Experiments in which a less than an equivalent amount (based on substrate) of hydrofluoric acid and boron trifluoride were used gave excellent isomerization of octahydrophenanthrene to octahydroanthracene (Table IV). For example, an OHA:OHP ratio of between 15 and 16 was obtained with low catalyst to substrate mole ratios (run 27). This isomerization resulted in OHA:OHP ratios that were substantially higher than were normally realized from isomerization experiments in which a large excess of hydrofluoric acid was used, as illustrated by run 23. Undoubtedly, the hydrofluoric acid becomes rapidly saturated with dissolved hydrocarbon, after which the OHA begins to separate. The highest OHA:OHP ratios were generally obtained when the HF:OHP mole ratio was 0.3–1.5, and the BF_3:OHP was 0.5–1.0. Within the concentration ranges specified the conversion of OHP into products varied from a low of 86% to a high of almost 95%. The yield of OHA within this same catalyst concentration range was 88–96%. The equilibrium constant obtained under these conditions was significantly higher than that previously reported in the literature.[6]

Distribution experiments were made between OHA–OHP, OHA–durene, and OHP–prehnitene using a

TABLE IV

ISOMERIZATION OF OHA AT 30° USING A MINIMUM CATALYST CONCENTRATION[a]

Run no.	23	24	25	26	27
HF:OHP (mole/mole)	10.0	1.0	1.3	0.3	0.5
BF_3:OHP (mole/mole)	1.1	1.0	0.4	0.3	0.6
Product composition (wt %)[b]					
OHA	63.4	75.8	83.6	89.2	87.4
OHP	36.4	13.9	8.8	7.0	5.5
Conversion[c]	63.6	86.1	91.2	93.0	94.5
% yield OHA[d]	99.5	88.0	91.9	96.0	92.5
OHA:OHP[e]	1.6	5.5	9.5	12.7	15.8

[a] All reactions were run for 60 min. [b] Only OHA and OHP are noted in the table. The balance of the product mixture consists of by-products already discussed in another part of this paper. [c] The conversion was based upon 100 − $[OHP]_{final}$ divided by $[OHP]_{original}$ times 100. [d] The yield was calculated from the $[OHA]_{formed}$ divided by $[OHP]_{converted}$ times 100. [e] OHA:OHP = $([OHA]_{acid} + [OHA]_{HC}):([OHP]_{acid} + [OHP]_{HC})$.

method similar to McCaulay's.[9] The results of the competition experiments are illustrated in Table V and show the following relative order of basicity: OHA > OHP; OHA > durene; and OHP ≥ prehnitene and prehnitene > durene (from the work of McCaulay[9]).

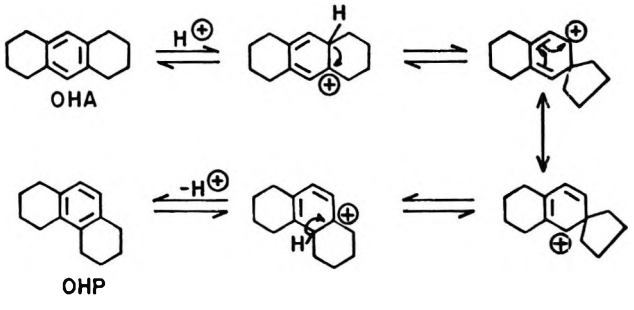
TABLE V
DISTRIBUTION EXPERIMENTS[a]

				Extract layer product —composition (wt %)[b]—		
Run no.	28[c]	29	30	28	29	30
Component A	OHP	OHA	OHA	51.0	57.0	60.5
Component B	Prehnitene	Durene	OHP	49.0	43.0	39.5

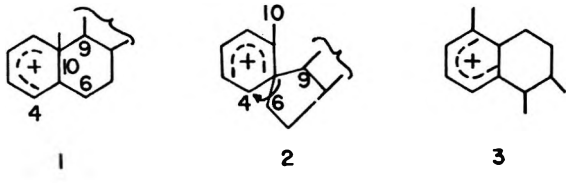
[a] A more detailed description may be found in the Experimental Section. [b] The product composition data have been normalized. A slight amount of isomerization of OHA and OHP was unavoidable even at 0° and a short reaction time. [c] Run number.

Mechanism.—The mechanism proposed by Schroeter many years ago[1] for the isomerization of OHA and OHP assumed the formation of an aluminum chloride–hydrogen chloride complex of the tricyclic in question. This complex was thought to stabilize the intermediate formed by fragmentation of one of the alicyclic ring systems. A mechanism based on protonation of the ring system followed by rearrangement to form a spiro-carbonium ion appears to be more plausible. The proposed reaction path may be depicted as shown in Scheme I.

SCHEME I



There is an abundance of evidence in the literature which offers support to this view. Probably, the example that is most familiar to us is the dienone–phenol rearrangement.[10] More recently Caspi and coworkers[11] carried out labeling experiments to show that the dienol–benzene rearrangement occurred by breakage of the 9(10) bond of the intermediate cation **1**, forming the spiro cation, **2**, followed by reattachment of C-9 to C-4 to give **3**.

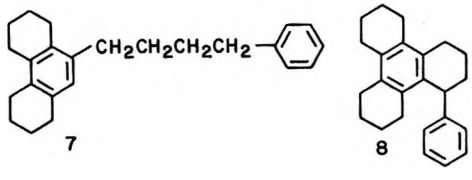


These samples all illustrate "ring migration" involving a saturated six-membered ring. A similar type of intermediate, but one involving a saturated five-membered ring is exemplified in the anthra steroid rearrangement.[12]

Many other examples[13-23] involving polycyclic aromatic systems may be considered to proceed by way of some "skeletal rearrangement" rather than simple substituent displacement. Balaban and Farcasiu[24] recently advanced a mechanism based upon a spiro carbonium ion intermediate in order to explain the isotopic scrambling that resulted when naphthalene-1-^{14}C was heated with aluminum chloride in the presence of benzene.

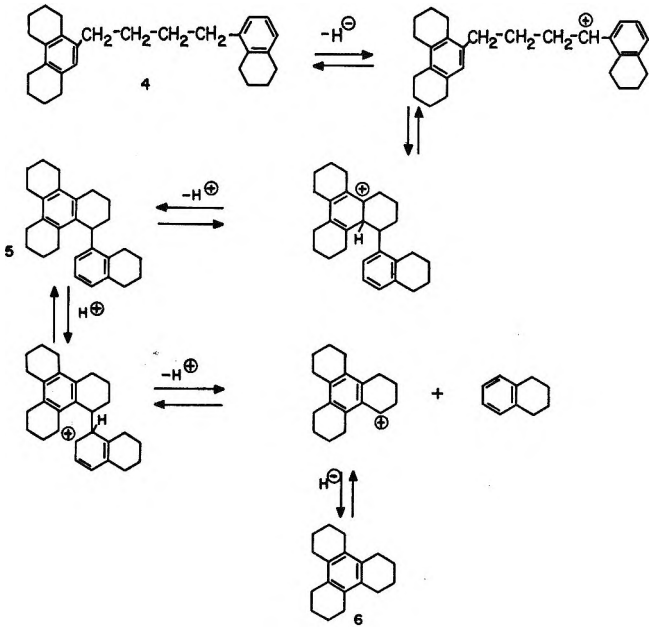
By-product Fraction.—This fraction may vary from 2–3% to several per cent depending upon the severity of the experimental conditions. Most of what has been determined about the components that make up this fraction was based upon mass spectrometry results, since the experimental runs themselves were of such a small scale that little material was available for any extensive characterization work. As already mentioned, dodecahydrotriphenylene was isolated and identified. To speculate, one might conceive that its occurrence can stem from the presence of 1,2,3,4,5,6,7,8-octahydro-9-(4-tetralylbutyl)phenanthrene (**4**), suggested many years ago by Schroeter[1] as being present in the product mixture resulting from the isomerization of OHA and OHP. Grove[2a] has analogously proposed that "octahydrobenzonaphthopyrene," mentioned previously, may occur by the self-alkylation of OHA. Compound **4** (with tetralin attached through C-5 or C-6) may undergo cyclization followed by loss of tetralin to give dodecahydrotriphenylene (**6**) according to Scheme II.

Evidence for the existence of **4** and **5** is based upon *m/e* 372 and 370, respectively. An *m/e* 316 was also observed and could be accounted for by the formation of 1-phenyldodecahydrotriphenylene (**8**), which can result from 1,2,3,4,5,6,7,8-octahydro-9-(4-phenylbutyl)-phenanthrene (**7**), *m/e* 318 undergoing a sequence of rearrangements similar to that shown for compound **4**.

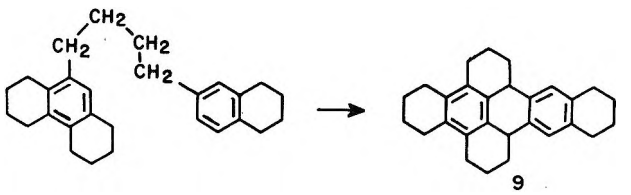


(9) D. A. McCaulay and A. P. Lien, *J. Amer. Chem. Soc.*, **73**, 2013 (1951).
(10) (a) P. J. Kropp, *ibid.*, **85**, 3280 (1963); (b) B. R. Davis and T. G. Halsall, *J. Chem. Soc.*, 1833 (1962); (c) E. Caspi, P. K. Grover, and Y. Shimizu, *J. Amer. Chem. Soc.*, **86**, 2463 (1963); (d) E. Caspi and P. K. Grover, *Tetrahedron Lett.*, 591 (1963).
(11) E. Caspi, D. M. Piatak, and P. K. Grover, *J. Chem. Soc.*, **6**, 1034 (1966).
(12) N. L. Wender in "Molecular Rearrangements," Vol. 2, P. de Mayo, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1963, p 1063.
(13) A. Dansi and E. Salvioni, *Gazz. Chim. Ital.*, **71**, 549 (1949).
(14) N. P. Buu-Hoi and D. Lavit, *Proc. Chem. Soc.*, 120 (1960).
(15) N. P. Buu-Hoi and D. Lavit-Lamy, *Bull. Soc. Chim. Fr.*, 1657 (1961); 102, 1962 (1962); 341 (1963).
(16) M. Zander, *Naturwissenschaften*, **49**, 300 (1962).
(17) A. Dansi, *Bull. Soc. Chim. Fr.*, 101 (1962).
(18) D. Lavit-Lamy and N. P. Buu-Hoi, *ibid.*, 2613, 2619 (1966).
(19) D. Lavit-Lamy and N. P. Buu-Hoi, *Chem. Commun.*, **92** (1966).
(20) N. P. Buu-Hoi, D. Lavit-Lamy, and O. Roussel-Perin, *Bull. Soc. Chim. Fr.*, 1771 (1967).
(21) A. T. Balaban and C. D. Nenitzescu in "Friedel-Crafts and Related Reactions," part 1, Vol. 2, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1964, p 1006.
(22) E. Clar, "Polycyclic Hydrocarbons," Vol. 1, Academic Press, New York, N. Y., 1964, pp 252, 313, 329.
(23) F. A. Vingiello and A. K. Youssef, *Chem. Commun.*, 863 (1967).
(24) A. T. Balaban and D. Fărcaşiu, *J. Amer. Chem. Soc.*, **89**, 1958 (1967).

SCHEME II



In addition, *m/e* 368 was obtained and suggests the presence of 1,2,3,4,5,6,7,8,9,10,12,13,14,15,17,21-hexadecahydrodibenzo[*fg*,*st*]pentacene (**9**), which can arise by ring closure of **4**, according to the following equation, rather than by the route depicted in Scheme I, for the formation of dodecahydrotriphenylene.



Based upon mass spectrometry results, other components which involve various degrees of hydrogen disproportionation are also present. The *trans,syn,-trans*-tetradecahydroanthracene found in the gross reaction product is thought to be formed from the hydrogen derived from some of the high molecular weight components that make up the by-products fraction. Although other perhydrogenated anthracene and phenanthrene isomers would also be anticipated to be present, they were not observed. It is known that, in the presence of aluminum chloride,[25,26] aluminum bromide,[8] or aluminum bromide–olefin complex,[27] perhydrogenated anthracenes and phenanthrenes are converted almost completely into the most thermodynamically stable isomer, *trans,syn,trans*-tetradecahydroanthracene.

Conclusions

We have demonstrated that, in the presence of at least 0.5 mol of boron trifluoride/mol of substrate and an excess of anhydrous hydrofluoric acid, equilibrium is achieved when ~70% of the OHP has isomerized to OHA. The OHA:OHP ratio in the hydrocarbon and acid layers was found to be 1.1 and 1.6, respectively. A catalytic amount of $HF–BF_3$ was used in the former determination while an excess of catalyst was employed in the latter case. An isomerization, with a minimum of both hydrofluoric acid and boron trifluoride, resulted in a yield of OHA well in excess of 90%. This facile isomerization allows one to obtain either the symmetrical or unsymmetrical tricyclic by crystallization and distillation techniques which, as an intermediate, can be chemically transformed into several interesting and useful compounds.

Registry No.—OHA, 1079-71-6; OHP, 5326-97-3.

Acknowledgments.—The author expresses his appreciation to Mr. Robert W. Warren for analytical assistance, Professor Wayland E. Noland for helpful discussions, and Mr. Everett Cassel for obtaining many of the experimental data.

(25) J. W. Cook, N. A. McGinnis, and S. Mitchell, *J. Chem. Soc.*, 286 (1944).

(26) E. I. Prokopets and S. M. Boguslauskaya, *J. Appl. Chem. USSR*, **11**, 1471 (1938); *Chem. Abstr.*, **33**, 5816[9] (1939).

(27) (a) A. Schneider, R. W. Warren, and E. J. Janoski, *J. Amer. Chem. Soc.*, **86**, 5365 (1964); (b) *J. Org. Chem.*, **31**, 1617 (1966).

The Synthesis and Stereochemistry of 5-Substituted 2-Methylcycloheptanones

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The *cis* and *trans* isomers of 5-methyl- (**2b**), 5-isopropyl- (**2c**), 5-*t*-butyl- (**2d**), 5-isopropylol- (**2e**), and 5-carbethoxy-2-methylcycloheptanone (**2f**) were prepared in 80–90% yield *via* treatment of the appropriate 4-substituted cyclohexanone with diazoethane in 20% ethanol–ether. The initial (kinetic) distribution of the isomeric pairs was approximately 1:1. Equilibration of **2b–e** in methanolic sodium carbonate afforded isomer distributions of 2.5:1 (**2b**), 2:1 (**2c**), 3:1 (**2d**), and 3:1 (**2e**), respectively, favoring the *trans* isomer in each case. Stereorational syntheses of *trans*-2,5-dimethylcycloheptanone and *trans*-2-methyl-5-isopropylolcycloheptanone were carried out to determine the stereochemistry of the products derived from the ring-expansion reactions.

In connection with synthetic work on the guaiazulene sesquiterpenes[2] we required a number of 5-substituted 2-methylcycloheptanones. Of the potential routes to such compounds, the direct ring expansion of 4-substituted cyclohexanones with diazoethane[3] appeared most promising because of its directness and the ready availability of suitable starting materials. After some initial difficulties we discovered exceedingly efficient conditions for effecting the ring-expansion reaction. This discovery prompted us to examine the stereochemistry of the resulting disubstituted cycloheptanones with a view to obtaining the first concrete data on conformational–configurational relationships in such compounds.[4]

Previous workers[5] have noted that the conversion of cyclohexanone into 2-methylcycloheptanone *via* ring expansion with ethereal diazoethane proceeds very slowly and in poor yield. Our best efforts along this line resulted in a 38% yield of fairly pure 2-methylcycloheptanone after a reaction time of 4 days. Even then, over 30% of the unchanged cyclohexanone remained. Moreover, this material could be effectively removed from the product only through its bisulfite adduct, thereby rendering the over-all procedure not only time consuming, but laborious as well. We therefore decided to study the ring-expansion reaction further in the hope of improving its efficiency.

Some years ago, Mosettig[5a] found that methanol accelerated the reaction of cyclohexanone with diazomethane. Later work, which showed that this catalytic effect involves the addition step of the reaction,[6] suggested that this phenomenon might be general for a variety of ketones, diazoalkanes, and alcohols. Accordingly, we examined the effect of ethanol on the reaction of cyclohexanone with diazoethane.

The addition of ethanol to an ether solution of diazoethane and cyclohexanone caused the brisk evolution of nitrogen which subsided markedly and nearly ceased after several hours at room temperature. We made no attempt to determine the optimum solvent composition since our first choice of 20% ethanol in diethyl ether gave excellent results. The reaction was complete within 2 hr and afforded a 9:1 mixture of 2-methylcycloheptanone (**2a**) and the oxide **3a** in over 90% yield. Table I summarizes these findings and shows

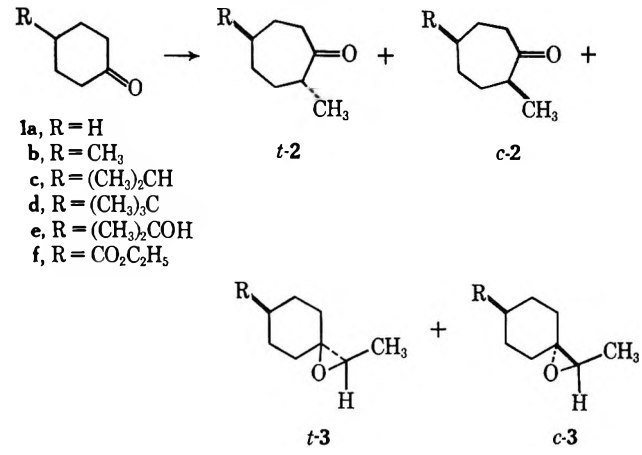
TABLE I
PRODUCT COMPOSITION OF DIAZOETHANE RING-EXPANSION REACTIONS

Cyclohexanone	2-Methylcycloheptanone (2), %	Oxide 3, %	Yield, %
1a	95	Trace	38[a]
1a	91	9	92[b]
1b	88	12	92[b]
1c	82	18	91[b]
1d	86	14	91[b]
1e	100	...	81[b]
1f	98	2	91[b]

[a] Diethyl ether was employed as the solvent. [b] A solution of 20% ethanol in diethyl ether was employed as the solvent.

the results of our studies on a number of 4-substituted cyclohexanones (**1b–f**) of interest in our projected synthetic work. In all cases, nitrogen evolution essentially ceased within 2–5 hr at room temperature signaling completion of the reaction. The 4-alkylcyclohexanones **1b–d**, as well as cyclohexanone itself, gave varying amounts (10–20%) of the related oxides **3a–d** in addition to the desired 2-methylcycloheptanones **2a–d** (Chart I). Surprisingly, those cyclohexanones (**1e**

CHART I



1a, R = H
b, R = CH_3
c, R = $(CH_3)_2CH$
d, R = $(CH_3)_3C$
e, R = $(CH_3)_2COH$
f, R = $CO_2C_2H_5$

and **1f**) with polar C-4 substituents gave high proportions of the cycloheptanone products **2e** and **2f**, and little or no oxides. Nmr analysis suggested that oxide **3b** derived from 4-methylcyclohexanone (**1b**) consisted

(1) (a) Fellow of the Alfred P. Sloan Foundation, 1966–1968. (b) National Institutes of Health Predoctoral Fellow, Division of General Medical Sciences (GM-29,694), 1966–1968.

(2) *Cf.* J. A. Marshall and J. J. Partridge, *J. Amer. Chem. Soc.*, **90**, 1090 (1968), and references therein.

(3) For a review, see C. D. Gutsche, *Org. Reactions*, **8**, 364 (1964).

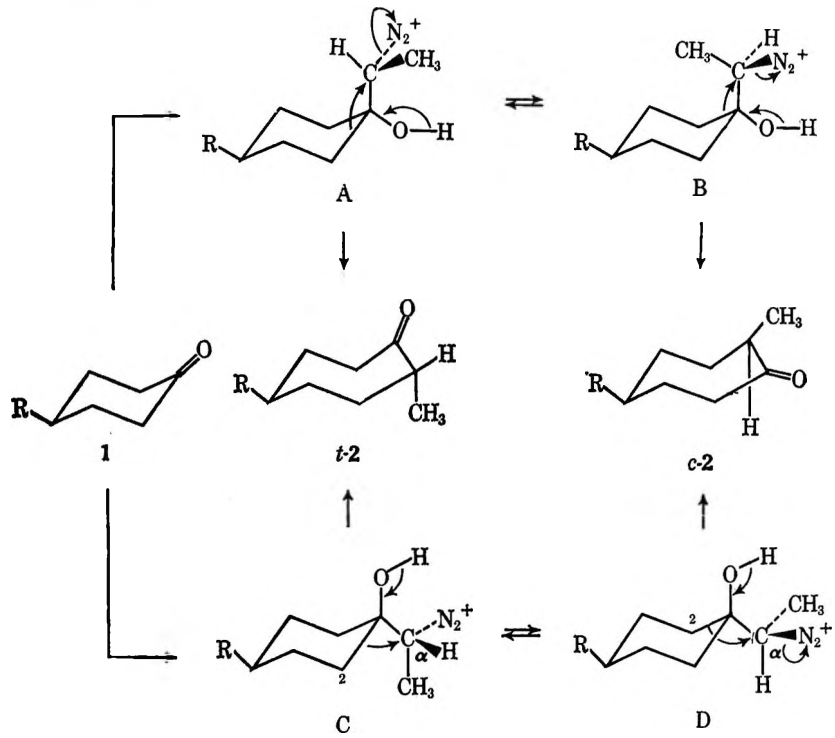
(4) *Cf.* J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7043 (1967); **84**, 3355 (1962). J. B. Jones, J. M. Zander, and P. Price, *ibid.*, **89**, 94 (1967).

(5) (a) E. Mosettig and A. Burger, *ibid.*, **52**, 3456 (1930); (b) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *ibid.*, **61**, 1057 (1939); (c) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939).

(6) J. N. Bradley, G. W. Cowell, and A. Ledwith, *ibid.*, 4334 (1934).

Scheme I

Pathways to *cis*- and *trans*-5-Substituted 2-Methylcycloheptanones



of a nearly 1:1 mixture of the *trans* and *cis* isomers *t*-**3b** and *c*-**3b**, whereas the oxides **3c** and **3d** derived from 4-isopropyl- and 4-*t*-butylcyclohexanone appeared to be single stereoisomers.

As can be seen from Table II, the cycloheptanones **2b–f**, as obtained from the ring-expansion reaction, consist of nearly 1:1 mixtures of *cis* (*c*-**2**) and *trans* (*t*-**2**) isomers. Precise *cis*/*trans* ratios for the 5-alkylcycloheptanone mixtures **2b–d** could be obtained directly *via* gas chromatography, but the stereoisomers of the more polar compounds **2e** and **2f** failed to separate on a variety of columns. However, a fairly accurate estimate of isomer ratios could be secured from the integrated nmr spectra of these mixtures.

Table II

Isomer Composition of 5-Substituted 2-Methylcycloheptanones

Cycloheptanone	Conditions	Composition, % *t*-2	Composition, % *c*-2
2b	Kinetic	46	54[a]
	Equilibrium	71	29[a]
2c	Kinetic	46	54[a]
	Equilibrium	67	33[a]
2d	Kinetic	50	50[a]
	Equilibrium	75	25[a]
2e	Kinetic	~50	~50[b]
	Equilibrium	~75	~25[b]
2f	Kinetic	~50	~50[b]

[a] Gas chromatography was employed for the analysis. [b] The analysis is based on the integrated nmr spectrum.

Since the ring-expansion reactions were conducted under mild conditions in neutral solution, the observed 1:1 ratios of *cis* and *trans* isomers 2b–f should represent the kinetic distribution and reflect the relative transition-state energies of the reactions leading to each. Scheme I outlines reasonable reaction pathways to each isomer.[7] From an inspection of molecular models, we estimate the energy of the transition state leading from conformer A to the *trans* product *t*-**2** to be lower than that of the transition state leading from conformer B to the *cis* product *c*-**2**. By the same token, the transition state leading from conformer D to *c*-**2** appears more favorable than that leading from conformer C to *t*-**2**. In the latter case the developing bond between C-2 and C-α restricts rotation of the ethyl diazonium grouping thereby forcing the methyl grouping to maintain an axial orientation. In the process leading from D to *c*-**2** this methyl grouping can remain equatorial.

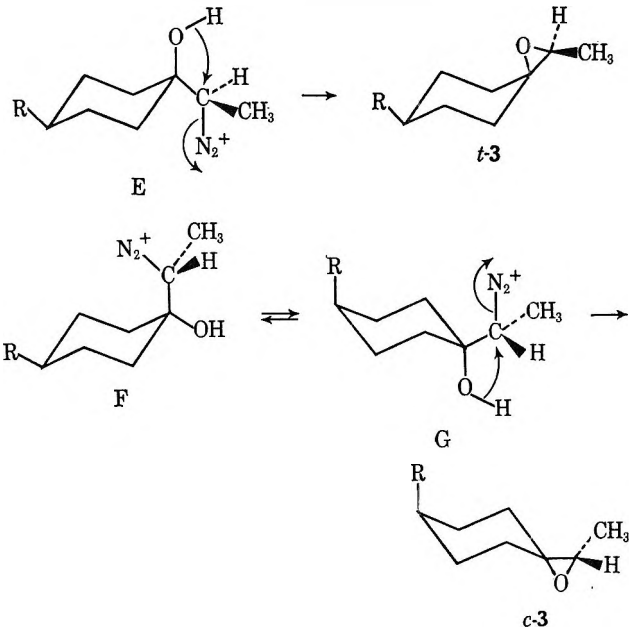
The adducts A and B, with axial ethyldiazonium groupings, should be somewhat higher in energy than their equatorially substituted counterparts C and D. However, this factor would influence the stereochemistry of the cycloheptanone products only if the additions leading to these intermediates were appreciably reversible. Such is probably not the case here, since protonation by ethanol should favor the addition reaction.[7] Thus, a reactantlike transition state for the addition process,[8] where topside and bottomside attack are about equally favored, followed by the rapid loss of nitrogen and synchronous bond migration preferentially *via* the lower energy transition states derived from adducts A and D, adequately accounts for the observed ratio of isomeric cycloheptanone products. We offer the foregoing explanation merely as one possible working hypothesis. Other possibilities exist, and we must await additional experimental evidence before a firm choice can be made.

(7) The assumption of protonated intermediates in this scheme seems justified in view of the high ethanol content of the reaction medium.

(8) See J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965), for comments bearing on this point.

As noted above, the oxide **3b** derived from 4-methylcyclohexanone (**1b**) consists of a 1:1 mixture of the stereoisomers *t*-**3b** and *c*-**3b**, whereas the oxides **3c** and **3d** appear stereochemically homogenous. This finding can be accommodated with the aid of Scheme II.[9]

SCHEME II
PATHWAYS TO *cis*- AND *trans*-4-SUBSTITUTED CYCLOHEXYLIDENE OXIDES



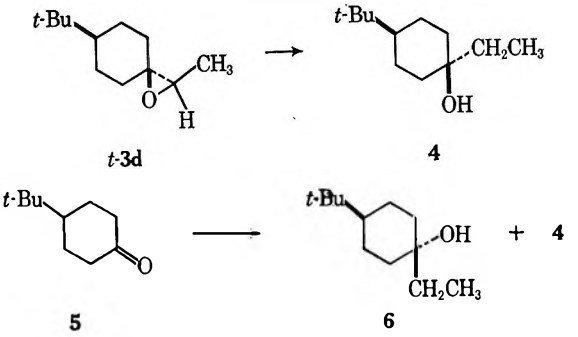
The transition states leading to the cyclohexylidene oxide products *t*-**3** and c-**3** require a *trans* relationship between the attacking hydroxyl oxygen and the departing diazonium grouping. Conformer E provides a low-energy pathway to the *trans* isomer *t*-**3**, but an analogous low-energy pathway to the *cis* isomer *c*-**3** must proceed mainly *via* conformer G as the transition state derived from F suffers from adverse steric crowding. The conversion of conformer F into conformer G requires reorientation of the R grouping from the equatorial to the axial position, a change which would be more favorable for a small group such as methyl than the larger isopropyl and *t*-butyl groupings present in cyclohexanones **1c** and **1d**. This analysis predicts the stereochemistry of the latter oxides to be *trans* (*t*-**3c** and *t*-**3d**).

The conversions outlined in Chart II confirmed this prediction for the *t*-butyl derivative **3d**. Reduction of this oxide with lithium aluminum hydride afforded the corresponding cyclohexanol **4**. This cyclohexanol was identical with the major alcohol, previously shown to be the *trans* isomer, obtained from the addition of ethylmagnesium bromide to 4-*t*-butylcyclohexanone.

Treatment of the 1:1 mixtures of epimeric 2-methylcycloheptanones **2b–e** with refluxing methanolic sodium carbonate led to new mixtures ranging in composition from 3:1 (**2d** and **2e**) to 2:1 (**2c**) as shown in Table II. The major epimers of the alkyl-substituted cycloheptanones **2b–d** exhibited the shorter gas chromato-

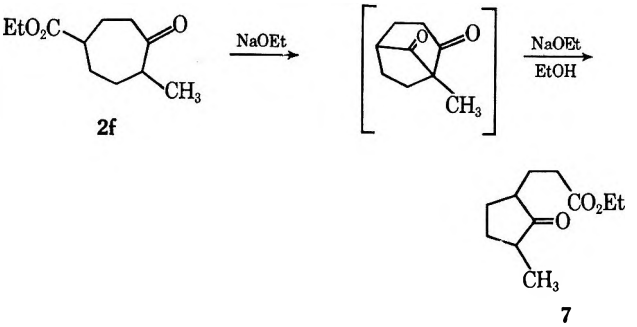
(9) Essentially the same analysis has been used by R. G. Carlson and N. S. Behn [*J. Org. Chem.*, **33**, 2069 (1968)] in their studies on the Tiffeneau–Demjanov rearrangement. Their findings also lend support to Scheme I. For an alternative mechanism of oxirane formation, see C. D. Gutsche and J. E. Bowers, *ibid.*, **32**, 1203 (1967).

CHART II



graphic retention times. As noted above, the epimers derived from the isopropylol derivative **2e** failed to separate on a variety of columns. Interestingly, the predominant component of this mixture, and the mixtures related to **2b–d** as well, gave rise to higher field methyl doublets in the nmr spectrum. These observations suggest that the major epimer of each pair belongs to the same stereochemical series.

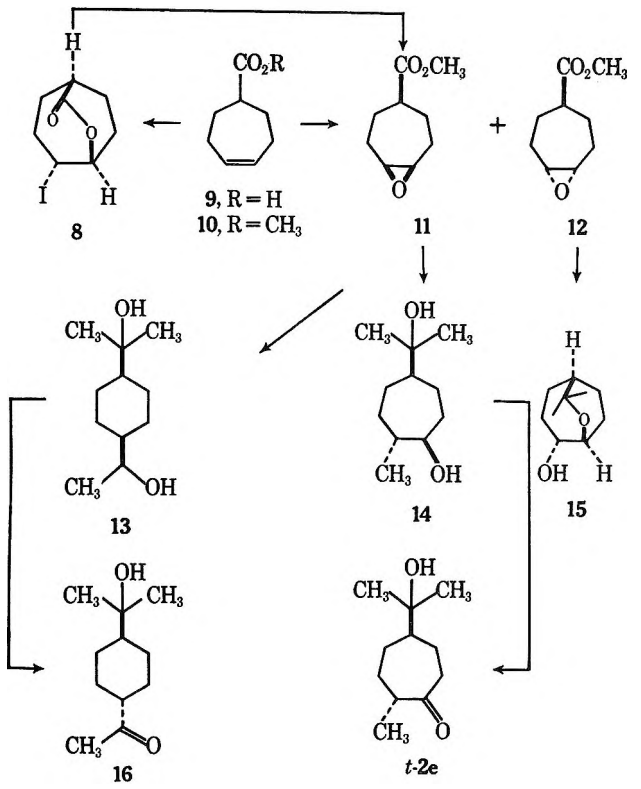
Our efforts to equilibrate the carbethoxy-substituted cycloheptanone **2f** were foiled by a combination of circumstances. Fearing saponification of this keto ester under the equilibrating conditions (Na_2CO_3–H_2O–CH_3OH) employed for the other cycloheptanones **2b–e**, we attempted to carry out this reaction with ethanolic sodium ethoxide. Unfortunately, this reagent effected skeletal isomerization of the cycloheptanone **2f** leading, as shown below, to the cyclopentanone derivative **7**.



The conformational analysis of cycloheptane and its derivatives has been considered in great detail by Hendrickson.[4] We applied his concepts to the calculation of conformational energies of the *cis*- and *trans*-2,5-disubstituted cycloheptanones (**2**) in an attempt to deduce the correct stereochemistry of these compounds. Each of these cycloheptane derivatives can adopt 14 different pseudorotomeric forms. For each of these forms there exists an energetically distinct chair–twist, chair–boat, and twist–boat conformation. To simplify our calculations we rejected those conformers which appeared from an inspection of models to possess serious nonbonded eclipsing interactions. Considering the remaining conformers in the light of Hendrickson's ring-substituent energy values,[4] we computed an energy difference of 0.1 kcal/mol favoring the *trans*-dimethylcycloheptanone *t*-**2b** over the *cis* isomer *c*-**2b**.

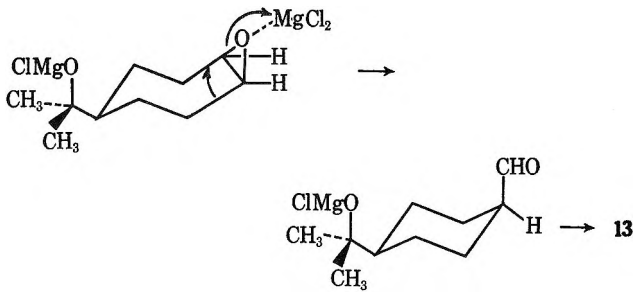
Since conformational analysis failed to provide a clear-cut assignment of stereochemistry to the 2,5-disubstituted cycloheptanones **2b–f**, we decided to seek this information through the stereoselective synthesis

CHART III



of selected members of this group. Our first efforts, outlined in Chart III, were directed toward the isopropylolcycloheptanones *t*-**2e** and *c*-**2e**. The methyl ester **10** of 4-cycloheptenecarboxylic acid (**9**) afforded a nearly 1:1 mixture of the *cis* and *trans* oxides **11** and **12** upon treatment with *m*-chloroperoxybenzoic acid in benzene. A pure sample of each isomer was secured *via* preparative gas chromatography. The iodo lactone **8**, derived from the unsaturated acid **9**, yielded an authentic sample of the *cis*-oxido ester **11** when treated with slightly less than 1 mol equiv of sodium methoxide in 1,2-dimethoxyethane at room temperature. Equilibration in refluxing methanolic sodium methoxide afforded a 62:38 mixture of the *cis* (**11**) and *trans* (**12**) isomers.

Our initial plans called for the conversion of the isomeric oxido esters **11** and **12**, respectively into the corresponding 2-methyl-5-isopropylolcycloheptanols (*e.g.*, **11** → **14**) with the methyl Grignard reagent. Subsequent oxidation of these alcohols would then complete the stereochemically rational synthesis of *c*-**2e** and *t*-**2e**. However, ensuing developments forced a slight tactical modification of both methodology and objectives. The *cis*-oxido ester **11**, upon treatment with either methylmagnesium chloride or bromide in refluxing tetrahydrofuran, yielded a crystalline diol in high yield. Although the spectral properties of this substance seemed in accord with those expected for the desired diol **14**, its subsequent oxidation to the methyl ketone **16** betrayed its true identity as the rearranged cyclohexane derivative **13**. Related rearrangements of oxiranes are well documented.[10] In the present case the pinacolic-type rearrangement of the oxido ester **11** or, more likely, its isopropylol derivative can be viewed as shown below. The methyl ketone **16**

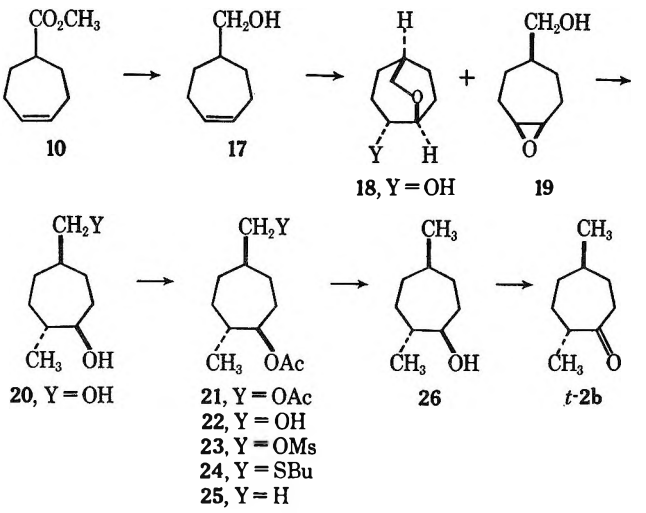


failed to epimerize in refluxing methanolic sodium carbonate and can therefore be regarded as the more stable *trans* isomer. Since concerted rearrangement of the above *cis* oxide would afford the *cis*-diol **13**, isomerization of the initially formed labile[11] axial acetyl grouping of the *cis* product must occur under the acidic conditions of the oxidation step.

Dimethylmagnesium smoothly added to the oxido ester **11** in refluxing dioxane to give the desired cycloheptanol **14** in high yield.[10] Upon oxidation with chromic acid, this material afforded *trans*-2-methyl-5-isopropylolcycloheptanone (*t*-**2e**). The nmr spectrum of this substance corresponded to that of the major component in the equilibrium mixture. Unfortunately, the above sequence could not be employed to synthesize the minor component of this mixture. The addition of dimethylmagnesium to the *trans*-oxido ester **12** afforded the bicyclic hydroxy ether **15** as the only isoluble product.

We next set out to synthesize stereorationally the 2,5-dimethylcycloheptanones *t*-**2b** and *c*-**2b** using an approach which parallels that described above for the isopropylol analog *t*-**2e**. Once again, a transannular reaction prevented us from fully realizing complete success. Nonetheless, a satisfactory synthesis of the *trans* isomer *t*-**2b** could be effected as shown in Chart IV. The alcohol **17**, obtained *via* reduction of the

CHART IV



unsaturated ester **10** with lithium aluminum hydride, afforded a 35:65 mixture of hydroxy ethers **18** and **19** upon treatment with *m*-chloroperoxybenzoic acid in

(10) *Cf.* B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirschmann, and J. M. Chemerda, *J. Amer. Chem. Soc.*, **82**, 3995 (1960).

(11) *Cf.* H. E. Zimmerman, *ibid.*, **79**, 6554 (1957).

benzene. The major hydroxy ether **19** decomposed during attempts at column or preparative gas chromatography, but these techniques could be used to purify the minor isomer **18**. Since this substance was unaffected by dimethylmagnesium in refluxing dioxane, the 35:65 mixture of hydroxy ethers **18** and **19** could be subjected to this reagent whereupon the unreacted isomer **18** and the desired diol **20** could be easily separated by column chromatography.

In view of the *cis* relationship between the alcohol functions of diol **20** and the marked propensity of such compounds for transannular reactions, we rejected some of the usual sequences for converting methylol into methyl groupings. Thus, no attempts were made at hydrogenolysis of the methylol tosylate or mesylate derivatives (*e.g.*, **20**, Y = OTs or OMs). Instead a more circuitous but less hazardous route was chosen which began with the conversion of diol **20** into diacetate **21** with acetic anhydride in pyridine. Selective saponification afforded the hydroxy acetate **22**, which was subsequently converted into the mesylate derivative **23**. Displacement of the mesylate grouping without cleavage of the acetate could be readily effected with a combination of butanethiol and sodium hydride in tetrahydrofuran. The resulting thio ether **24** underwent reductive desulfurization upon treatment with Raney nickel in ethanol giving the dimethylcycloheptyl acetate **25**. Cleavage of the acetate with lithium aluminum hydride followed by oxidation of the resulting alcohol **26** yielded *trans*-2,5-dimethylcycloheptanone (*t*-**2b**) identical with the thermodynamically favored isomer of the mixture **2b**. In view of the similar physical properties found for the mixtures of 5-substituted 2-methylcycloheptanones **2b–e**, we feel justified in assigning the *trans* stereochemistry to the thermodynamically favored isomer of the isopropyl (**2c**) and *t*-butyl (**2d**) ketones, as well.

Experimental Section[12]

Ring Expansion of Cyclohexanones with Diazoethane in 20% Ethanol–Diethyl Ether.—Ethereal diazoethane was prepared by a modification of the procedure of Arndt[13] and Werner.[14] In a typical preparation, a mixture of 100 ml of 50% aqueous potassium hydroxide and 500 ml of ether in a 1-l. erlenmeyer flask was cooled to −10°, and 62.0 g of solid N-ethyl-N-nitrosourea[15] was added in small portions over a 1.5-hr period. The mixture was stirred magnetically with cooling for 0.5 hr, and 400 ml of the solution was decanted into a second 1-l. erlenmeyer flask containing 25 g of potassium hydroxide pellets. An additional 100 ml of ether was added to the initial erlenmeyer flask, and, after 15 min of continued stirring, 160 ml of the ethereal solution was decanted into the second flask bringing the total volume to about 560 ml. Titration with ethereal benzoic acid and back titration with standard aqueous sodium hydroxide to the phenolphthalein end point indicated that the solution was 0.64 *M* in diazoethane.

The ring-expansion reactions were carried out by adding dropwise a solution of the cyclohexanone in ethanol to 1.25 mol equiv of 0.4–0.5 *M* ethereal diazoethane maintained at −10° and stirred magnetically. Sufficient ethanol was used to bring the final solvent composition to 20% ethanol in ether. After the addition was complete, the cooling bath was removed, a mercury bubbler was attached, and the mixture was stirred until nitrogen evolution ceased (2–5 hr). The excess diazoethane was destroyed by the dropwise addition of acetic acid, and the mixture was washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate.

2-Methylcycloheptanone (2a).—According to procedure described above, 8.4 g of cyclohexanone was converted into 9.8 g (91%) of a 91:9 mixture of 2-methylcycloheptanone (**2a**) and the oxide **3a**, bp 66–71° (15 mm). The pure ketone, obtained *via* preparative gas chromatography,[16] had the following properties: $n^{25}D$ 1.4576; λ_{max}^{film} 5.87 (CO), 7.27 8.51, 8.60, and 10.65 μ; $\delta_{TMS}^{CCl_4}$ 1.02 ppm (CH_3, doublet, J = 7 Hz); semicarbazone derivative mp 129–130° (lit.[17] mp 129–131°).

2-Methyl-1-oxaspiro[2.5]octane (3a).—The sample secured from the above mixture *via* preparative gas chromatography[16] had the following properties: λ_{max}^{film} 7.23, 9.68, 9.84, 10.08, 11.13, and 11.77 μ; $\delta_{TMS}^{CCl_4}$ 2.70 (H-2, quartet, J = 5.5 Hz), 1.55 (ring envelope), and 1.23 ppm (CH_3, doublet, J = 5.5 Hz). The analytical sample, bp 55° (bath temperature) at 24 mm, was secured by distillation.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.4; H, 11.3.

***trans*-2,5-Dimethylcycloheptanone (*t*-2b). A. From *trans,cis*-2,5-Dimethylcycloheptanol (26).**—To a solution of 48 mg of alcohol **26** in 5 ml of acetone at 0° was added 5 drops of standard chromic acid reagent.[18] After 5 min, isopropyl alcohol was added to destroy the excess oxidizing agent; the mixture was diluted with water; and the product was isolated with ether[12a] giving 42 mg (89%) of ketone *t*-**2b** which gave a single peak on gas chromatography.[19] The spectral and chromatographic properties of this substance exactly matched those of the thermodynamically favored dimethylcycloheptanone whose isolation is described below.

B. *Via* Ring Expansion of 4-Methylcyclohexanone (1b) with Diazoethane.—By the procedure described above, 10.0 g of 4-methylcyclohexanone (**1b**) was converted into 11.6 g (92%) of a 41:47:12 mixture of ketones *t*-**2b** and c-**2b** and oxide **3b**,[20] bp 77–83° (14 mm). The pure *trans* isomer *t*-**2b**, secured from the above mixture *via* preparative gas chromatography,[16] had the following properties: $n^{25}D$ 1.4534; λ_{max}^{film} 5.88 (CO), 7.48, 8.50, 9.53, 10.84, and 11.3 μ; $\delta_{TMS}^{CCl_4}$ 0.98 ppm (CH_3, doublet, J = 7 Hz).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.1; H, 11.6.

***cis*-2,5-Dimethylcycloheptanone (*c*-2b).**—The sample secured from the ring-expansion reaction mixture *via* preparative gas chromatography[16] had the following properties: $n^{25}D$ 1.4576; λ_{max}^{film} 5.88 (CO), 8.60, 8.82, 9.33, 9.53, 9.68, 9.89, and 11.1 μ; $\delta_{TMS}^{CCl_4}$ 1.00 (CH_3, doublet, J = 7 Hz) and 0.91 ppm (CH_3, doublet, J = 7 Hz).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.0; H, 11.6.

2,6-Dimethyl-1-oxaspiro[2.5]octane (3b).—The sample secured from the ring-expansion reaction mixture *via* preparative gas chromatography[16] had the following properties: $n^{25}D$ 1.4464; λ_{max}^{film} 7.25, 9.65, 10.10, 10.25, 11.30, and 14.80 μ; $\delta_{TMS}^{CCl_4}$ 2.73 (H-2, quartet, J = 6 Hz), 1.22 (CH_3, doublet, J = 6 Hz), and 0.98 ppm (two pairs of unresolved CH_3 doublets). The relative intensities of the latter peaks indicated that this sample was approximately a 1:1 mixture of *t*-**3b** and c-**3b**.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.9; H, 11.5.

Equilibration of *cis*- and *trans*-2,5-Dimethylcycloheptanones (*c*-2b and *t*-2b).—A 1.4-g sample of a 54:46 mixture of ketones *c*-**2b** and *t*-**2b** was heated at reflux for 18 hr in 10 ml of methanol containing 1 ml of *M* aqueous sodium carbonate. The product was isolated with hexane[12a] and distilled affording 1.3 g (92%)

(12) (a) The isolation procedure consisted of diluting the reaction mixture with water or saturated brine, thoroughly extracting the mixture with the specified solvent, washing the combined extracts with saturated brine, and drying the organic phase over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator. (b) Gas chromatography was performed on an F & M Model 700 or 720 instrument using helium as the carrier gas. (c) Microanalyses were performed by Micro-Tech Laboratories, Inc. Skokie, Ill.

(13) F. Arndt, "Organic Syntheses," Coll. Vol II, John Wiley & Sons, Inc., New York N. Y., 1943, p 165.

(14) J. Werner, *J. Chem. Soc.*, 1093 (1919).

(15) Reference 13, p 461.

(16) A 12 ft by 0.5 in. column packed with 16% Carbowax 20M on 60–80 mesh Diatoport S was used for this separation.

(17) O. Wallach, *Ann.*, **346**, 146 (1906).

(18) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(19) A 17 ft by 1/4 in. column packed with 12% Carbowax 20M on 60–80 mesh Chromosorb W was used for this analysis.

(20) A 20 ft by 1/8 in. column packed with 20% Carbowax 20M on 60–80 mesh Chromosorb W was used for this analysis.

of a 29:71 mixture of *c*-**2b** and *t*-**2b**,[20] bp 75–85° (15 mm). The same mixture was obtained when each of the pure ketones was subjected to the equilibration conditions.

Ring Expansion of 4-Isopropylcyclohexanone (1c) with Diazoethane.—By the procedure described above, 9.6 g of 4-isopropylcyclohexanone (**1c**) was converted into 10.6 g (91%) of a 38:44:18 mixture of ketones *t*-**2c** and *c*-**2c** and oxide **3c**,[21] bp 101–110° (15 mm). The *cis* and *trans* ketones could be separated from the oxide, but not from each other, by preparative gas chromatography.

2-Methyl-6-isopropyl-1-oxaspiro[2.5]octane (*t*-3c).—The sample secured from the above ring-expansion reaction mixture *via* preparative gas chromatography[16] had the following properties: $n^{25}D$ 1.4605; λ_{max}^{film} 7.25, 9.65, 9.99, 10.78, 11.25, and 14.81 μ; $\delta_{TMS}^{CCl_4}$ 2.72 (H-2, quartet, J = 6 Hz), 1.21 (CH_3, doublet, J = 6 Hz), and 0.92 ppm [$(CH_3)_2C$, doublet, J = 6 Hz].

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, C, 78.3; H, 12.1.

Equilibration of *cis*- and *trans*-2-Methyl-5-isopropylcyclohexanones (*c*-2c and *t*-2c).—The previously described procedure was applied to 1.7 g of a 54:46 mixture of ketones *c*-**2c** and *t*-**2c**, affording 1.5 g (91%) of a 33:67 mixture[21] of the same ketones, bp 103–110° (15 mm). Those ketones could not be separated by preparative gas or column chromatography and were therefore characterized as the equilibrium mixture: λ_{max}^{film} 5.86 (CO), 7.20, 7.29, 7.48, 8.54, 10.80, and 11.10 μ; $\delta_{TMS}^{CCl_4}$ 1.02 (CH_3, doublet of *c*-**2c**, J = 7 Hz), 0.99 (CH_3, doublet of *t*-**2c**, J = 7 Hz), and 0.88 ppm [$(CH_3)_2C$ doublet, J = 7 Hz].

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.7; H, 12.0.

Ring Expansion of 4-*t*-Butylcyclohexanone (1d) with Diazoethane.—By the procedure described above, 12.0 g of 4-*t*-butylcyclohexanone (**1d**) was converted into 13.0 g (91%) of a 43:43:14 mixture of ketones *t*-**2d** and *c*-**2d** and oxide *t*-**3d**,[21] bp 118–123° (16 mm). The *cis* and *trans* ketones could be separated from the oxide, but not from each other by preparative gas chromatography.

2-Methyl-6-*t*-butyl-1-oxaspiro[2.5]octane (*t*-3d).—The sample secured from the above ring-expansion reaction mixture *via* preparative gas chromatography[16] had the following properties: $n^{25}D$ 1.4639; λ_{max}^{film} 7.30, 9.67, 10.00, 10.78, 11.26, and 14.70 μ; $\delta_{TMS}^{CCl_4}$ 2.73 (H-2, quartet, J = 6 Hz), 1.22 (CH_3, doublet, J = 6 Hz), and 0.89 ppm [$(CH_3)_3C$].

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.2; H, 12.3.

Equilibration of *cis*- and *trans*-2-methyl-5-*t*-Butylcycloheptanones (*c*-2d and *t*-2d).—The previously described procedure was applied to 1.8 g of a 50:50 mixture of ketones *c*-**2d** and *t*-**2d** affording 1.6 g (92%) of a 25:75 mixture[21] of the same ketones, bp 120–124° (17 mm). These ketones could not be separated by preparative gas chromatography or column chromatography and were therefore characterized as the equilibrium mixture: λ_{max}^{film} 5.87 (CO), 7.31, 8.09, 8.53, 9.90, 10.78, and 11.23 μ; $\delta_{TMS}^{CCl_4}$ 1.01 (CH_3, doublet of *c*-**2d**, J = 7 Hz), 0.98 (CH_3, doublet of *t*-**2d**, J = 7 Hz), and 0.88 ppm [$(CH_3)_3C$].

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.2; H, 12.2.

4-(1-Hydroxy-1-methylethyl)cyclohexanone (1e).—A solution of 1.3 g of ethyl 4-hydroxycyclohexanecarboxylate[22] in 50 ml of ether was slowly added to a stirred solution of 50 ml of 1.8 *M* ethereal methyllithium at 0°. The mixture was allowed to reach room temperature, and after 24 hr aqueous ammonium chloride was added slowly. The product was isolated with ethyl acetate,[12a] affording 1.04 g (89%) of a sticky oil that crystallized on standing: λ_{max}^{film} 3.00 (OH), 7.28, 8.68, 9.32, 9.66, 10.33, 10.48, and 10.95 μ.

A 402-mg sample of the above diol in 25 ml of acetone was treated at 0° with 1.0 ml of standard chromic acid reagent.[18] Isopropyl alcohol was added after 5 min, and the product was isolated with ether[12a] and distilled affording 390 mg (84%) of an oil, bp 72° (bath temperature) at 0.2 mm, that crystallized on standing. The analytical sample, mp 37–38°, was obtained *via* recrystallization from ether–hexane: λ_{max}^{KBr} 2.88 (OH), 5.83 (CO), 8.40, 8.72, 10.56, 10.92, and 11.68 μ; $\delta_{TMS}^{CCl_4}$ 2.25 (OH), and 1.19 ppm [$(CH_3)_2C$-].

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.4; H, 10.2.

Ring Expansion of 4-(1-Hydroxy-1-methylethyl)cyclohexanone (1e) with Diazoethane.—By the procedure described above, 208 mg of hydroxy ketone **1e** was converted into 198 mg (81%) of a 50:50 mixture (nmr analysis—see below) of ketones *t*-**2e** and *c*-**2e**, bp 58° (bath temperature) at 0.05 mm. Only one component was detected by gas chromatography.[19]

Equilibration of *cis*- and *trans*-2-Methyl-5-(1-hydroxy-1-methylethyl)cycloheptanones (*c*-2e and *t*-2e).—The previously described procedure was applied to 88 mg of a 50:50 mixture of ketones *c*-**2e** and *t*-**2e** affording 79 mg (90%) of a 25:75 mixture (by nmr analysis) of the same ketones: bp 60° (bath temperature) at 0.05 mm; λ_{max}^{film} 2.90 (OH), 5.87 (CO), 7.27, 8.57, 8.82, 10.70, and 11.22 μ; $\delta_{TMS}^{CCl_4}$ 2.01 (OH), 1.12 [$(CH_3)_2C$], 1.04 (CH_3, doublet of *c*-**2e**, J = 7 Hz), and 1.01 ppm (CH_3, doublet of *t*-**2e**, J = 7 Hz).

***trans*-2-Methyl-5-(1-hydroxy-1-methylethyl)cycloheptanone (*t*-2e).**—To a stirred solution of 97 mg of diol **1e** in 5 ml of acetone at 0° was added 0.2 ml of standard chromic acid reagent.[18] Isopropyl alcohol was added after 10 min, and the product was isolated with ether.[12a] Distillation afforded 82 mg (85%) of a colorless oil: bp 60° (bath temperature) at 0.05 mm; λ_{max}^{film} 2.90 (OH), 5.88 (CO), 7.27, 8.57, 8.82, 10.72, and 11.20 μ; $\delta_{TMS}^{CCl_4}$ 3.38 (OH), 1.12 [$(CH_3)_2C$-], and 1.01 ppm (CH_3, doublet, J = 7 Hz). The spectra indicated that this hydroxy ketone is identical with the major isomer of the above equilibration experiment. Satisfactory analytical values could not be obtained for this material.

Ethyl 5-Methyl-4-oxocycloheptanecarboxylate (2f).—By the ring-expansion procedure described above, 55.6 g of keto ester **1f** was converted into 58.8 g (91%) of a 1:1 mixture (nmr analysis) of ketones *t*-**2f** and *c*-**2f**, bp 69–72° (0.1 mm). The gas chromatogram indicated the presence of 2% shorter retention time component, conceivably the oxide **3e**. The analytical sample, bp 68–70° (0.05 mm), was secured after three distillations: λ_{max}^{film} 5.78 (ester CO), 5.87 (ketone CO), 7.25, 7.62, 8.01, 8.45, and 9.62 μ; $\delta_{TMS}^{CCl_4}$ 4.10 (OCH_2 quartet, J = 7 Hz), 1.23 (CH_3, triplet, J = 7 Hz), 1.02 (CH_3, doublet, J = 7 Hz, 1.5 H), and 1.00 ppm (CH_3, doublet, J = 7 Hz, 1.5 H). Only one component was detected in the gas chromatogram[23] of this sample.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 67.0; H, 9.2.

***trans*-1-Ethyl-4-*t*-butylcyclohexanol (4). A. From Oxide *t*-3d.**—A solution of 108 mg of oxide *t*-**3d** in 1 ml of ether was added to a stirred suspension of 80 mg of lithium aluminum hydride in 5 ml of ether. After 14 hr, 0.16 ml of water and 0.12 ml of 10% aqueous sodium hydroxide were carefully added, and the mixture was stirred for 1 hr and filtered. Distillation of the filtrate gave 89 mg (82%) of an oil: bp 46° (bath temperature) at 0.1 mm; $n^{25}D$ 1.4675 (lit.[24] $n^{25}D$ 1.4638); λ_{max}^{film} 2.97 (OH), 7.30, 8.35, 9.92, 10.52, and 12.04 μ; $\delta_{TMS}^{CCl_4}$ 1.33 (OH), 0.98 (CH_3, triplet, J = 7 Hz), and 0.82 ppm [$(CH_3)_3C$-]. The gas chromatogram[23] showed a single peak.

B. From 4-*t*-Butylcyclohexanone (5).—A 69:31 mixture of *trans*- and *cis*-1-ethyl-4-*t*-butylcyclohexanols (**4** and **6**) was prepared by the addition of ethylmagnesium bromide to 4-*t*-butylcyclohexanone (**5**) in diethyl ether according to the procedure of Hennion and O'Shea.[24] The major alcohol (**4**) was shown to be identical with the alcohol obtained *via* reduction of oxide *t*-**3d**, as outlined above, by comparison of the ir spectra and the gas chromatographic retention times (peak enhancement).[23]

Attempted Equilibration of Ethyl 5-Methyl-4-oxocycloheptanecarboxylate (2f). Ethyl 3-(3-Methyl-2-oxocyclopentyl)propanoate (7).—A solution of 15 mg of sodium ethoxide and 1.02 g of keto ester **2f** in 10 ml of ethanol was heated at reflux for 5 hr. The product was isolated with ether[12a] and distilled affording 0.80 g (79%) of an oil: bp 80° (bath temperature) at 0.1 mm; λ_{max}^{film} 5.77 (CO), 7.27, 7.58, 8.05, 8.46, and 9.62 μ; $\delta_{TMS}^{CCl_4}$ 4.08 (OCH_2, quartet, J = 7 Hz), 1.23 (CH_3, triplet, J = 7 Hz), and 1.06 ppm (CH_3 doublet, J = 6.5 Hz). The gas chromatogram[23] exhibited a single peak. The 2,4-dinitrophenylhydrazone derivative had mp 120–121° after three recrystallizations from ethanol.

(21) A 40 ft by 1/8 in. column packed with 8% Carbowax 20M on 60 mesh Chromosorb W was used for this analysis.

(22) R. A. Finnegan and P. L. Bachman, *J. Org. Chem.*, **30**, 4145 (1965).

(23) A 15 ft by 1/8 in. column packed with 10% DC-550 oil on 60–80 mesh Chromosorb W was used for this analysis.

(24) G. F. Hennion and F. X. O'Shea, *J. Amer. Chem. Soc.*, **80**, 614 (1958).

Anal. Calcd for $C_{17}H_{22}N_4O_6$: C, 53.96; H, 5.86; N, 14.81. Found: C, 54.1; H, 5.8; N, 14.9.

trans,cis-**5-Iodo-4-hydroxycycloheptanecarboxylic Acid Lactone (8).**—The method of van Tamelen[25] was employed. A solution of 4.9 g of 4-cycloheptenecarboxylic acid[26] in 210 ml of 0.5 *M* sodium bicarbonate was added to a solution of 12.7 g of iodine and 24.9 g of potassium iodide in 75 ml of water. The mixture was allowed to stand in the dark for 12 hr at room temperature, and the product was isolated with ether[12a] affording 9.3 g of yellow solid. Recrystallization from ether–hexane gave 8.3 g (89%) of white elongated prisms: mp 77–78°; λ_{max}^{KBr} 5.73 (CO), 7.22, 7.92, 7.98, 9.42, 9.72, 10.44, 10.68, 13.18, and 14.38 μ; $\delta_{TMS}^{CCl_4}$ 4.91 (H-4, broad doublet, J = 4 Hz), 4.47 (H-5, triplet, J = 8.5 Hz); and 2.78 ppm (H-1, broad unresolved peak). An additional recrystallization afforded the analytical sample, mp 77–78°.

Anal. Calcd for $C_8H_{11}IO_2$: C, 36.11; H, 4.17; I, 47.69. Found: C, 36.1; H, 4.4; I, 47.9.

Methyl 4-Cycloheptenecarboxylate (10).—To 500 ml of 0.28 *M* ethereal diazomethane at −10° was added slowly a solution of 14.4 g of acid 9[26] in 100 ml of ether. The solution was magnetically stirred at 0° for 30 min, and acetic acid was added to destroy the excess diazomethane. Distillation afforded 14.5 g (92%) of oily ester **10**: bp 106–109° (22 mm); $n^{25}D$ 1.4661; λ_{max}^{film} 5.77 (CO), 6.02 (C=C), 8.29, 8.56, and 14.42 μ; $\delta_{TMS}^{CCl_4}$ 5.74 (H-4 and H-5, triplet, J = 3.5 Hz) and 3.61 ppm (CH_3). The gas chromatogram[21] showed a single peak.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.0; H, 9.1

Methyl *cis*-4,5-Oxidocycloheptanecarboxylate (11). A. From Iodo Lactone 8.—To a mixture of 460 mg of sodium hydride and 5.12 g of iodo lactone **8** in 25 ml of 1,2-dimethoxyethane (DME) was added *via* hypodermic syringe 608 mg of dry methanol in 2 ml of DME. The mixture was stirred magnetically for 12 hr, and the product was isolated with ether[12a] and distilled affording 2.76 g (85%) of oily ester **11**: bp 54–56° (0.05 mm); $n^{25}D$ 1.4702; λ_{max}^{film} 5.78 (CO), 7.52, 7.82, 8.12, 8.52, 9.53, 10.52, 11.64, 12.97, and 13.70 μ. The gas chromatogram showed a single peak.[27]

B. From Unsaturated Ester 10.—A solution of 4.3 g of 80% *m*-chloroperoxybenzoic acid and 1.98 g of methyl 4-cycloheptenecarboxylate (**10**) in 80 ml of benzene was stirred in the dark for 5 hr. An equal volume of ethyl acetate was added, and the solution was washed successively with 10% aqueous sodium hydroxide, water, and saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was distilled affording 2.02 g (92%) of a 47:53 mixture[27] of the *cis*- and *trans*-oxido esters **11** and **12**. The major isomer, isolated by preparative gas chromatography,[28] was identical with the authentic *cis*-oxido ester **11** prepared in A.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.3; H, 8.3.

Methyl *trans*-4,5-Oxidocycloheptanecarboxylate (12).—The minor component of the oxido ester mixture described above, isolated by preparative gas chromatography,[28] displayed the following properties: bp 58° (bath temperature) at 0.1 mm; $n^{25}D$ 1.4697; λ_{max}^{film} 5.78 (CO), 8.30, 8.57, 9.30, 9.54, 10.60, 10.68, and 12.25 μ.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.2; H, 8.1.

Equilibration of Methyl *cis*- and *trans*-4,5-Oxidocycloheptanecarboxylates (11 and 12).—A solution containing 105 mg of the *cis*-oxido ester **11** and 20 mg of sodium methoxide in 5 ml of methanol was stirred at reflux for 18 hr. The base was neutralized with acetic acid, and the product was isolated with ether[12a] affording 96 mg (92%) of a 62:38 mixture[27] of the *cis* and *trans* isomers **11** and **12**.

A 115-mg sample of the *trans*-oxido ester **12** was converted in the same manner into 103 mg (90%) of an identical mixture of isomers **11** and **12**.

cis-**4-(1-Hydroxy-1-methylethyl)-1-(1-hydroxyethyl)cyclohexane (13).**—A mixture containing 525 mg of *cis*-oxido ester **11** in 4 ml of tetrahydrofuran (THF) and 25 ml of 3 *M* methylmagnesium chloride in THF was heated at reflux for 48 hr. Aqueous ammonium chloride was added, and the product was isolated with ether[12a] affording 571 mg of solid material. Recrystallization from ethyl acetate–heptane yielded 478 mg (84%) of diol **13** as white platelets: mp 120–122°; λ_{max}^{KBr} 3.02 (OH), 7.22, 7.29 8.78, 8.98, 9.24, 9.36, 10.58, and 10.76 μ; $\delta_{TMS}^{CDCl_3}$ 3.54 [–CH(OH)–, broad peak], 1.38 (OH), 1.15 [$(CH_3)_2COH$], and 1.14 ppm (CH_3, doublet, J = 6.5 Hz). The analytical sample, mp 122–123°, was secured after two additional recrystallizations.

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.8; H, 11.7.

The same product was obtained in high yield when the above procedure was repeated with methylmagnesium bromide.

cis-**5-(1-Hydroxy-1-methylethyl)-*trans*-2-methylcycloheptanol (14).**—The method of Christensen, *et al.*,[10] was employed. A mixture of 75 ml of 0.5 *M* dimethylmagnesium in dioxane and 600 mg of *cis*-oxido ester **11** in 5 ml of dioxane was heated at reflux for 48 hr. Aqueous ammonium chloride was added, and the product was isolated with ether[12a] affording 520 mg (80%) of crystalline diol **14**: λ_{max}^{KBr} 2.98 (OH), 7.30, 8.81, 9.70, 9.80, 10.83, and 11.24 μ; $\delta_{TMS}^{CDCl_3}$ 3.37 [–CH(OH)–, broad peak], 1.72 (OH), 1.15 [$(CH_3)_2COH$], and 1.04 ppm (CH_3, doublet, J = 5.5 Hz). The analytical sample, mp 87–88°, was secured after one recrystallization from benzene followed by sublimation.

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.9; H, 11.6.

exo-**3,3-Dimethyl-2-oxabicyclo[3.2.2]nonan-7-ol (15).**—The above procedure, based on the method of Christensen, *et al.*,[10] was employed with 367 mg of *trans*-oxido ester **12** and 50 ml of 0.5 *M* dimethylmagnesium, whereupon 307 mg (83%) of alcohol **15**, a viscous oil, bp 77° (bath temperature) at 0.05 mm, was obtained: λ_{max}^{film} 2.96 (OH), 8.97, 9.28, 9.56, 10.00, 10.23, 11.60, and 11.94 μ; $\delta_{TMS}^{CDCl_3}$ 3.70 (H-1 and H-7, broad peak), 2.60 (OH), 1.28 (CH_3, singlet), and 1.18 ppm (CH_3, singlet).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.4; H, 10.6.

trans-**4-(1-Hydroxy-1-methylethyl)-1-acetylcyclohexane (16).**—To a solution of 133 mg of diol **13** in 10 ml of acetone at 0° was added, with efficient swirling, 0.25 ml of chromic acid reagent.[18] After 10 min, the excess oxidizing agent was destroyed with isopropyl alcohol, and the product was isolated with ether[12a] affording 126 mg (96%) of crystalline keto alcohol **16**. Recrystallization from ether–hexane gave 98 mg of white prisms: mp 77–78°; $\lambda_{max}^{CCl_4}$ 2.90 (OH), 5.83 (CO), 7.29, 7.38, 8.02, 8.42, 8.68, and 10.92 μ; $\delta_{TMS}^{CCl_4}$ 2.04 (CH_3CO–), 1.34 (OH), and 1.11 ppm [$(CH_3)_2COH$]. The analytical sample, mp 77–78°, was secured *via* sublimation.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.6; H, 10.8.

A 97-mg sample of ketone **16**, after treatment with 1 ml of *M* aqueous sodium carbonate in 4 ml of methanol at reflux for 18 hr, afforded 48 mg (50%) of recovered crystalline ketone **16**, mp 75–77°, and 28 mg (29%) of an oily residue whose spectral properties closely resembled those of the starting *trans* ketone **16**.

5-(Hydroxymethyl)cycloheptene (17).—A mixture containing 1.60 g of lithium aluminum hydride and 6.5 g of ester **10** in 100 ml of ether was stirred at room temperature for 12 hr. After treatment with 3.2 ml of water and 2.6 ml of 10% aqueous sodium hydroxide, the mixture was stirred for several hours, filtered, and distilled affording 5.0 g (94%) of alcohol **17**: bp 102–105° (20 mm); λ_{max}^{film} 3.02 (OH), 6.02 (C=C), 9.20, 9.33, 9.53, 9.63, 9.88, and 14.20 μ; $\delta_{TMS}^{CCl_4}$ 5.74 (vinylic H, triplet, J = 3.5 Hz), 3.54 (OH), and 3.34 ppm (CH_2, doublet, J = 5.5 Hz). The gas chromatogram[29] displayed two peaks of comparable retention time in the ratio 93:7, favoring the desired alcohol **17**. The *p*-bromobenzenesulfonate derivative, mp 39.5–40° (lit.[30] mp 55–56°), was prepared for analysis.

Anal. Calcd for $C_{14}H_{17}BrO_3S$: C, 48.70; H, 4.96; Br, 23.14; S, 9.29. Found: C, 48.5; H, 4.9; Br, 23.0; S, 9.2.

exo-**2-Oxabicyclo[3.2.2]nonan-7-ol (18) and *cis*-1-Hydroxymethyl-4,5-oxidocycloheptane (19).**—To a stirred, chilled (10°) solution containing 15.9 g of 80% *m*-chloroperoxybenzoic acid in 125 ml of benzene was added 4.64 g of unsaturated alcohol **17** in 25 ml of benzene. After 4 hr at room temperature, the solution was diluted with an equal volume of ethyl acetate, washed

(25) E. E. van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, **76**, 2315 (1954).

(26) G. Stork and H. K. Landesman, *ibid.*, **78**, 5129 (1965).

(27) A 17 ft by 1/4 in. column packed with 12% Carbowax 20M on 60–80 mesh Chromosorb W was used for this analysis.

(28) A 15 ft by 1/2 in. column packed with 8% FFAP on 60–70 mesh Chromosorb G was used for this separation.

(29) A 20 ft by 1/4 in. column packed with 4% FFAP on 70–80 mesh AW-DMCS Chromosorb G was employed for this analysis.

(30) G. Le Ny, *Compt. Rend.*, **251**, 1526 (1960).

with 10% aqueous sodium hydroxide, dried over anhydrous magnesium sulfate, and distilled affording 4.76 g (91%) of a 35:65 mixture[28] of alcohols **18** and **19**. The minor alcohol (**18**) was secured *via* preparative gas chromatography[28] or column elution chromatography on silica gel. A sample secured *via* gas chromatography exhibited the following properties: mp 132–138° from hexane; λ_{max}^{KBr} 2.94 (OH), 8.26, 8.82, 9.48, 9.67, 9.98, 11.35, and 11.67 μ. The acetate derivative, bp 94° (bath temperature) at 18 mm, was prepared for combustion analysis.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.9; H, 8.6.

The major alcohol (**19**) of the above mixture decomposed during attempted chromatographic purifications.

cis-**5-Hydroxymethyl-*trans*-2-methylcycloheptanol** (**20**).—A 4.03-g sample of the above 35:65 mixture of alcohols **18** and **19** in 5 ml of dioxane was refluxed with 250 ml of 0.5 *M* dimethylmagnesium[10] in dioxane for 36 hr. Aqueous ammonium chloride was added, and the product was isolated with ethyl acetate and distilled affording 3.25 g of an oil. A 440-mg sample was chromatographed on deactivated alumina.[31] The unchanged bicyclic alcohol **18** (126 mg) was eluted with 50% ether–benzene. Elution with ether afforded 250 mg of diol **20**: λ_{max}^{film} 3.00 (OH), 9.12, 9.47, and 11.30 μ; $\delta_{TMS}^{CDCl_3}$ 3.41 (CH_2OH, broad peak), 3.33 (H-1, broad peak), 2.51 (OH), and 1.04 ppm (CH_3, doublet, J = 6 Hz).

The diacetate derivative, bp 66° (bath temperature) at 0.1 mm, was prepared for analysis.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.4; H, 9.2.

exo-**2-Oxabicyclo[3.2.2]nonan-7-yl Acetate** (**18**, Y = OAc) **and** *cis*-**5-Acetoxymethyl-*trans*-2-methylcycloheptyl Acetate** (**21**).—A 610-mg sample of the *ca.* 1:2 mixture of alcohols **18** and **20**, prepared in the experiment described above, was allowed to stand with 1.25 g of acetic anhydride in 10 ml of pyridine at room temperature for 24 hr. The product was isolated with ether[12a] affording 840 mg of an oil shown by gas chromatography to be a 30:70 mixture of acetates **18** (Y = OAc) and **21**. This mixture was chromatographed on silica gel. The diacetate **21** was eluted with 5% ether in benzene and distilled affording 450 mg of oil: bp 66° (bath temperature) at 0.1 mm; λ_{max}^{film} 5.74–5.76 (CO), 7.28, 8.02, 9.72, and 10.16 μ; $\delta_{TMS}^{CCl_4}$ 4.54 (H-1, broad peak), 3.81 (CH_2OAc, doublet, J = 5.5 Hz) 1.93 (CH_3CO), and 0.92 ppm (CH_3, doublet, J = 6.5 Hz). This material was identical with the acetate derivative prepared from a purified sample of diol **20**.

Acetate **18** (Y = OAc) was eluted from the aforementioned column with 10% ether in benzene and distilled giving 155 mg of an oil: bp 94° (bath temperature) at 18 mm; λ_{max}^{film} 5.74 (CO), 7.28, 8.03, 8.26, 8.78, 9.28, 9.58, 9.68, 10.17, and 11.46 μ; $\delta_{TMS}^{CCl_4}$ 4.80 (H-7, broad peak), 3.92, (H-1, broad peak), 3.70 (H-3, doublet, J = 5 Hz), and 1.93 ppm (CH_3CO). This material was identical with the acetate derivative prepared from a purified sample of alcohol **18**.

cis-**5-Hydroxymethyl-*trans*-2-methylcycloheptyl Acetate** (**22**).—A solution containing 650 mg of diacetate **21** in 85 ml of ethanol and 27 ml of 0.1 *M* aqueous sodium hydroxide was stirred at room temperature for 14 hr. The product was isolated with ether and distilled affording 496 mg (93%) of hydroxy acetate **22**: bp 88° (bath temperature) at 0.1 mm; λ_{max}^{film} 2.92 (OH), 5.77, 5.81 (split CO), 7.26, 8.00, 9.74, and 10.12 μ; $\lambda_{max}^{CCl_4}$ 5.77 μ (CO); $\delta_{TMS}^{CCl_4}$ 4.50 (H-1, broad peak), 3.31 (CH_2OH, broad peak), 3.24 (OH), 1.97 (CH_3CO), and 0.93 ppm (CH_3, doublet, J = 6 Hz). The analytical sample was secured after two additional distillations.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.9; H, 10.2.

(31) The deactivated alumina was prepared by stirring 1 kg of Fisher alumina with 1 l. of benzene 10 g of pyridine, and 20 g of water for 1 hr.

cis-**5-(2-Thiahexyl)-*trans*-2-methylcycloheptyl Acetate** (**24**).—A stirred solution of 384 mg of hydroxy acetate **22** in 8 ml of pyridine was cooled to 0°, and 242 mg of methanesulfonyl chloride was carefully added. After 2 hr at 0°, the mixture was poured onto crushed ice, and the product was isolated with ether,[12a] after the pyridine had been removed *via* thorough washing with 2% aqueous sulfuric acid, affording 498 mg (93%) of oily mesylate **23**: λ_{max}^{film} 5.78 (CO), 7.38, 8.00, 8.49, 9.73, 10.2–10.8, and 11.8–12.2 μ.

To a mixture derived from 85 mg of sodium hydride and 324 mg of butanethiol in 20 ml of tetrahydrofuran (THF) was added 498 mg of mesylate **23** in 5 ml of THF. The resulting mixture was heated at reflux for 12 hr, and the product was isolated with ether[12a] affording 388 mg (80%) of oily sulfide **24**: bp 96° (bath temperature) at 0.1 mm; λ_{max}^{film} 5.76 (CO), 7.26, 8.00, 9.72, 10.16, and 10.30 μ; $\delta_{TMS}^{CCl_4}$ 4.53 (H-1, broad peak), 2.42 ($-SCH_2$, broad triplet), 2.35 ($-SCH_2$, doublet, J = 6.5 Hz), 1.94 (CH_3CO), 0.98 (CH_3, triplet, J = 4 Hz), and 0.90 ppm (CH_3, doublet, J = 5 Hz). The analytical sample was secured after an additional distillation.

Anal. Calcd for $C_{15}H_{28}O_2S$: C, 66.13; H, 10.36; S, 11.77. Found: C, 66.1; H, 10.5; S, 12.0.

trans, *cis*-**2,5-Dimethylcycloheptyl Acetate** (**25**).—A mixture containing 258 mg of the sulfide **24** and 6 g of W-2 Raney nickel in 100 ml of ethanol was heated at reflux for 2 hr. The cooled mixture was filtered, and the product was isolated with ether[12a] and distilled affording 133 mg (76%) of acetate **25**: bp 82° (bath temperature) at 16 mm: λ_{max}^{film} 5.75 (CO), 7.26, 8.00, 9.77, 10.05, and 10.27 μ; $\delta_{TMS}^{CCl_4}$ 4.53 (H-1, broad peak), 1.94 (CH_3CO), and 0.92 ppm (CH_3, doublet, J = 6 Hz). The analytical sample was secured after an additional distillation.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.6; H, 10.8.

trans,*cis*-**2,5-Dimethylcycloheptanol** (**26**).—To a stirred suspension of 40 mg of lithium aluminum hydride in 3 ml of ether was added 97 mg of acetate **25** in 2 ml of ether. After 4 hr, 0.08 ml of water and 0.07 ml of 10% aqueous sodium hydroxide was added, and the mixture was stirred for several hours, filtered, and distilled, affording 62 mg (83%) of alcohol **26**: bp 65° (bath temperature) at 16 mm: λ_{max}^{film} 2.97 (OH), 7.23, 9.58, 9.70, and 9.90 μ; $\delta_{TMS}^{CCl_4}$ 3.29 (H-1, broad peak), 2.01 (OH), and 0.99 ppm (CH_3, doublet, J = 6 Hz).

Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 75.8; H, 12.6.

Registry No.—**1e**, 17328-67-5; **2a**, 932-56-9; *t*-**2b**, 17328-68-6; *c*-**2b**, 17328-69-7; **2c**, 17328-98-2; **2d**, 17328-70-0; *c*-**2e**, 17328-71-1; *t*-**2e**, 17477-88-2; **2f**, 17328-73-3; **3a**, 17328-74-4; **3b**, 17328-75-5; *t*-**3c**, 17328-76-6; *t*-**3d**, 17328-77-7; **4**, 17328-78-8; **7**, 17328-79-9; **7** 2,4-dinitrophenylhydrazene derivative, 17328-80-2; **8**, 17328-99-3; **10**, 17328-81-3; **11**, 17328-82-4; **12**, 17329-00-9; **13**, 17328-83-5; **14**, 17328-84-6; **15**, 17328-85-7; **16**, 17328-86-8; **17**, 17328-87-9; **18**, 17328-88-0; **18** (Y = OAc), 17328-89-1; **19**, 17328-90-4; **19** acetate, 17329-01-0; **20**, 17328-91-5; **21**, 17328-92-6; **22**, 17328-93-7; **23**, 17328-94-8; **24**, 17328-95-9; **25**, 17328-96-0; **26**, 17328-97-1.

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The Stereochemistry of the Oxidation of Oximes to Nitrocycloalkanes with Peroxytrifluoroacetic Acid. Protonation of Nitronic Acid Derivatives in Cyclohexane Systems[1a]

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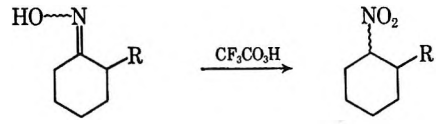
A series of 2-substituted cyclohexanone oximes has been shown to give predominantly *cis*-2-substituted nitrocyclohexanes upon peroxytrifluoroacetic acid oxidation. Analysis, by nmr spectroscopy, of 2-phenylnitrocyclohexane and methyl 2-nitrocyclohexaneacetate obtained from the appropriate oximes showed that the *cis* product predominated in both reactions. The extent of *cis* isomer was >95% in the former case and about 77% in the latter. Gas chromatographic and nmr analyses have shown that oxidation of 2-methylcyclohexanone oxime gives a mixture of *cis*- and *trans*-2-methylnitrocyclohexanes containing 80% *cis* isomer. The isomeric mixture of *cis*- and *trans*-ethyl 2-nitrocyclohexanepropionates from the appropriate oxime was shown to consist of about 85% *cis* isomer by converting the nitro ester mixture into a mixture of *cis*- and *trans*-decahydroquinolines which could be analyzed by glpc. Oxidation of norcamphor oxime gave mainly *endo*-2-nitronorbornane. The results are discussed in terms of the stereochemistry of protonation of nitronic acids and nitronate anions.

The oxidation of oximes with peroxytrifluoroacetic acid[2] is one of the general methods for synthesis of nitroalkanes.[3] We were interested in the stereochemistry of this reaction in connection with the synthesis of functionally substituted nitroalkanes. The steric outcome of the reaction is also of interest in connection with stereoselective synthesis of amines since it is possible to reduce nitroalkanes to amines with retention of configuration.[4] While little is known about the stereochemistry of per-acid oxidation of oximes to nitro compounds, some information is available for two other general procedures for converting oximes into nitroalkanes as the result of syntheses of nitro steroids. The Iffland procedure[5] involving bromination of the oxime, oxidation, and sodium borohydride reduction of the resulting α-bromonitroalkane gives 17β-nitro[6] and 3β-nitro steroids[7] from the appropriate oximino steroids. Nitric acid oxidation of steroidal oximes to *gem*-dinitro derivatives followed by catalytic reduction gives 4β-, 6β-, 7α-, and 17β-mononitro steroids. In each case the less hindered nitro group is selectively removed. Mixtures of 3α-nitro- and 3β-nitro-5α-cholestanes were obtained when this procedure was applied to 3-oximinocholestane.[8]

Results

We have investigated the stereochemistry of the oxidation of the 2-substituted cyclohexanone oximes **1a–d** and norcamphor oxime (**8**) to the corresponding nitro compounds. For nitro compounds **2a–c** and **3a–c** it was possible to determine the relative amounts of the isomers by nmr analysis. The crude reaction mixtures were purified by absorption chromatography on silicic acid and then were analyzed directly. Control experiments with *cis*- and *trans*-1-methyl-2-nitrocyclohexanes showed that the isomer ratio was unchanged by silicic acid chromatography.



1a, R = C_6H_5
b, R = CH_3
c, R = $CH_2CO_2CH_3$
d, R = $CH_2CH_2CO_2C_2H_5$

cis **2a–d** *trans* **3a–d**

cis- and *trans*-1-nitro-2-phenylcyclohexanes (**2a** and **3a**) have been well characterized,[9] and authentic samples were prepared. Comparison of the nmr spectrum of the mixture of **2a** and **3a** obtained by oxidation of the oxime **1a** showed that the product was at least 95% *cis* isomer **2a**. The triplet of doublets at 4.68 ppm characteristic of the axial C-1 proton in **3a** was not detectable.

The isomeric 2-methylnitrocyclohexanes (**2b** and **3b**) from oxidation of 2-methylcyclohexanone oxime were separated by preparative gas chromatography. The nmr spectrum of the major isomer shows a quintet assigned to the proton on C-1 at 4.52 ppm ($W_{1/2}$ = 15 Hz). The minor isomer shows a broader signal at 4.06 ppm. The major isomer was assigned the *cis* structure **2b** on the basis of the downfield position and narrower band width of the proton adjacent to the nitro group, relative to the corresponding signal in the minor isomer.[10,11] This assignment was confirmed by using sodium bicarbonate to isomerize[9,12] a sample of the major isomer **2b** to a mixture containing 92% the thermodynamically more stable isomer **3b** and 8% **2b** (glpc analysis). Analysis of the product obtained by oxidation of **1b** gave average values of 81 ± 4% **2b** by nmr analysis and 83 ± 1% **2b** by glpc analysis.

Oxidation of methyl 2-hydroxyiminocyclohexane acetate (**1c**) gave a 39% yield of a mixture of the nitro

(1) (a) This work was supported in part by funds from an Institutional Grant to the University of Virginia by the National Science Foundation. (b) NDEA Fellow, 1965–1968.

(2) W. D. Emmons and A. S. Pagano, *J. Amer. Chem. Soc.*, **77**, 4557 (1955).

(3) N. Kornblum, *Org. Reactions*, **12**, 101 (1962).

(4) F. G. Bordwell and R. L. Arnold, *J. Org. Chem.*, **27**, 4426 (1962); A. J. Nielsen, *ibid.*, **27**, 1998 (1962).

(5) D. C. Iffland, G. X. Criner, M. Koral, F. J. Lotspeich, Z. B. Papanastassiou, and S. M. White, Jr., *J. Amer. Chem. Soc.*, **75**, 4044 (1953); D. C. Iffland and G. X. Criner, *ibid.*, **75**, 4047 (1953); D. C. Iffland and T.-F. Yen, *ibid.*, **76**, 4083 (1954).

(6) A. A. Patchett, F. Hoffman, F. F. Giarrusso, H. Schwam, and G. A. Arth, *J. Org. Chem.*, **27**, 3822 (1962).

(7) M. E. Wolff and R. G. Boguslaski, *J. Med. Chem.*, **11**, 285 (1968).

(8) J. R. Bull, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2601 (1965).

(9) H. E. Zimmerman and T. E. Nevins, *J. Amer. Chem. Soc.*, **79**, 6559 (1957).

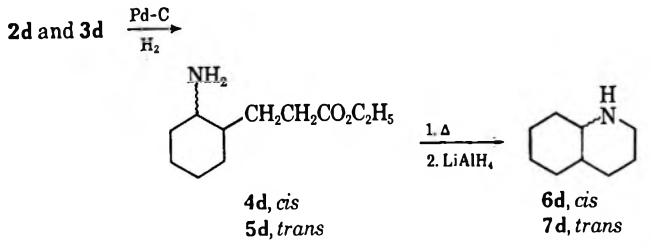
(10) W. Trager, F. F. Vincenzi, and A. C. Huitric, *J. Org. Chem.*, **27**, 3006 (1962).

(11) H. Feltkamp, N. C. Franklin, F. Koch, and T. N. Thanh, *Ann.*, **707**, 87 (1967).

(12) E. H. Massey, H. E. Smith, and A. W. Gordon, *J. Org. Chem.*, **31**, 684 (1966).

esters **2c** and **3c** after separation, by absorption chromatography, from the methyl 2-oxocyclohexaneacetate formed as a by-product. Two multiplets were visible in the nmr spectrum in the region expected for protons geminal to a nitro group. On amplification of the spectrum the higher field multiplet revealed the sextet structure expected for an axial proton. The shape of the lower field multiplet was typical of those found for compounds in the *cis* series and accounted for 76–78% of the area under the two signals. Epimerization with sodium bicarbonate reversed the relative intensity of the two signals. In the isomerized sample 82% of the area was under the higher field multiplet. Thus, the oxidation product consisted mostly (about 77%) of the thermodynamically less stable *cis* isomer **2c**.

A 49% yield of **2d** and **3d** was obtained by oxidation of **1d**. A multiplet having the characteristics of the equatorial proton of the *cis* series appears at 4.6 ppm, but precise nmr analysis of the mixture was precluded by the fact that the higher field multiplet of the *trans* isomer was partially obscured by the methylene quartet of the ethoxy group. The low-field multiplet corresponded to about 70% of the area expected for the pure *cis* isomer suggesting that **2d** must be the major component of the mixture. Confirmation of this conclusion was obtained by catalytically reducing the mixture to **4d** and **5d** under conditions expected to maintain the stereochemistry of the C–N bond.[4] Lactamization of the **4d–5d** mixture, followed by lithium aluminum hydride reduction, gave an over-all 61% yield of a mixture of *cis*- and *trans*-decahydroquinolines (**6d** and **7d**). Compounds **6d** and **7d** were isolated by preparative glpc. The mixture **6d–7d** was 85 ± 4% *cis* isomer (glpc analysis) supporting the conclusion that **2d** is the major component of the original nitro ester mixture. Isomerization of the **2d–3d** mixture, obtained by oxidation, with ethanolic sodium bicarbonate gave a sample containing about 75% **3d**.



Oxidation of norbornanone oxime provided a sample of 2-nitronorbornane (**9**, 31% yield) which showed melting point behavior similar to that of a previously described[13] sample of *endo*-2-nitro-3-^{14}C-norbornane. The nmr spectrum corresponded closely to that reported by Fraser[14] showing, in particular, a quintet at 4.84 ppm (lit.[14] 4.73 ppm) assigned[14] to an *exo* proton at C-2. Amplification of the signal reveals a multiplet at 4.39 ppm which becomes the major signal in the 4.0–5.0-ppm region after isomerization[13] of the sample to predominantly *exo*-2-nitronorbornane. Integration of the H-2 signals in three spectra by planimetry gave a value of 86 ± 4% for the percentage of *endo* isomer in the oxidation product. The stereochemical data and the pertinent nmr data are recorded in Tables I and II, respectively. Literature data on the oxidation of 4-*t*-butylcyclohexanone oxime[15] (**10**) is also included.

(13) J. D. Roberts, C. C. Lee, and W. H. Saunders, *J. Amer. Chem. Soc.*, **76**, 4501 (1954).

(14) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

TABLE I

STEREOCHEMISTRY OF OXIDATION

Compound	% yield	% *cis* (*endo*)[a]	% *trans* (*exo*)[a]	Analysis[b]
1a	38	>95	<5	Nmr
1b	24	81 ± 4	19 ± 4	Nmr
		83 ± 1	17 ± 1	Glpc
1c	39	77 ± 1	23 ± 1	Nmr
1d	49	>70	<30	Nmr
		85 ± 4	15 ± 4	*c*
8	31	86 ± 4	14 ± 4	Nmr
10	33[d]	31[d]	69[d]	Glpc[d]

[a] Except for **1a** the values quoted are the average values for two or three runs. [b] The estimated maximum relative error in determination of the per cent of the major isomer by nmr is ±5%. [c] Chemical transformation to **6d–7d** followed by glpc analysis. [d] Reference 15.

TABLE II

NMR DATA FOR $HCNO_2$

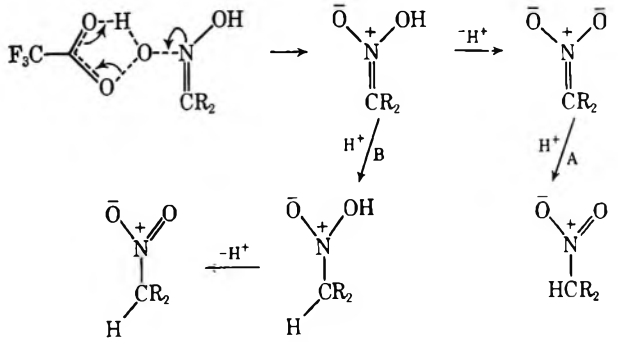
Compound	Chemical shift, ppm	$W_{1/2}$, Hz	J_{ee}, Hz	J_{ua}, Hz	J_{ae}, Hz	J_{ea}, Hz
2a	4.90	9.0		*a*	*a*	
3a	4.68	28.0		10.7	3.8	
2b	4.52	15.0		*a*	*a*	
3b	4.06	*b*		11.2	4.0	
2c	4.71	11.5	2.1			4.5
3c	4.36	22.5		11.0	4.0	
2d	4.6	12.5		*a*	*a*	
3d	4.2	*c*		*c*	4.5	

[a] Resolution is insufficient for first-order analysis. [b] The signal has the triplet of doublets structure characteristic of the *trans* series. The splitting between the outer doublets is about 22 Hz. [c] Obscured by O–CH_2CH_3.

Attempts to oxidize camphor oxime to 2-nitrobornane gave insufficient amounts of the desired nitro compound for adequate characterization. The peroxytrifluoroacetic oxidation of oximes is known to fail in highly hindered systems.[2]

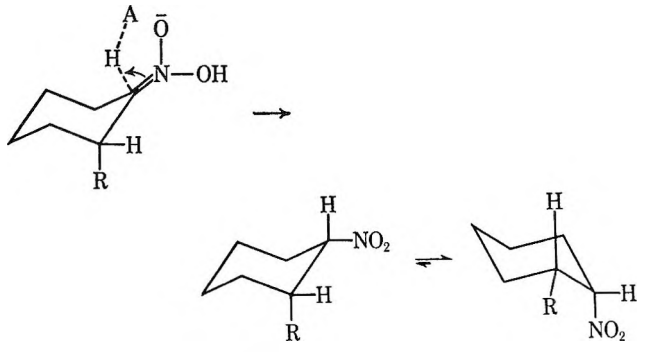
Discussion

Emmons[2] represented the oxidation of oximes as occurring *via* the nitronic acid tautomer. Two slightly different sequences can be considered for subsequent proton transfers. The nitronate anion might be formed and undergo C protonation (process A) or the final step might involve C protonation on a nitronic acid intermediate (process B). The generation of



(15) A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962).

ketones as important by-products during the Emmons–Pagano oxidation seems to be quite general.[2,15] This observation implicates nitronate anions or nitronic acids as intermediates since they could give rise to the observed ketones *via* Nef reactions.[16] In either protonation process the stereochemistry of the reaction is determined by a proton transfer to an sp^2 carbon atom. The data of Huitric[15] concerning the oxidation of 4-*t*-butylcyclohexanone oxime shows that, in the absence of a substituent on C-2, there is a slight preference (3:1) for axial protonation giving the more stable *trans*-4-*t*-butylnitrocyclohexane. In the 2-substituted compounds **1a–d** there is, in contrast, a preference, ranging from ~4:1 to >19:1, for introduction of the proton such that its final conformation is equatorial, generating *cis* products. Our data clearly show that the oxidation products are the result of kinetic and not thermodynamic control. The discussions of Johnson and Malhotra[17] and of Bordwell and Vestling[18] on the C protonation of nitronates and nitronic acids are of direct interest. Malhotra and Johnson[17] conclude that the stable conformations of nitronic acids and nitronate anions in the cyclohexane system will have 2 substituents in the axial position if the substituent is large enough to give rise to nonbonded interaction with the nitronate group. They then anticipate protonation of the nitronate from the least hindered side of the molecule, *trans* to the 2 substituent, generating the *cis* product. Their theory explains our data satisfactorily.



Bordwell and Vestling[18] discuss this problem further in connection with their observation that *cis*-*p*-chlorophenylnitrocyclohexane undergoes proton loss about 200 times faster than the *trans* isomer. They attribute the rate retardation in the *trans* isomer to deformation of the cyclohexane ring resulting from the aryl and nitro groups bending away from one another. They suggest that in this deformed conformation the equatorial aryl group shields the axial proton more effectively from the abstracting base. They conclude, in agreement with Malhotra and Johnson,[17] that the 2-aryl substituent is in an axial position in the transition state for protonation. We suggest that, if the conclusion of Malhotra and Johnson[17] about the conformation of the nitronate anion of 2-phenylnitrocyclohexane is correct, then $A^{(1,3)}$ strain will result in resistance to proton abstraction from 2-arylnitrocyclohexanes having equatorial aryl groups. Proton abstraction from 2-arylnitrocyclohexanes may take place instead from conformations in which the aryl group occupies an axial or nearly axial position. The attainment of such a conformation would be more difficult in the *trans* system than in the *cis* since there would be two axial or nearly axial substituents in the *trans* case. This conformational effect offers an alternative explanation of the low rate of proton abstraction in the *trans* series. Malhotra and Johnson[17] have advanced an analogous explanation for the resistance of *trans*-2-phenylcyclohexyl phenyl ketone toward bromination.

The formation of *endo*-2-nitronorbornane from norbornanone oxime is also readily explained as a steric preference for proton delivery to the least hindered side of the nitronic acid or nitronate anion intermediate.

(16) W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

(17) F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, **87**, 5492 (1965); S. K. Malhotra and F. J. Johnson, *ibid.*, **87**, 5493 (1965); F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(18) F. G. Bordwell and M. M. Vestling, *ibid.*, **89**, 3906 (1967).

Experimental Section

Except for compound 9 the nmr analyses of the products were carried out on a Varian HA-100 instrument using dilute deuteriochloroform solutions containing about 5% tetramethylsilane. A Varian A-60 instrument was used in the case of compound 9. Glpc analyses were carried out on an Aerograph A90-P3 instrument. Absorption chromatography was carried out using 100 mesh silicic acid, redistilled hexane, reagent grade chloroform, and anhydrous reagent grade ether. Melting points were obtained on a calibrated Fisher-Johns apparatus. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

General Oxidation Procedure.—A mixture of 10 mmol of oxime, 0.2 g (3 mmol) of urea, 7.8 g (54 mmol) of disodium hydrogen phosphate,[19] and 20–25 ml of acetonitrile was stirred mechanically and heated to gentle reflux. A solution of peroxytrifluoroacetic acid was prepared by adding, dropwise during 10 min, trifluoroacetic anhydride (3.4 ml, 24 mmol) to a solution of 90% hydrogen peroxide (0.55 ml, 20 mmol) and acetonitrile (6 ml) chilled in an ice bath. *Extreme caution should be used in handling 90% hydrogen peroxide and the oxidizing solution.* The peroxytrifluoroacetic acid solution was then added dropwise over 1 hr to the stirred, heated oxime mixture. In most cases, the mixture turned blue or green as the oxidizing solution was added but became yellow by the time addition was complete. The reaction mixture was stirred at reflux for 1 hr after addition of peroxytrifluoroacetic acid was complete. The mixture was then centrifuged, and the yellow supernatant liquid was decanted and concentrated *in vacuo*. The residue was treated with water (15 ml) and then extracted with 3 portions (15 ml each) of methylene chloride. The combined organic extracts were washed with 5% aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated.

1-Nitro-2-phenylcyclohexanes (2a and 3a).—The crude product obtained by the standard oxidation procedure was a yellow-green oil (1.61 g). A portion of the oil (0.75 g) in chloroform (8 ml) was placed on a silicic acid column (1.3 × 52 cm, 25 g) packed using 10% chloroform in hexane. The column was eluted with hexane solutions containing increasing amounts of chloroform ranging from 10 to 25% (total 2 l.), and then with methanol. Fractions of 20-ml were collected. Like fractions were combined on the basis of tlc comparison. Evaporation of fractions 36–92 gave **2a–3a** (0.36 g, 38%): ir (KBr) 1725 (C=O, weak) and 1550 cm^{-1} (NO_2); nmr δ 4.89. At maximum spectrum amplitude there was no signal detectable at δ 4.68 (authentic **3a**, nmr δ 4.68). Fractions 99–103 afforded 0.11 g (13%) of oily solid shown to be 2-phenylcyclohexanone. No other fractions showed nitro absorptions in the ir spectrum. Total recovery from the column was 95%).

1-Methyl-2-nitrocyclohexanes (2b and 3b).—The yellow oil (0.99 g) obtained by the general oxidation procedure was subjected to absorption chromatography on a 1.3 × 53 cm silicic acid (25 g) column packed in 10% chloroform in hexane. Elution with 10% chloroform–hexane gave fractions 1–39 shown by tlc to contain nitro compounds **2b–3b** (24% yield). Glpc analysis

(19) The disodium hydrogen phosphate was prepared by grinding the heptahydrate with a mortar and pestle, drying overnight at 100°, and then grinding to a powder before use.

indicated 84% **2b** and 16% **3b**. Preparative glpc on a 5-ft acid-washed column of 5% Dow Corning 550 silicone oil on Chromosorb at 116° separated the material into two components. The material of shorter retention time was a clear liquid: ir ($CHCl_3$) 1545 cm^{-1} (NO_2); nmr δ 4.06 (sextet, 1 H, J = 11.2, 4.0 Hz, axial $-CHNO_2$). The material of longer retention time was a clear liquid: $n^{25}D$ 1.4627 (lit.[20] $n^{25}D$ 1.4608); ir ($CHCl_3$) 1542 cm^{-1} (NO_2); nmr δ 4.52 (quintet, 1 H, $W_{1/2}$ = 15.0 Hz, apparent J = 4.2 Hz, equatorial $-CH-NO_2$).

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.98; H, 9.28; N, 9.84.

In a duplicate experiment, analysis of the crude product prior to chromatography showed the presence of 2-methylcyclohexanone (35% yield) and an unidentified component of high retention time as well as **2b** and **3b**. The total yield of **2b** and **3b** was 24% by glpc, and the ratio was 4.85:1 (83% *cis*). After silicic acid chromatography, nmr analysis indicated 85% *cis* isomer.

Isomerization of 2b to 3b.—A solution of 45 mg (0.3 mmol) of **2b** obtained by preparative gas chromatography in 95% ethanol (2 ml) was added to 5 ml of saturated sodium bicarbonate in 95% ethanol. The solution was refluxed for 21 hr, cooled, and concentrated. Water (5 ml) was added to the residue, and the mixture was extracted three times with 5-ml portions of ether. The dried extract was concentrated giving 13 mg (29%) of a liquid residue which was analyzed by glpc. The peak of shorter retention time (**3b**) accounted for 92% of the total area and that of longer retention time (**2b**) for 8%. No 2-methylcyclohexanone was present in the sample.

Methyl 2-Hydroxyiminocyclohexaneacetate (1c).—To a solution of methyl 2-oxocyclohexaneacetate[21] (10.2 g, 60 mmol) in methanol (200 ml) there was added a solution of hydroxylamine hydrochloride (11.1 g, 160 mmol) and anhydrous sodium acetate (22 g, 268 mmol) in water (45 ml). The resulting mixture was refluxed 1 hr, cooled, and concentrated, giving a pink slurry. Water (50 ml) was added, and the mixture was extracted with ether. The ether was washed with 5% sodium carbonate, dried, and evaporated, giving **1c** (4.95 g, 45%). Several recrystallizations from hexane gave white prisms, mp 82.5–84.5°.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.09; H, 8.23; N, 7.39.

Methyl 2-Nitrocyclohexaneacetates (2c and 3c).—The oxidation of 10 mmol of **1c** by the general procedure gave 1.33 g of crude **2c–3c** containing methyl 2-oxocyclohexaneacetate as a significant contaminant (27% yield by glpc analysis). Chromatography on silicic acid using 5 and 10% ether in hexane as the eluting solvents gave fractions containing **2c–3c** (0.79 g, 39%). Short-path distillation (0.02 mm) gave a clear liquid: $n^{24}D$ 1.4708; ir (film) 1740 (C=O) and 1545 cm^{-1} (NO_2); nmr δ 4.71 (quintet, < 1 H, $W_{1/2}$ = 11.5 Hz, J = 2.1, 4.5 Hz, equatorial $-CHNO_2$), 4.35 (sextet, <<1 H, $W_{1/2}$ = 28 Hz, axial $-CHNO_2$), and 3.66 (s, 3 H, OCH_3). Integration of the signals at δ 4.71 and 4.35 indicated 78% **2c** and 22% **3c**.

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.91; H, 7.72; N, 6.86.

Isomerization of 2c to 3c.—A solution of 0.40 g (2 mmol) of the **2c–3c** mixture described above in 41 ml of a saturated solution of sodium bicarbonate in 95% ethanol was refluxed for 21 hr, cooled, and concentrated. Water (15 ml) was added to the residue, and the mixture was extracted with ether. After drying and concentration the residue (0.34 g, 84%), was distilled (short path, 0.02 mm) giving a clear liquid: $n^{23}D$ 1.4666; ir (film) 1740 (C=O) and 1545 cm^{-1} (NO_2); nmr δ 4.7 (m, <<1 H, $W_{1/2}$ = 13 Hz, equatorial $-CHNO_2$), 4.36 (sextet, <1 H, $W_{1/2}$ = 22.5 Hz, J = 4.0, 11.0 Hz, axial $-CHNO_2$), and 3.62 (s, 3 H, OCH_3). From integration of the spectrum the sample is 82% **3c** and 18% **2c**.

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.75; H, 7.68; N, 6.89.

Ethyl 2-Hydroxyiminocyclohexanepropionate (1d).—Ethyl 2-oxocyclohexanepropionate[22] was converted into **1d** using the procedure described for **1c**, except that ethanol was used in place of methanol as solvent. Distillation of the crude product gave **1d** as a viscous oil (67% yield): bp 135–138° (0.15 mm); $n^{23}D$ 1.4887.

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.86; H, 8.93; N, 6.67.

Ethyl 2-Nitrocyclohexanepropionates (2d and 3d).—The oxidation of **1d** was carried out using the general procedure but on a 0.1-mol scale. The crude product (20.0 g) was obtained as a yellow oil containing about 20% ethyl 2-oxocyclohexanepropionate (glpc analysis). The oil was placed on a 4.5 × 52 cm column of silicic acid (400 g) packed in 10% ether in hexane. The column was eluted with 10% ether in hexane (650 ml) and with 15% ether–hexane (2.2 l.). Compounds **2d** and **3d** were detected in fractions 24–53 by glpc, and these fractions were combined, concentrated, and distilled in a short-path apparatus giving 11.3 g (49%) of a clear liquid: bp 124–126° (0.35 mm); ir (film) 1740 (C=O) and 1545 cm^{-1} (NO_2); nmr δ 4.6 (m, 0.7 H, $W_{1/2}$ = 12.5 Hz, equatorial $-CHNO_2$), 4.2 (m, <<1 H, axial $-CHNO_2$), 4.1 (q, 2 H, J = 7.0 Hz, OCH_2), 2.4 (t, 2 H, J = 7.5 Hz, $CH_2CO_2C_2H_5$), and 1.3 (t, 3 H, J = 7.0 Hz, OCH_2CH_3).

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.78; H, 8.42; N, 6.11.

Isomerization of 2d to 3d.—The procedure described for **2c** was used, except that a 15 hr reflux period was used. Short-path distillation (0.02 mm) gave a 69% yield of a clear liquid: $n^{24}D$ 1.4675; ir (film) 1735 (C=O), 1538 cm^{-1} (NO_2); nmr δ 4.63 (m, <<1 H, equatorial $-CHNO_2$), 4.2 (sextet, <1 H, axial $-CHNO_2$), 4.1 (q, 2 H, OCH_2CH_3), 2.28 (m, $CH_2CO_2C_2H_5$), and 1.24 (t, 3 H, OCH_2CH_3). By integration of the nmr spectrum at 4.63 and 4.2 ppm the composition of the mixture was calculated to be 75% **3d** and 25% **2d**.

Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.91; H, 8.37; N, 6.31.

***cis*- and *trans*-Decahydroquinolines (6d and 7d).**—A solution of **2d–3d** (2.5 g, 11 mmol), obtained by chromatography of the crude oxidation product as described above in methanol (50 ml) and concentrated H_2SO_4 (1.3 ml), was hydrogenated over 10% palladium-on-charcoal catalyst (1.0 g) for 4 hr at an initial H_2 pressure of 45 psi; the mixture was filtered through a Celite pad into water (50 ml) and washed with methanol. The combined filtrates were concentrated, chilled in an ice bath, and brought to pH 9 with 5% aqueous sodium hydroxide. The mixture was extracted five times with 50-ml portions of ether and the extracts were dried over $MgSO_4$. Then the solution was refluxed for 22 hr. The solution was cooled and concentrated giving a mixture of *cis*- and *trans*-octahydrocarbostyrils.[23,24] The residue was dissolved in dry ether and added slowly to a stirred mixture of lithium aluminum hydride (1.04 g, 27.5 mmol) in dry ether (200 ml). After addition was complete the mixture was refluxed in a nitrogen atmosphere for 24 hr. The reaction mixture was cooled, and water was carefully added until aluminum salts precipitated as a granular mass. The mixture was filtered, and the precipitate was washed with hot tetrahydrofuran. After drying, the combined filtrates were concentrated to a clear oil, and the basic product was isolated by a standard extraction sequence, giving a clear oil (0.85 g, 61%). Preparative glpc was carried out on a 10-ft column of 10% Apiezon L, 5% KOH on Chromosorb G at 197°. The peak of low retention time was collected as white needles: mp 45.5–46.0° (lit. mp 48,[25,26] 45–47,[27] and 47.5–48.5° [28] for *trans*-decahydroquinoline[26]). The ir spectrum was superimposable with that of authentic[26] *trans*-decahydroquinoline. The peak of longer retention time was collected as a liquid and converted into a benzamide: mp 96.5–99.5° (lit. mp 96[26] and 99–100° [29] for *cis*-decahydroquinoline benzamide). The area of the two peaks was measured by planimetry and indicated that the decahydroquinoline mixture consisted of 86% *cis* isomer and 14% *trans* isomer.

(20) The literature[5] value is on a product of unspecified stereochemistry.

(21) H. O. House, R. G. Carlson, H. Muller, A. W. Noltes, and C. D. Slater, *J. Amer. Chem. Soc.*, **84**, 2614 (1962).

(22) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(23) In one run this mixture was purified by chromatography. The ir spectrum of the purified octahydrocarbostyril mixture was compared with published spectra[24] of the pure *cis* and *trans* isomers. This comparison indicated that the product consisted of a mixture of the isomers.

(24) G. Di Maio and P. A. Tardella, *Gazz. Chim. Ital.*, **91**, 1345 (1961).

(25) W. Hückel and F. Stept, *Ann.*, **453**, 163 (1927).

(26) C. F. Bailley and S. M. McElvain, *J. Amer. Chem. Soc.*, **52**, 4013 (1938).

(27) T. Henshall and E. W. Parnell, *J. Chem. Soc.*, 661 (1962).

(28) N. J. Leonard, L. A. Miller, and P. D. Thomas, *J. Amer. Chem. Soc.*, **78**, 3463 (1956).

(29) C. A. Grob, H. P. Fischer, H. Link, and E. Renk, *Helv. Chim. Acta*, **46**, 1190 (1963).

2-Nitronorbornane.—The general oxidation procedure performed on a 20-mmol scale gave a yellow-green liquid (1.95 g). Chromatography on silicic acid (60 g) using chloroform–hexane mixtures increasing from 10 to 30% chloroform was followed by tlc. Fractions 47–113 were combined and concentrated giving crude 2-nitronorbornane (0.86 g, 31%). Short-path distillation (0.08 mm) gave a solid: mp 64–68°, softening from 45° (lit.[13] mp 64–67° for >90% *endo*-2-nitronorbornane-3-^{14}C; nmr δ 4.84 (quintet, <1 H, J = 5.0 Hz, *exo* $-CHNO_2$) and 4.39 (m, <<1 H, *endo* $-CHNO_2$) (lit.[14] δ 4.73 for *exo* $-CHNO_2$). The nmr spectrum was integrated by planimetry and indicated 91% *endo*-2-nitronorbornane and 9% *exo*-2-nitronorbornane.

Isomerization of 2-Nitronorbornane.—The method of Roberts[13] gave after distillation a liquid: nmr δ 4.8 (m, <<1 H, *exo* $-CHNO_2$) and 4.39 (m, <1 H, *endo* $-CHNO_2$). Integration of the peaks at δ 4.8 and 4.39 ppm indicated that the product was at least 72% *exo* isomer. Roberts[13] estimated the composition as 70–80% *exo* by another method.

Attempted Oxidation of Camphor Oxime.—The general procedure was applied to *anti*-camphor oxime, but the yield of material showing nitro absorption was <5%. Camphor was recovered and identified.

Registry No.—**1c**, 17448-49-6; **1d**, 17448-51-0; **2a**, 17448-50-9; **2b**, 17448-52-1; **2c**, 17448-53-2; **2d**, 17448-54-3; **3a**, 17448-55-4; **3b**, 17448-56-5; **3c**, 17448-57-6; **3d**, 17448-46-3; **6d**, 10343-99-4; **7d**, 767-92-0.

Cyclopropanes. XXV. Cleavage of Cyclopropane Rings by Solutions of Sodium in Liquid Ammonia[1]

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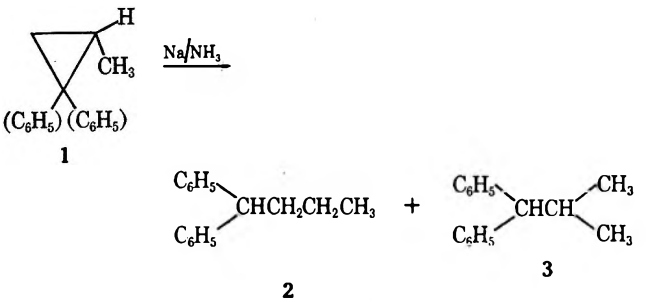
Reduction of 1-methyl-2,2-diphenylcyclopropane (**1**) in sodium and liquid ammonia led to ring cleavage with the formation of 1,1-diphenylbutane (**2**) and 1,1-diphenyl-2-methylpropane (**3**). Under similar conditions (−)-(*R*)-1-*n*-pentyl-1-methyl-2,2-diphenylcyclopropane and (+)-(*R*)-1-methyl-2,2-diphenylcyclopropaneearboxylic acid yielded racemic 1,1-diphenyl-3-methyloctane and 4,4-diphenyl-2-methylbutanoic acid, respectively. A mechanism for this reductive cleavage, involving ion-radical intermediates, is presented.

It has been known for some time that alkali metals in liquid ammonia solutions in the presence of a suitable acid (*i.e.*, NH_4X^-) causes cleavage of the cyclopropane ring in α-cyclopropyl ketones. Thus Van Volkenburg and coworkers[2] have found that the ring in cyclopropyl methyl ketone is opened to give a mixture of methyl propyl ketone and 2-pentanol by reaction with sodium and liquid ammonia in the presence of ammonium sulfate. Similarly, in some recent studies, Norin[3] and Dauben[4] have observed that solutions of lithium in liquid ammonia bring about a stereospecific opening of the cyclopropane ring in such a manner that the bond cleaved is the one possessing the maximum overlap with the π orbital of the carbonyl group. It has also been demonstrated that cyclopropyl esters[5] (but not acids) will undergo an analogous cleavage. On the other hand it has been shown that the cyclopropane ring in 2-cyclopropylpent-1-ene is not opened by sodium in liquid ammonia alone nor in the presence of ammonium bromide.[6] In the presence of methanol the double bond is reduced but the ring remains intact. Nefedov[7] has reported that the sodium–liquid ammonium reduction of 1,1-dichloro-2-phenylcyclopropane produced, besides the expected phenylcyclopropane, a 17% yield of propylbenzene.

During our studies on the reduction of optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane with solutions of sodium in liquid ammonia[8] we found that the primary reduction product, 1-methyl-2,2-diphenylcyclopropane (**1**), was further reduced under the reaction conditions to give a mixture of 1,1-diphenylbutane (**2**) and 1,1-diphenyl-2-methylpropane (**3**). This observation has led us to study the cleavage of such compounds by sodium in liquid ammonia in more detail, and we now wish to report our results.



1 2 3

The yields of **2** and **3** produced by reduction of **1** have been found to vary with the concentration of the sodium in liquid ammonia solution used as reducing agent. In particular, when solutions of sodium in liquid ammonia of above 8% are used no reaction occurs over a 2-hr period; at concentrations of from 1 to 8% a mixture of **2**, **3**, and recovered **1** is produced; and at concentrations of less than 1% only **2** and **3** are formed. The yields of the two products and of recovered starting material are shown in Table I as a function of the concentration of the sodium in liquid ammonia reducing solutions. The yields shown represent the relative yields of each product as determined by gas chromatography of the reaction mixture. The total yield of these products was always greater than 90%. It will be noted that the ratio of the yields of **2** and **3**, when they are produced, remains fairly constant over

(1) Support of this work by grants from the Petroleum Research Fund of the American Chemical Society and the National Science Foundation is gratefully acknowledged.

(2) R. Van Volkenburgh, K. M. Greenlee, J. W. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **71**, 3595 (1949).

(3) T. Norin, *Acta Chem. Scand.*, **19**, 1289 (1965).

(4) M. G. Dauben and E. I. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

(5) H. O. House and C. J. Blankley, *ibid.*, **33**, 47 (1968).

(6) H. Greenfield, R. A. Friedel, and W. Orchin, *J. Amer. Chem. Soc.*, **76**, 1258 (1954).

(7) O. W. Nefedov, N. N. Novitskaya, and A. D. Petrov, *Dokl. Akad. Nauk SSSR*, **152**, 629 (1963).

(8) H. M. Walborsky, F. P. Johnson, and J. B. Pierce, *J. Amer. Chem. Soc.*, **90**, 5222 (1968).

TABLE I
REDUCTION OF 1-METHYL-2,2-DIPHENYLCYCLOPROPANE WITH SODIUM IN LIQUID AMMONIA

Na, g/100 m	Yield of 1, %	Yield of 2, %	Yield of 3, %	2/3
12.2[a]	100			
12.0	100			
5.2[a]	57.0	35.8	7.2	5.0
3.1	22.0	66.0	12.0	5.5
1.3	15.0	72.1	12.6	5.7
0.05	0.00	79.6	14.1	5.7

[a] Optically active material was used and recovered with the same optical purity.

a wide concentration range. This suggests that these two substances are probably produced from a common intermediate.

In view of the known ability of phenyl groups to accept electrons from sodium in liquid ammonia solutions[9] we propose that a plausible mechanism for the opening of the cyclopropane ring in this and other phenyl-substituted cyclopropanes is as shown in Figure 1.[10] It is noted that, because of the reported comparable acidities ($pK_a \sim 35$) of ammonia and diphenylmethane, the diphenyl carbanions **7** and **8** produced as a result of the ring opening are not expected to be completely protonated in liquid ammonia.[11] Indeed these reductions are always accompanied by the production of deep red solutions which presumably contain anions **7** and **8** in equilibrium with amide ions and the corresponding hydrocarbon. We have been able to trap the predominant carbanion **8** by alkylation with benzyl chloride, a method used previously by Hauser and Hamrick.[12]

In support of the mechanism proposed in Figure 1 we have found that at least one phenyl group attached to the cyclopropane ring is a necessary condition for the ring to be opened by sodium in liquid ammonia solution. Whereas the cyclopropane rings of the sodium salts of 2,2-diphenylcyclopropanecarboxylic acid and *trans*-2-phenylcyclopropanecarboxylic acid are opened by sodium in liquid ammonia solutions to yield 4,4-diphenylbutanoic acid and 4-phenylbutanoic acid, respectively, the rings in 2,2-dimethylcyclopropanecarboxylic acid and cyclopropanecarboxylic acid are not opened under similar conditions. The role of the phenyl group in our case or the carbonyl[3,4] and carbethoxy groups[5] in previously reported cases is to accept an initial electron from the sodium in liquid ammonia to form the short-lived anion-radical species (**4**) or it may simply stabilize the resulting carbanion when ring cleavage does occur and promote the reaction in this way. This latter explanation, however, would seem less likely in view of the previous observation that 2-cyclopropylpent-1-ene does not react with sodium in liquid ammonia.[6]

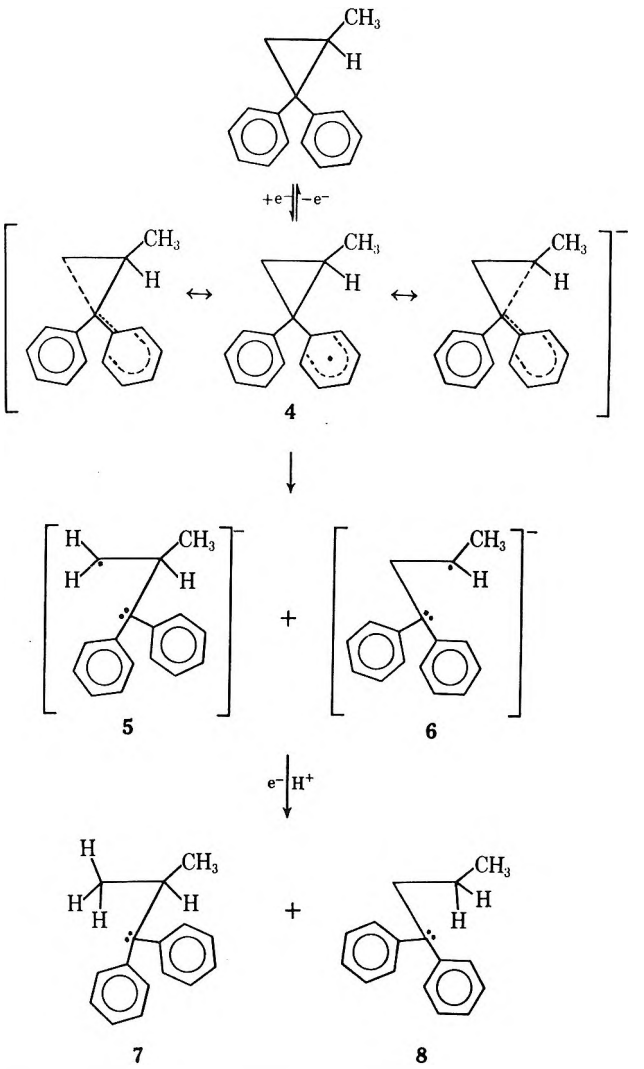


Figure 1.—Mechanisms for the sodium in liquid ammonia reduction of 1-methyl-2,2-diphenylcyclopropane.

In connection with the possibility of anion radicals such as **4**–**6** being involved in these reactions we were interested in attempting to observe them by esr spectroscopy. However, esr spectra of these red solutions (when less than 1 equiv of sodium is used) do not show the presence of any paramagnetic species. This does not mean that **4** cannot be an intermediate, but does indicate that if it is produced it must rapidly open to form **5** and **6** which themselves must quickly add another electron to form a dianion which is protonated by the solvent. Moreover, the ring opening of **4** to **5** and **6** is an irreversible reaction, since, when optically active **1** is used in the reaction, it is recovered without loss of optical activity (Table I). Intermediates such as **6** would be expected to cause at least some loss of optical activity. Indeed, (−)-(*R*)-1-*n*-pentyl-1-methyl-2,2-diphenylcyclopropane (**9**)[13] which upon reduction should lead to ion radical **11** (R = *n*-pentyl) did in fact result in the formation of racemic **12** (R = *n*-pentyl). This was also the case when **10** was reduced under similar conditions. We interpret these results to mean that the species formed by the opening of the cyclopropane ring is such that rapid racemization can occur at the optically active center and is consistent with this species being **11**.

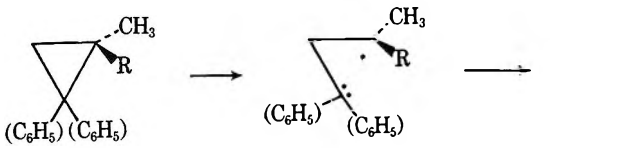
(9) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).

(10) In a sense, our reaction is somewhat of a modified Birch reduction. An electron adds, but, since there is no proton donor (*i.e.*, ethanol), this step is reversible.

(11) H. Smith in "Chemistry in Non Aqueous Ionizing Solvents," Vol. 1, part 2, Interscience Publishers, New York, N. Y., 1963, p 254.

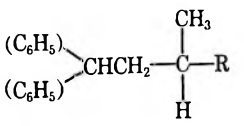
(12) C. R. Hauser and P. J. Hamrick, Jr., *J. Amer. Chem. Soc.*, **79**, 3142 (1957). Based on the amount of stilbene formed (60%) and using the arguments presented by these workers, one would conclude that the equilibrium lies largely in favor of the carbanion and therefore the pK_a of the conjugate hydrocarbon acid is lower than that of ammonia by somewhere between 1 and 2 pK_a units.

(13) J. B. Pierce and H. M. Walborsky, *J. Org. Chem.*, **33**, 1962 (1968).



9, R = *n*-pentyl
10, R = COO^-Na^+

11



12

Furthermore, it should be noted that the reduction of 1-methyl-2,2-diphenylcyclopropane (**1**) results in the cleavage of both 1,2 and 2,3 bonds of the cyclopropane ring. The predominant product, however, is that resulting from 1,2 cleavage as might be expected on the basis of the fact that anion radical **6** would be predicted to be more stable than **5**.

There remains to comment on what we believe to be the reason for the variation in the yields of **2** and **3** with changes in concentration of the sodium in liquid ammonia reducing solution in the reduction of **1**. It is felt that this variation is connected with the solubility of **1** in these solutions. The sodium salt of 2,2-diphenylcyclopropanecarboxylic acid, which is moderately soluble in liquid ammonia, is reduced to 4,4-diphenylbutanoic acid at all concentrations. On the other hand, 1-*n*-pentyl-1-methyl-2,2-diphenylcyclopropane (**9**) which appears to be insoluble in liquid ammonia is not reduced at any concentration of sodium in liquid ammonia at −33° and for similar reaction times. In order to realize the reduction of **9** it was necessary to carry out the reaction in a sealed tube at room temperature over a period of about 15 hr. These observations suggest that 1-methyl-2,2-diphenylcyclopropane presents an intermediate case in which the solubility is such that reaction can occur at a reasonable rate in dilute solutions but not in the highly metallic concentrated solutions.

Experimental Section

The reductions were carried out in apparatus that has been previously described.[8] The composition of the reaction mixtures produced by the reduction of 1-methyl-2,2-diphenylcyclopropane at various concentrations was determined by gas chromatography at 200° on a 6-ft column of 15% Carbowax on acid-washed Chromosorb P. The products 1,1-diphenylbutane (**2**) and 1,1-diphenyl-2-methylpropane (**3**) were identified in a manner previously described.[8]

Trapping the Carbanion Involved in the Reduction of 1-Methyl-2,2-diphenylcyclopropane.—A solution containing the anions **7** and **8** was prepared by the reaction of 230 mg (0.00110 mol, an excess) of 1-methyl-2,2-diphenylcyclopropane (**1**) with 48 mg (0.00104 g-atom) of sodium in 40 ml of liquid ammonia. After stirring for 1 hr there was added dropwise, *via* a syringe, 0.240 ml (0.264 g, 0.00208 mol) of benzyl chloride to the red solution. After stirring an additional 5 min hexane was added and the ammonia was allowed to evaporate. The sodium salts were then removed from the hexane solution by filtration, and after removal of the hexane the residue was crystallized from 95% ethanol. Gas chromatography showed that the mother liquors consisted mainly of 1,1-diphenylbutane (**2**) and 1,1-diphenyl-2-methylpropane along with recovered 1-methyl-2,2-diphenylcyclopropane. Infrared and nmr spectra and gas chromatography of the crystalline material indicated that it consisted of a mixture of stilbene and 1,2,2-triphenylpentane. A total of 224 mg of this material was obtained and the gas chromatogram on a 4-ft column of SF-96 at 275° indicated that about one-half of it was stilbene. The yield of stilbene is hence calculated to be about 60%. The stilbene was removed from the desired 1,2,2-triphenylpentane by dissolving the crystalline material in 3.5 ml of acetic acid and adding 0.160 g of pyridinium perbromide; the precipitated stilbene dibromide was then filtered off and recrystallized from methanol, mp 228–234°. Most of the acetic acid was then removed from the filtrate by heating on a steam bath with a stream of air blowing over the solution. Water was then added, and the residue was extracted with hexane. The hexane layer was washed once with sodium bisulphite solution and water and finally was dried with sodium sulfate. Removal of the solvent gave a residue which was crystallized from methanol: mp 110–111°. On analysis, nmr and ir spectra were consistent with this material being 1,2,2-triphenylpentane: nmr (CCl_4) δ 7.05 (10 H, singlet, *gem*-diphenyl), phenyl attached to –CH– (5 H, complex multiplet),[14] 3.2 (1.8 H, singlet), 2.1–1.86 (1.8 H, complex multiplet), 1.4–0.8 (5.3 H, complex multiplet, CH_2CH_3).

Anal. Calcd for $C_{23}H_{24}$: C, 91.94; H, 8.06. Found: C, 91.87; H, 8.12.

Reduction of the Sodium Salt of 2,2-Diphenylcyclopropanecarboxylic Acid.—A solution consisting of 78.0 mg (0.00339 g-atom) of sodium in 37 ml of predried liquid ammonia was prepared using the usual vacuum apparatus,[8] and then 0.282 g (0.00108 mol) of sodium 2,2-diphenylcyclopropanecarboxylate was added. After stirring for 0.5 hr near −33°, dry hexane was added to the red solution and the ammonia was allowed to evaporate. Water was then added, and the hexane layer was separated. The hexane layer was washed once with dilute base, and this aqueous layer was combined with the previous one. After drying the solvent was removed from the hexane layer, but nothing remained. The aqueous layers were acidified with HCl and then extracted with ether. The ether layers were dried, and the solvent was removed to leave a residue which was crystallized from hexane to give 0.227 g (81%) of 4,4-diphenylbutanoic acid, mp 104–105°. Infrared and nmr spectra were identical with those of authentic material.[15] A similar experiment performed at a much higher concentration of sodium in liquid ammonia (11 g/100 ml) gave essentially the same result as that above.

Reduction of the Sodium Salt of 1-Methyl-2,2-diphenylcyclopropanecarboxylic Acid.—The sodium salt of racemic 1-methyl-2,2-diphenylcyclopropanecarboxylic acid was prepared from the corresponding acid in a manner analogous to that described above for the preparation of the sodium salt of 2,2-diphenylcyclopropanecarboxylic acid. A solution consisting of 56.4 mg (0.00245 g-atom) of sodium dissolved in 50 ml of predried ammonia was prepared, and then 0.200 g (0.000730 mol) of the solid sodium salt was added. Work-up in the manner described above gave 0.189 g (94%) of 4,4-diphenyl-2-methylbutanoic acid, mp 101–102°. Infrared and nmr spectra were identical with those of the authentic material.[16] A second reaction was performed using the sodium salt prepared from optically active (+)-(*R*)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid, $[\alpha]_{Hg}$ +40.3°. The resulting 4,4-diphenyl-2-methylbutanoic acid was found to be completely racemic.

Reduction of the Sodium Salt of *trans*-2-Phenylcyclopropanecarboxylic Acid.—A solution consisting of 72 mg (0.00314 g-atom) of sodium dissolved in 50 ml of ammonia was prepared in the usual manner, and then 0.229 g (0.00141 mol) of sodium *trans*-2-phenylcyclopropanecarboxylate was added. In this case the solution did not turn red. After the usual work-up the residue was crystallized from cold hexane to give 0.164 g (72%) of 4-phenylbutanoic acid, mp 50–51°. Infrared and nmr spectra were identical with those of the authentic material.[17]

Reduction of Sodium 2,2-Dimethylcyclopropanecarboxylate.—A solution consisting of 81 mg (0.00352 g-atom) of sodium dissolved in 31 ml of ammonia was prepared in the usual manner, and then 150 mg (0.00132 mol) of sodium 2,2-dimethylcyclopropanecarboxylate was added. The solid salt dissolved, and the solution was allowed to stand for 0.5 hr. The reaction was worked up in the usual manner to yield 100 mg (84%) of the free acid. The acid was converted into the methyl ester by reaction

(14) *ortho* protons produce a quadruplet centered at 6.4 ppm and the *meta,para* protons form a multiplet centered at 6.4 ppm.

(15) S. Wawzonek and J. Kozikowski, *J. Amer. Chem. Soc.*, **76**, 1641, (1954).

(16) Prepared by J. L. Webb, unpublished results.

(17) Purchased from Aldrich Chemical Co., Milwaukee, Wis.

with diazomethane and was analyzed by vpc (EGIP column) and nmr which showed the sample to be pure and uncontaminated with acyclic esters.

Reduction of Sodium Cyclopropanecarboxylate.—A solution consisting of 80 mg (0.00348 g-atom) of sodium dissolved in 34 ml of ammonia was prepared in the usual manner; then 150 mg (0.00167 mol) of sodium cyclopropanecarboxylate was added; and the solution was stirred for 45 min. The reaction mixture was worked up in the usual manner to yield 0.087 g (73%) of the free acid. The acid was converted into the methyl ester by reaction with diazomethane, was analyzed by vpc (PEDS column) and nmr, and was shown to be pure and uncontaminated by methyl butyrate or methyl isobutyrate.

Reduction of 1-*n*-Pentyl-1-methyl-2,2-diphenylcyclopropane.—A solution consisting of 24 mg (0.00104 g-atom) of sodium in 35 ml of predried liquid ammonia was prepared in the usual manner, and then 0.0919 g (0.000331 mol) of crystalline 1-pentyl-1-methyl-2,2-diphenylcyclopropane was added. This material was seen to float on the surface of the solution and did not appear to dissolve. The solution was stirred for 3 hr near −33°; then dry hexane was added; and the ammonia was allowed to evaporate. The hexane solution was then filtered to remove the remaining sodium, and the solvent was then removed. The residue crystallized on standing, mp 55–56.5°. Recovered was 85 mg (94%) of the starting material.

A result similar to that above was obtained when the reduction was carried out in a much more concentrated sodium in liquid ammonia solution (3.78 g in 37 ml).

In one part of a modified U tube, made from thick-walled tubing, was placed 80.0 mg (2.9×10^{-4} mol) of the hydrocarbon, $[\alpha]_{546}^{30}$ −43.3°, and in the other part was placed 24 mg (9.6×10^{-4} g-atom) of sodium. The tube was then connected to the vacuum system and evacuated. Predried ammonia (25 ml) was distilled into the part of the tube containing the sodium, and the tube was then sealed and allowed to come to room temperature. The solid hydrocarbon was then tipped into the ammonia solution. The crystals did not dissolve but turned red at the surface. The mixture was allowed to remain at room temperature for about 15 hr. The reaction mixture was worked up in the usual manner. The residue was shown by vpc to consist of two components with the minor component being only 2–3% of the mixture. Since the residue was completely racemic, we did not attempt to isolate the components in the pure state. The nmr spectrum was consistent with the major components being 1,1-diphenyl-3-methyloctane: nmr (CCl_4) δ 7.05 (10 N, singlet), 3.95 (1 H, J = 8 cps), 2.35–0.75 (18.2 H, complex).

Registry No.—Sodium, 7440-23-5; ammonia, 7664-41-7; 1,2,2-triphenylpentane, 6393-07-3; 4,4-diphenylbutanoic acid, 14578-67-7; 4-phenylbutanoic acid, 1821-12-1; 4,4-diphenyl-2-methylbutanoic acid, 17413-46-6; 1,1-diphenyl-3-methyloctane, 17413-47-7; **1**, 17413-48-8.

Acknowledgment.—We wish to express our appreciation to Dr. B. Garrett for the esr spectra. Thanks are also due to Dr. G. Davis for repeating several experiments.

Oxymercuration–Demercuration of 7-Substituted Norbornenes and Norbornadienes

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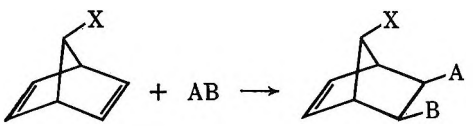
The oxymercuration–demercuration of *syn*- and *anti*-7-hydroxy- and -acetoxynorbornenes gave high yields of *exo,syn*- and *exo,anti*-2,7-dihydroxynorbornanes, respectively. 7-Acetoxynorbornadiene was converted into a mixture of *exo,syn*-2,7-dihydroxynorbornene-5 and *endo,endo*-3,5-dihydroxynortricyclene. 7-Hydroxynorbornadiene experienced an oxidative rearrangement to yield benzaldehyde as the sole reaction product. The synthetic utility and mechanistic implications of these reactions are discussed.

Recent papers from these[1,2] and other laboratories[3,4] have described the marked propensity for certain 7-substituted norbornenes and norbornadienes to react with electrophilic reagents through the *syn* double bond (eq 1). The stereochemistry of the resultant



(1)

X = OH, $OOCCH_3$, $OC(CH_3)_3$

syn adduct is generally *exo,cis* although in some cases concomitant *endo,cis* addition to the *syn* double bond has been noted.[3,4] The tendency of these mono- and diolefins to experience preferential reaction of the *syn* double bond in spite of the potentially adverse steric factors presented by the 7 substituent was unanticipated.[5] The observed selectivity for *syn* addition has been rationalized by the proposition that apparently adverse steric factors were overcome by a strong electronic effect.[1,3,4] While the nature of this electronic effect was vague, it seemed likely that stabilization of the *syn* transition state by coordination of the attacking electrophile by both the double bond and the oxygen-bearing 7 substituent was an important feature of these reactions.[1,6,7]

Brown and coworkers have recently described the oxymercuration–demercuration of olefins as a convenient synthetic route to Markovnikov-oriented alcohols.[8] Particularly pertinent results described by

(1) Diimide reduction: W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).

(2) Silver nitrate complexation: B. Franzus, W. C. Baird, Jr., E. I. Snyder, and J. H. Surridge, *J. Org. Chem.*, **32**, 2845 (1967).

(3) Peroxidation, alkyllithium, carbene additions: G. W. Klumpp, A. H. Veefkind, W. L. deGraaf, and F. Bickelhaupt, *Ann.*, **706**, 47 (1967).

(4) Diazomethane addition: J. Haywood-Farmer, R. E. Pincock, and J. I. Wells, *Tetrahedron*, **22**, 2007 (1966).

(5) For example, calculations based on molecular models indicated that the diimide reduction of 7-acetoxy- or *t*-butoxynorbornadiene would favor the *anti* double bond by a factor of 24:1. See ref 1.

(6) A chelated structure has been suggested to account for the remarkable stability of the silver nitrate–*syn*-7-acetoxynorbornene complex.[2] This complex has been isolated from ethanolic solution as a stable, crystalline compound, mp 146–149° dec. W. C. Baird, Jr., and J. H. Surridge, unpublished results.

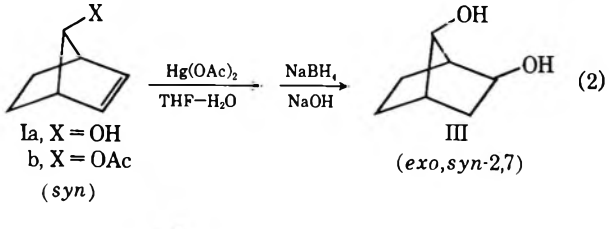
(7) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **85**, 468 (1963), discuss the directive effects of the hydroxyl group on the Simmons–Smith reaction. See also ref 4.

(8) (a) H. C. Brown and P. Geoghegan, Jr., *ibid.*, **89**, 1522 (1967); (b) H. C. Brown and W. J. Hammar, *ibid.*, **89**, 1524 (1967); (c) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **89**, 1525 (1967).

Brown, and previously by Traylor and Baker,[9] are the facts that (1) oxymercuration of norbornene and of alkylnorbornenes occurs exclusively in an *exo,cis* manner,[8b,c,9] (2) no rearrangements of the norbornyl skeleton occur,[8c] and (3) the oxymercuration reaction occurs predominantly from the less hindered side of the molecule.[8b] Furthermore, Brown has noted that the time required for the discharge of the yellow color associated with the suspension of mercuric acetate in the aqueous tetrahydrofuran reaction solvent is a qualitative indicator of the rate of oxymercuration.[8a] For example, norbornene and 2-methylnorbornene experienced rapid oxymercuration, ~30 sec being required for the disappearance of the yellow color.[8c] 7,7-Dimethylnorbornene, on the other hand, required 15 min for the yellow color to vanish.[8c] While these three olefins all gave high yields (84–100%) of exclusively *exo* alcohols (>99.8% *exo*), the diminished rate in the latter case is attributed to steric inhibition presented by the 7-methyl group to reaction of the *syn* double bond.

These observations coupled with a continuing interest in the chemistry of 7-substituted norbornenes and norbornadienes prompted a study of the oxymercuration–demercuration reactions of these olefins utilizing Brown's techniques. The remainder of this paper describes the results of this study and the synthetic utility and mechanistic implications of these reactions.

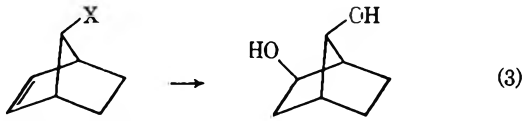
Equations 2 and 3 illustrate the oxymercuration–demercuration of various *syn*- and *anti*-7-substituted norbornenes and the products derived from them.



Ia, X = OH
b, X = OAc
(*syn*)

III
(*exo,syn*-2,7)

(2)



IIa, X = OH
b, X = OAc
(*anti*)

IV
(*exo,anti*-2,7)

(3)

Table I summarizes the experimental conditions and product yields. These reactions were performed according to Brown's procedure[8a] wherein the olefin was added to a suspension of mercuric acetate in aqueous tetrahydrofuran. Subsequent to the discharge of the yellow color the reaction mixture was stirred at the specified temperature for 0.5–10 min. The resultant oxymercuration adduct was decomposed by treatment with sodium hydroxide–sodium borohydride solution. The reaction was stirred for an additional 30–60 min to saponify any acetate functionality.

All of these oxymercuration reactions (eq 2 and 3) proceeded cleanly and in high yield to a single product. Both *syn*-7-hydroxy- (Ia) and -acetoxynorbornenes (Ib) were converted exclusively into *exo,syn*-2,7-dihydroxynorbornane (III). Similarly, the corresponding *anti*-7 alcohol (IIa) and -acetate (IIb) yielded only *exo,anti*-2,7-diol (IV). In all cases the reactions occurred with the introduction of the 2-hydroxyl group in an *exo* configuration; the diol products (III, IV) were not contaminated by any isomeric compounds that might have arisen through isomerization or carbon skeleton rearrangement reactions. In these respects these oxymercuration reactions are in complete accord with Brown's previous experience with norbornene and its alkyl derivatives.[8c] The reactions described here constitute unequivocal syntheses of the isomeric 2,7-norbornanediols (III, IV) and offer vastly improved routes to these compounds relative to previously published methods.[10]

TABLE I
OXYMERCURATION–DEMERCURATION OF 7-SUBSTITUTED NORBORNENES

Olefin	Temp, °C	Time, sec[a]	Product	Yield, %
Ia, X = OH	25	6	III	83
Ib, X = OAc	25	20	III	90
IIa, X = OH	25	13	IV	96
IIb, X = OAc	25	900	IV	92
Norbornene[b]	25	30	*exo*-Norborneol	100
7,7-Dimethylnorbornene[b]	25	900	Apoisoborneol	84

[a] Approximate time in seconds for disappearance of yellow color. [b] Reference 8c.

Inspection of the data of Table I reveals two interesting deviations from the oxymercurations of those norbornyl compounds previously studied.[8c] The first of these is the facile introduction of an *exo,syn*-hydroxyl group into Ia and Ib in spite of the apparent steric hindrance presented by the *syn*-7-hydroxyl and acetoxyl groups in these compounds. Brown has shown that the introduction of a *syn*-7-methyl group reduces the rate of oxymercuration by a factor of 30 relative to that of norbornene.[8c] Table I indicates that the presence of a *syn*-7-hydroxyl or -acetoxyl group has no such effect and, in fact, appears to slightly accelerate the oxymercuration reaction. The second noteworthy distinction is the slow reaction experienced by *anti*-7-acetoxynorbornene (IIb), which exhibits a reactivity comparable with that of 7,7-dimethylnorbornene (Table I) in spite of the total absence of any steric inhibition.

The relative reactivities of the *syn*- and *anti*-7-substituted norbornenes toward oxymercuration would seem to be of diagnostic value with regard to the observed preference for reaction of the *syn* double bond.[1–4] Comparison of the relative reactivities of the *syn*- (Ib) and the *anti*-7-acetates (IIb), ~20 and ~900 sec, respectively, suggests that the oxymercuration reaction of these isomeric esters is sensitive to the same electronic and steric factors that influence the stabilities of the silver nitrate complexes of these olefins.[2,6,11–13] In the case of *anti*-7-acetoxynorbornene

(9) T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963).

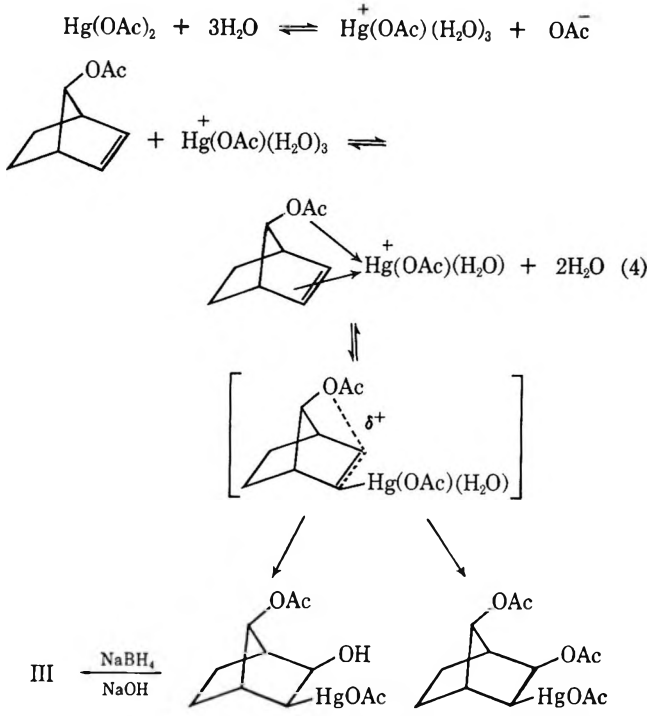
(10) (a) K. Alder, H. Wirtz, and H. Koppelberg, *Ann.*, **601**, 138 (1956); (b) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1959). Both of these procedures gave diol mixtures containing ~50% *exo,syn*-2,7-, ~23% *exo,anti*-2,7-, and ~10% other isomeric diols (2,5- and 2,6-).

(11) Analogies among silver(I) and mercury(II) olefin complexes have previously been reviewed.[9,12]

(12) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).

(13) Silver(I) and mercury(II) possess similar ionic and covalent radii. T. Moeller, "Inorganic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1952, pp 136–143.

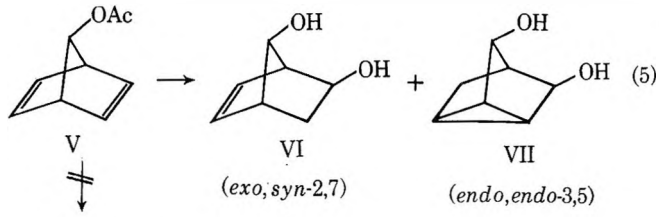
(IIb) withdrawal of the *anti* double-bond electrons by the 7-acetoxyl group quite obviously would diminish the reactivity of this olefin. In the case of the *syn*-7-acetate (Ib), however, inhibition by electron withdrawal and steric effects is more than compensated by stabilization of the mercury(II)–olefin complex through chelation of the mercury ion by the olefinic bond and the *syn*-7 oxygen (eq 4).[14] Oxymercuration of the *syn* isomer (Ib) is further abetted by the eventual stabilization of the partial positive charge that develops on carbon in the transition state (eq 4).[9,15–17]

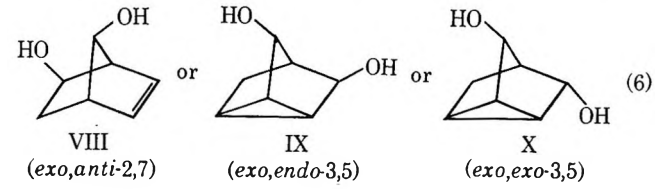


Precedence for such charge stabilization resides in the oxymercuration of certain unsaturated acyclic alcohols where enhanced reaction rates and the formation of cyclized products (ethers) have been attributed to stabilization of the mercurinium ion by the hydroxyl group.[12] Similar stabilization of the mercurinium ion derived from the *anti*-7-acetate is clearly not possible.

The reactivities of the *syn*- (Ia) and *anti*-7-hydroxynorbornenes (IIa) may be rationalized by a similar argument although distinctions here are not so apparent as in the case of the corresponding acetates. The *syn*-7-ol (Ia) exhibits a high degree of reactivity for the same reasons as discussed above for the oxymercuration of the *syn*-7-acetate, *i.e.*, chelation of the mercury(II) ion and subsequent stabilization of the mercurinium ion.[18] The high reactivity of the *anti*-7 alcohol (IIa) relative to that of the *anti*-7-acetate (IIb) is attributed to the inability of the *anti*-7-hydroxyl group to delocalize the olefinic electrons. Consequently, the *anti* alcohol assumes a reactivity comparable to that of the parent olefin, norbornene (Table I).

The oxymercuration–demercuration of 7-acetoxynorbornadiene (V) is illustrated by eq 5; the reaction





occurred at 20° and required ~9 sec for discharge of the yellow color. The combined yield of products VI and VII was 64%;[20] the selectivity to VI was 42% and to VII, 58%. The structure of VI (*exo,syn*-2,7-dihydroxynorbornene-5) was established by hydrogenation to the corresponding norbornanediol (III). The structure of VII (*endo,endo*-3,5-dihydroxynortricyclene) was established by comparison with an authentic sample.[21] The reaction of the acetoxydiene (V) was remarkably selective for the products shown. The formation of the isomeric *exo,anti*-2,7-norbornenediol (VIII) in an amount exceeding ~2–3% of the total product mixture was not detected (eq 6). Similarly, no evidence for the presence of the remaining two isomeric dihydroxynortricyclenes (IX, X) was apparent (eq 6). It is important to note that the formation of VI and VII occurred with the introduction of the hydroxyl group in an *exo* configuration and *syn* to the 7-acetoxyl group of the starting diene.

The high degree of reactivity demonstrated by 7-acetoxynorbornadiene toward oxymercuration and the exclusive introduction of an *exo,syn*-2-hydroxyl group is best rationalized by a reaction proceeding solely *via* the *syn* double bond. Mercury(II) complexation and charge stabilization identical with that previously discussed and illustrated by eq 4 led to the formation of the oxymercuration adduct XI (eq 7). This mercurial adduct (XI) subsequently experienced mercury-catalyzed rearrangement[22] involving carbon participation to generate the nortricyclic mercurial adduct (XII). Borohydride reduction of this mixture of adducts produced the isolated diol products, VI and VII. Precedence for the formation of the organomercurials, XI and XII, from the oxymercuration of 7-acetoxynorbornadiene is provided by the oxymercuration of norbornadiene itself (eq 8).[22] Both diene oxymercurations are completely analogous aside from the directive influence of the 7-acetate group in the reaction of V.

(14) A similar directive effect has been observed in the oxymercuration of certain 4-substituted cyclohexenes: H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959).

(15) Discussion of the structure of mercury(II) olefin π complexes (mercurinium ions), the influence of substituents, neighboring-group effects, and the nature of the transition state may be found in ref 9, 12, and 16.

(16) (a) T. G. Traylor, *J. Amer. Chem. Soc.*, **86**, 244 (1964); (b) W. L. Waters and E. F. Kiefer, *ibid.*, **89**, 6261 (1967); (c) Y. Saito and M. Matsuo, *Chem. Commun.*, 961 (1967).

(17) The stabilization of the partial positive charge on carbon may involve a 1,3-acetoxyonium ion. The reaction conditions and the structure of the product neither confirm nor deny the participation of such an intermediate. R. J. Ouellette and R. D. Robins, *Tetrahedron Lett.*, 397 (1968).

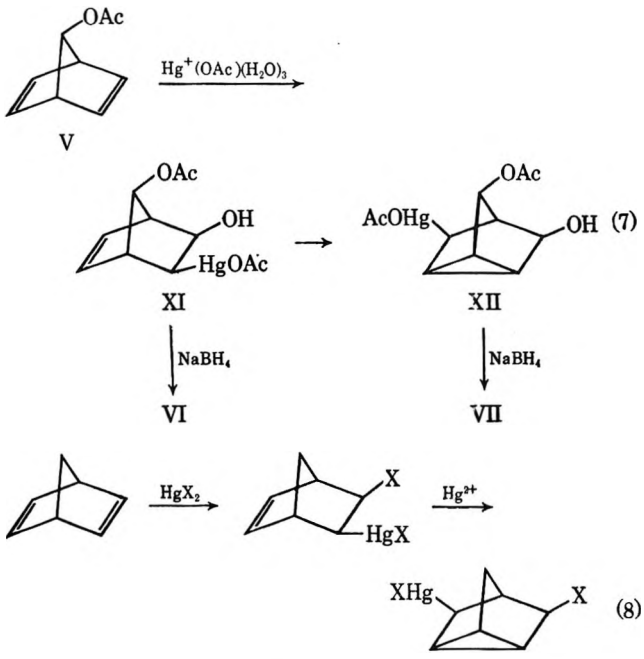
(18) The possibility that the reactivity of *syn*-7-hydroxynorbornene may be diminished by π bonding between the hydroxyl group and the double bond[19] is precluded by the experimental evidence.

(19) L. Joris, P. von R. Schleyer, and R. Gleiter, *J. Amer. Chem. Soc.*, **90**, 327 (1968).

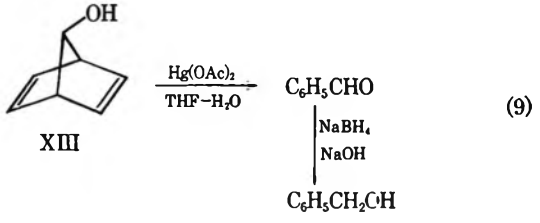
(20) The diminished yield is believed to be a reflection of the inherent instability of organomercurials derived from norbornadienes. The degree of spontaneous decomposition of these organomercury compounds is determined largely by the reaction conditions and by the nature of the mercury anion. See ref 9 and references cited therein.

(21) A. Ferretti and G. Tesi, *J. Chem. Soc.*, 5203 (1965).

(22) K. C. Pande and S. Winstein, *Tetrahedron Lett.*, 3393 (1964).



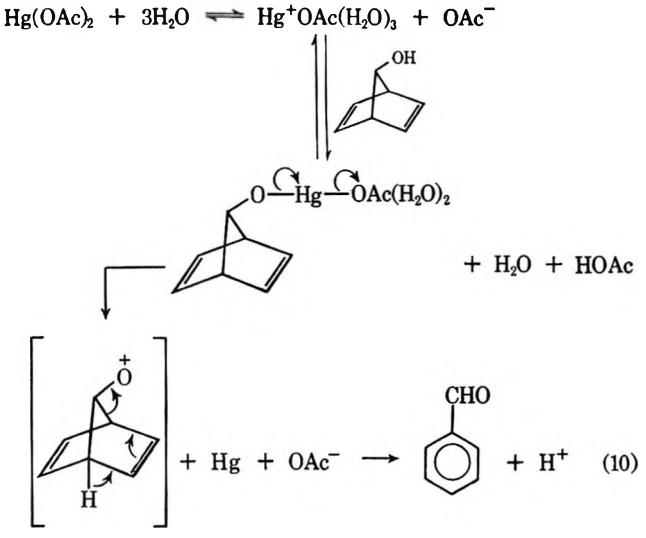
7-Hydroxynorbornadiene (XIII) failed to experience oxymercuration and instead underwent an oxidative rearrangement to yield benzaldehyde as the sole reaction product (eq 9). Addition of the dienol to a



suspension of mercuric acetate in aqueous tetrahydrofuran produced an instantaneous discharge of the yellow color and the precipitation of metallic mercury. Attempts to trap an oxymercuration adduct of XIII by performing the reaction at 0° and by treating the reaction mixture with sodium hydroxide–sodium borohydride immediately subsequent to the addition of dienol gave only benzyl alcohol in >80% yield. No trace of any of the potential diol products, VI–X, was found.

The formation of benzaldehyde from the attempted oxymercuration of 7-hydroxynorbornadiene is not readily rationalized. The dienol has been shown to be stable in aqueous perchloric acid,[23] and a ring-opening reaction catalyzed by aqueous acetic acid generated in the oxymercuration mixture may be reasonably precluded on this basis. Similarly, ring cleavage promoted by mercury(II) catalysis is equally unlikely. The available evidence implies that participation of a mercurinium ion in this reaction is not involved. This view is predicated on (1) the failure to detect any products of oxymercuration by a rapid borohydride quench at 0° and (2) the total absence of carbon skeleton rearrangements in other oxymercurations where such migrations might be reasonably anticipated.[8]

Consequently, the abnormal behavior of 7-norbornadienol (XIII) toward mercury(II) acetate in aqueous tetrahydrofuran demands an alternative explanation. Such a rationale may reside in an oxidative rearrangement to benzaldehyde similar to that experienced by norbornadienol when treated with manganese dioxide in chloroform.[24] Story has suggested that this reaction involves the initial formation of a manganese ester of 7-norbornadienol that subsequently experiences heterolytic oxygen–manganese bond cleavage. This electron transfer results in the reduction of manganese and the creation of a formally positively charged oxygen in the transition state. This mechanism has been extended to the oxidation of allylic and benzylic alcohols and has been employed to account for the insensitivity of the latter to different aryl substituents, the positive charge residing on oxygen rather than on the benzylic carbon. If this mechanism is applied to the present case, the transformation of the dienol to benzaldehyde may be depicted by eq 10.



While the oxidizing power of mercury(II) compounds is well known, it is equally true that the oxidation of normal alcohols by these reagents is not common. It may be that the reaction observed here is unique for 7-norbornadienol since the oxidation chemistry of this alcohol appears to be atypical.[24,25]

Experimental Section

Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Vapor phase chromatography (glpc) was performed using a Varian Aerograph Model 202 chromatograph and a Perkin-Elmer Model 226 capillary gas chromatograph. Preparative glpc was carried out using a Varian Aerograph Autoprep Model 700. Nmr spectra were recorded on a Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal standard. Melting points and boiling points are not corrected.

The following compounds were prepared by published synthetic procedures: 7-acetoxynorbornadiene (V),[26] 7-hydroxynorbornadiene (XIII),[26] *syn*-(Ia)[27] and *anti*-7-hydroxynorbornenes (IIa),[28] and *syn*-(Ib)[28] and *anti*-7-acetoxynorbornenes (IIb).[28] All other reagents were obtained from commercial sources and used as received.

Oxymercuration of *syn*-7-Acetoxynorbornene (Ib).—A solution of 1.5 g (10 mmol) of *syn*-7-acetoxynorbornene in 5 ml of tetra-

(23) H. Tanida, T. Tsuji, and T. Irie, *J. Amer. Chem. Soc.*, **88**, 864 (1966).

(24) T. K. Hall and P. R. Story, *ibid.*, **89**, 6759 (1967).

(25) S. Yankelevich and B. Fuchs, *Tetrahedron Lett.*, 4945 (1967).

(26) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961); the ester may be purchased from Frinton Labs, Vineland, N.J.

(27) W. C. Baird, Jr., *ibid.*, **31**, 2411 (1966).

(28) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964).

hydrofuran was added at room temperature to a suspension of 3.2 g (10 mmol) of mercuric acetate in 10 ml of water containing 5 ml of tetrahydrofuran. The reaction was stirred vigorously for 5 min; decolorization of the reaction mixture was complete after ~20 sec. At the conclusion of the reaction period a sodium hydroxide test for mercury(II) was negative. To the reaction mixture was added 10 ml of 3 *M* sodium hydroxide and 10 ml of 0.5 *M* sodium borohydride in 3 *M* sodium hydroxide. The reaction was stirred at room temperature for 2 hr, and the reaction mixture was then saturated with sodium chloride and extracted with ethyl acetate (six 10-ml portions). The combined ethyl acetate extracts were washed once with 25 ml of saturated sodium chloride solution and dried over magnesium sulfate. The solvent was removed on a rotary evaporator at 60° (20 mm) to give 1.3 g of crystalline product. A small sample of the crude product was treated with excess acetyl chloride in pyridine, and the resultant acetate mixture was analyzed by glpc on a 5 ft × 1/4 in. 20% polypropylene glycol column at 190° and 65 ml/min helium flow.[29]

The crude product was shown to contain 11–12% *syn*-7-acetoxynorbornene (3.8 min) and 88–89% *exo,syn*-2,7-diacetoxynorbornane (21.6 min). The yield of *exo,syn*-2,7-dihydroxynorbornane was 1.15 g (90%). Recrystallization of the crude diol from 25 ml of cyclohexane and sublimation at 100° (0.2 mm) gave 0.8 g (63%) of pure diol, mp 179–181° (lit.[30] mp 180–181°). A diphenylurethan was prepared and recrystallized from benzene, mp 227–229° (lit.[30] mp 221–222°). The nmr spectrum of the *exo,syn*-2,7-diol in deuterium oxide had the following pattern: δ 3.90–4.23 (m, 2, >CH–O), 2.13–2.44 (m, 2, bridgehead), 0.91–2.12 (m, 6, *exo,endo* >CH_2).

A 1.5-g sample of crude diol was acetylated with acetyl chloride–pyridine to give 1.85 g of acetate esters from which *exo,syn*-2,7-diacetoxynorbornane [n^{20}D 1.4642 (lit.[31] n^{20}D 1.4641); glpc purity 100%] was isolated by preparative glpc (12 ft × 3/8 in. 30% FFAP column, 190°, 180-ml/min helium flow). The diacetate had definitive ir absorptions (neat) at 1195, 1136, 1080, 1048, and 1016 cm^{-1}. The nmr spectrum ($CDCl_3$), had the following pattern: δ 4.53–4.83 (m, 2, >CH–OAc), 2.50 (m, 1, bridgehead), 2.30 (m, 1, bridgehead), 2.00 (d, 6, CH_3CO–), 1.00–1.96 (m, 6, *exo,endo* >CH_2).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 61.94; H, 7.80.

Oxymercuration of *syn*-7-Hydroxynorbornene (Ia).—To 1.6 g (5 mmol) of mercuric acetate in 5 ml of water and 2.5 ml of tetrahydrofuran was added a solution of 0.55 g (5 mmol) of *syn*-7-hydroxynorbornene in 2.5 ml of tetrahydrofuran. The oxymercuration was complete in ~6 sec, and the reaction was stirred at room temperature for 10 min. The adduct was decomposed with 5 ml of 3 *M* sodium hydroxide and 5 ml of 0.5 *M* sodium borohydride. The reaction mixture was extracted as previously described to yield 0.6 g of crude *exo,syn*-2,7-dihydroxynorbornane. Glpc analysis (see above) of the diacetate indicated a sample purity of 89%; the yield of diol was 83%. The product was identical with that described above.

Oxymercuration of *anti*-7-Acetoxynorbornene (IIb).—The oxymercuration of *anti*-7-acetoxynorbornene was performed according to the procedure described for the oxymercuration of *syn*-7-acetoxynorbornene. Decolorization of the reaction mixture required 15 min. From the ethyl acetate extract was isolated 1.3 g of crystalline diol; acetylation and analysis of the diacetate by glpc (5 ft × 1/4 in. 20% polypropylene glycol, 190°, 65 ml/min) showed the product to consist of 9.1% *anti*-7-acetoxynorbornene (3.6 min) and 90.9% *exo,anti*-2,7-diacetoxynorbornane (20.9 min). The yield of diol was 1.18 g (92%). Recrystallization from benzene and sublimation at 100° (0.2 mm) gave a pure sample of *exo,anti*-2,7-diol, mp 196–198° (lit.[32] mp 196.5–197.5°). Reaction with *p*-nitrobenzoyl chloride afforded a dinitrobenzoate, mp 195–197° (recrystallized from benzene).

Anal. Calcd for $C_{21}H_8N_2O_8$: C, 59.43; H, 3.80; N, 6.60. Found: C, 59.45; H, 4.18; N, 6.64.

The nmr spectrum of the diol in deuterium oxide had the following pattern: δ 4.50 (m, 1, *J* = 3.8 cps, *anti*-7-HC–O), 4.0 (q, 1, *J* = 11 cps, *exo*-2-HC–O), 1.17–2.50 (m, 8, bridgehead, *exo,endo*-CH_2).

A 0.6-g sample of *exo,anti*-2,7-diol was acetylated with acetyl chloride–pyridine to give 0.9 g of diacetate, which was purified by preparative glpc (12 ft × 3/8 in. 30% FFAP column, 190°, 180 ml/min). The pure diacetate had a melting point of ~18–20° and n^{20}D 1.4644. The nmr spectrum of the diacetate ($CDCl_3$) had the following pattern: δ, 4.97 (m, 1, *J* = 3.5 cps, *anti*-7-H–C–OAc), 4.58 (q, 1, *J* = 11 cps, *exo*-2-H–C–OAc), 2.22–2.42 (m, 2, bridgehead), 2.03 (d, 6, CH_3CO), 0.91–2.02 (m, 6, *exo,endo*-CH_2). The ir spectrum (neat) had characteristic absorption bands at 1176, 1150, 1128, and 1075–1015 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 61.95; H, 7.56.

Oxymercuration of *anti*-7-Hydroxynorbornene (IIa).—The reaction was performed using 2.2 g (20 mmol) of *anti*-7-hydroxynorbornene, 6.4 g (20 mmol) of mercuric acetate, 20 ml of tetrahydrofuran, and 20 ml of water. Decolorization of the reaction mixture required ~13 sec; the reaction was stirred at room temperature for 10 min prior to being decomposed with sodium borohydride solution. The ethyl acetate extract yielded 2.6 g of crude product which contained 94.6% *exo,anti*-2,7-dihydroxynorbornane by glpc analysis. The yield of diol was 2.46 g (96%); the diol was shown to be identical with that previously described.

Oxymercuration of 7-Acetoxynorbornadiene (V).—To a suspension of 6.4 g (20 mmol) of mercuric acetate in 20 ml of water and 10 ml of tetrahydrofuran was added a solution of 3 g (20 mmol) of 7-acetoxynorbornadiene in 10 ml of tetrahydrofuran. The reaction mixture decolorized in ~9 sec; stirring was continued for 10 min at 20°. The reaction mixture was decomposed with 20 ml of 3 *M* sodium hydroxide and 20 ml of 0.5 *M* sodium borohydride. The aqueous mixture was saturated with sodium chloride and extracted with ethyl acetate (five 25-ml portions). The extract was dried over magnesium sulfate, and the solvent was removed on a rotary evaporator to give 2.9 g of semicrystalline product. The crude diol was acetylated to yield 3.2 g of diacetate. The crude diacetate was dissolved in boiling *n*-heptane or cyclohexane, and the ester solution was decanted from intractable tars. Removal of the solvent gave 2.7 g (64%) of crystalline diacetate. The diacetate was analyzed by glpc, and the composition of the product is presented in Table II. The diacetate mixture (2.6 g) was triturated three times with 25-ml portions of pentane and separated into a pentane-soluble (1.35 g) and a pentane-insoluble fraction (1.2 g). The compositions of the two diacetate fractions are presented in Table II;

TABLE II

GLPC ANALYSIS OF DIACETATE FRACTIONS[a]

Compound	Retention time, min	Composition, % Reaction product	Pentane-soluble fraction	Pentane-insoluble fraction
exo,syn-2,7-Diacetoxynorbornene-5	17.6	42.4	90.5	6.8
endo,endo-3,5-Diacetoxynortricyclene	26.1	57.6	9.5	93.2

[a] On a 5 ft × 1/4 in. 20% polypropylene glycol column, 190°, 60 ml/min.

analysis by capillary glpc (200-ft 50:50 phenylnitrile–silicone column, 140°, 20 psig) gave identical results and did not further resolve the major peaks. The major product was separated from the pentane-soluble fraction by preparative glpc (12 ft × 3/8 in. 30% FFAP column, 190°, 180 ml/min) to give a sample of diacetate of 99% purity, mp ~30–35°. The nmr spectrum ($CDCl_3$) had the following pattern which was consistent with an *exo,syn*-2,7-diacetoxynorbornene-5 structure: δ 5.90–6.32 (m, 2, vinyl), 4.58–4.83 (m, 1, *J* = 12 cps, *endo*-H–C–OAc), 4.46–4.57 (m, 1, *J* = 4 cps, bridge H–C–OAc), 3.05–3.23 [m, 1, *J* = 7 cps, bridgehead (H_1)], 2.71–2.97 [m, 1, *J* = 6.5 cps, bridgehead (H_4)], 2.00 (d, 6, CH_3CO), 1.78–1.97 (m, 2, *exo,endo*-CH_2). Hydrogenation over 10% Pd–C in ethanol converted the unsaturated diacetate into *exo,syn*-2,7-diacetoxynorbornane which was shown to be identical with an authentic sample.

(29) Attempts to analyze the diol products directly by glpc on a variety of substrates were not successful owing to inadequate resolution of isomeric mixtures and sample decomposition on the column. These problems were successfully avoided by conversion of the products into acetate esters. Control analyses utilizing *t*-butylbenzene as an internal standard demonstrated that the analyses were quantitative.

(30) H. M. Walborsky and D. F. Loncrini, *J. Amer. Chem. Soc.*, **76**, 5936 (1954).

(31) K. Alder, F. H. Flock, and H. Wirtz, *Ber.*, **91**, 609 (1958).

(32) H. Krieger, *Suomen Kemistilehti*, **B35**, 127 (1962).

The pentane-insoluble fraction (1.2 g) was recrystallized from *n*-heptane or cyclohexane and sublimed [100° (0.2 mm)] to give 0.6 g of white crystalline product, mp 106–108°, glpc purity 97%. The nmr spectrum ($CDCl_3$) had the following pattern which was consistent with an *endo,endo*-3,5-diacetoxynortricyclene structure: δ 4.75–4.86 (m, 2, H–C–OAc), 2.34–2.50 (m, 1, bridgehead), 2.00 (d, 6, CH_3CO), 1.25–1.83 (m, 5, cyclopropyl, bridge).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.50; H, 6.80.

A sample of *endo,endo*-3,5-diacetoxynortricyclene (1.8 g) was refluxed in 15 ml of methanol containing 0.2 g of sodium methoxide for 1 hr; the methanol was removed by distillation until the total volume was reduced to ~3 ml. Saturated sodium chloride solution (15 ml) was added, and the product was extracted with ethyl acetate (five 10-ml portions). From the dried extract 1.1 g of semicrystalline diol was isolated. A sample was acetylated and analyzed by glpc to demonstrate that no degradation or rearrangement had occurred. The crude product was sublimed twice at 100° (0.3 mm) to give 0.5 g of waxy, hygroscopic diol, mp 152–154° (sealed capillary). The nmr spectrum of the diol in deuterium oxide had the following pattern: δ 4.40–4.54 (m, 2, H–C–O), 2.13–2.34 (m, 1, bridgehead), 1.50–1.97 (m, 5, bridge, cyclopropyl).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.72; H, 8.15.

A sample of diol was converted into its *p*-nitrobenzylidene derivative; recrystallization from cyclohexane and sublimation gave a white crystalline product, mp 161–163°. The ir spectrum (CCl_4) of the benzylidene derivative revealed the total absence of hydroxyl and carbonyl functionality. The formation of a benzylidene derivative can only be accommodated by *endo,endo*-3,5-dihydroxynortricyclene.

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.89; H, 5.05; N, 5.40. Found: C, 65.10; H, 5.46; N, 5.97.

A sample of the diol was converted into its dibenzoate; recrystallization from *n*-heptane gave white platelets, mp 115.5–117° (lit.[21] mp 116.5–117). The nmr and ir spectra of the dibenzoate were identical with the nmr and ir spectra of the dibenzoate of an authentic sample of *endo,endo*-3,5-dihydroxynortricyclene.[21]

Oxymercuration of 7-Hydroxynorbornadiene (XIII).—To a solution of 3.2 g (10 mmol) of mercuric acetate in 10 ml of water was added 10 ml of tetrahydrofuran and 1.1 g (10 mmol) of 7-hydroxynorbornadiene. The yellow suspension became white instantaneously, and within 10 sec a gray precipitate had separated. The reaction was quenched by the addition of 10 ml of 3 *M* sodium hydroxide; the reaction mixture was stirred at room temperature for 1 hr. The reaction was saturated with salt and extracted with ethyl acetate (five 25-ml portions). From the extract 1.0 g of crude product was isolated. Distillation gave 0.6 g (57%), bp 72° (14 mm), of benzaldehyde, which was identified by comparison of its ir spectrum with that of an authentic sample.

The reaction was repeated at 0° using the same quantities of reagents. The reaction mixture decolorized immediately, and a gray precipitate formed gradually during the subsequent 10 min. The reaction was decomposed with 10 ml of 3 *M* sodium hydroxide and 10 ml of 0.5 *M* sodium borohydride. The reaction mixture was stirred at 0° for 30 min and then at room temperature for 30 min. The standard work-up gave 1.1 g of oil which was acetylated with acetyl chloride–pyridine. The acetate product (1.6 g) was shown by glpc analysis to contain >80% benzyl acetate. The structure of the ester was confirmed by comparison of its nmr and ir spectra with those of an authentic sample.

The reaction was repeated at 0° using the same quantities of reagents. In this case the reaction mixture was treated with sodium hydroxide–sodium borohydride solution immediately subsequent to the addition of the dienol. The reaction was stirred at 0° for 15 min and then worked up as previously described. The reaction yielded 0.85 g (79%) of benzyl alcohol; acetylation gave 1.15 g (97%) of benzyl acetate.

Isolation of the Isomeric 3,5-Dihydroxynortricyclenes from the Peroxidation of Norbornadiene.—Norbornadiene underwent reaction with performic acid in ethyl acetate solution according to the literature procedure.[21,33] Carbonyl-containing impurities were removed from the diol mixture by extracting an aqueous solution of the diols with carbon tetrachloride. From the aqueous phase was recovered 17 g of crude hygroscopic diols, mp 139–149°. A 1.2-g sample of the diol mixture was acetylated and analyzed by glpc; the results are summarized in Table III. The remaining 15.6 g of diols were recrystallized four times from acetonitrile; the composition of the crystal crops was followed by glpc and is presented in Table III. The quantities of acetonitrile employed and the material balances are summarized in Table IV.

TABLE III

GLPC ANALYSIS OF ISOMERIC 3,5-DIHYDROXYNORTRICYCLENES[a]

Compound	Retention time, min	Composition, %				
		Crude product	Acetonitrile recrystallization 1st	2nd	3rd	4th
2,7-*exo,syn*	14.9	10.6	1.7			
3,5-*exo,endo*	18.5	19.4	21.6	15.0	5.6	
3,5-*exo,exo*	20.2	62.3	75.6	85.0	94.4	99.4
3,5-*endo,endo*	23.6	5.6				

[a] On a 5 ft × 1/4 in. 20% polypropylene glycol column, 190°, 75 ml/min.

TABLE IV

RECRYSTALLIZATION OF 3,5-DIHYDROXYNORTRICYCLENES

Recrystallization	CH_3CN, ml	Charge, g	Yield, g	Filtrate, g
1	40	15.6	9.3	6.5
2	30	9.3	7.4	1.8
3	40	7.4	5.6	1.6
4	25	5.6	4.4	0.9

This procedure yielded 4.4 g of *exo,exo*-3,5-dihydroxynortricyclene (purity by glpc 99%), mp 157–158° (lit.[21] mp 158–159°). The dibenzoate (recrystallized from *n*-heptane) had mp 113–114° (lit.[21] mp 110.5–111.5°). The nmr and ir spectra of the *exo,exo*-3,5-dibenzoate were identical with those previously reported.[21]

The 6.5 g of isomeric diols recovered from the filtrate of the first acetonitrile recrystallization (Table IV) was recrystallized from benzene (75 ml)–acetonitrile (4 ml) to give 3.5 g of crystalline material; the filtrate yielded 2.9 g of oily solids. These crystalline diols were combined with the residues recovered from the remaining acetonitrile filtrates (Table IV, 2–4) to give 7.1 g of mixed diols. This mixture was recrystallized from benzene (200 ml)–acetonitrile (10 ml) to give 5.6 g of hygroscopic diols. Acetylation gave 7 g of isomeric diacetates; the composition as shown by glpc analysis was 2.0% *exo,syn*-2,7-diacetoxynorbornene, 47.6% *exo,endo*-3,5-diacetoxynortricyclene, and 47.3% *exo,exo*-3,5-diacetoxynortricyclene. The diacetates were separated by preparative glpc (12 ft × 3/8 in. 30% FFAP column, 190°, 165 ml/min) to give 2.8 g of *exo,endo* isomer (71% pure). A second preparative glpc separation gave 1.1 g of *exo,endo*-diacetate of 92% purity. Saponification of the diacetate with sodium methoxide in methanol gave 0.6 g of diol; after sublimation at 120° (0.2 mm) the diol melted at 166–168° (lit.[21] mp 175–176°). The dibenzoate was prepared and recrystallized from ethanol–water: mp 86–88° (lit.[21] mp 87.5–88°). The nmr and ir spectra of the *exo,endo* dibenzoate were identical with those previously reported.

The 2.9 g of oily solids recovered from the first benzene–acetonitrile recrystallization were combined with 2.5 g of crude diols recovered from the carbon tetrachloride extraction of the original reaction mixture. Acetylation gave 7.4 g of diacetates which contained 9.5% *endo,endo*-3,5-diacetoxynortricyclene by glpc. The diacetate mixture was transferred to a centrifuge tube and stored at 0° to crystallize the *endo,endo* isomer. After 3 weeks the crystalline deposit was separated from the supernatant liquid by centrifugation. The *endo,endo* isomer content of the liquid phase had decreased to 4%. The crystalline solids (0.4 g) were washed with pentane, recrystallized twice from *n*-

(33) J. P. Schaefer, *J. Amer. Chem. Soc.*, **82**, 4091 (1960).

heptane, and sublimed to give 0.2 g of *endo,endo*-3,5-diacetoxynortricyclene, mp 111–112° (glpc purity 98%). The diacetate was identical with that isolated from the oxymercuration of 7-acetoxynorbornadiene.

Registry No.—III, 17366-25-5; III (diacetoxy), 2979-27-3; IV, 17289-99-5; IV (diacetoxy), 17290-00-5; IV dinitrobenzoate, 17290-07-2; VI, 17290-01-6; VII, 17290-02-7; VII (diacetoxy), 17290-03-8; VII nitrobenzylidine derivative, 17290-04-9; IX, 17290-05-0 X, 4054-88-0.

Acknowledgment.—The authors appreciate useful discussions of these results with Professor H. C. Brown and with Dr. W. H. Mueller and Dr. G. A. Knudsen, Jr. The authors wish to thank Mr. J. H. Surridge for the experiments utilizing 7-norbornadienol.

Stereochemistry of the Bromination and Deuterobromination of *anti*-7-Bromobenzonorbornadiene

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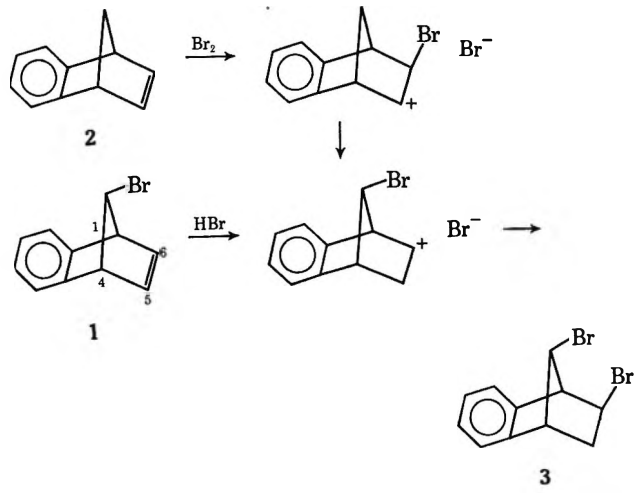
The polar addition of bromine and deuterium bromide to *anti*-7-bromobenzonorbornadiene (1) has been investigated. Even with the unfavorable steric factor *cis,exo* addition of both reagents is observed. Torsional strain effects are also ruled out as governing the "regiospecificity" of electrophilic attack on the double bond of this particular system. A stereoelectronic factor is felt to offer the best explanation and the possible origin of such a factor is discussed.

It has become increasingly apparent that steric,[1] torsional strain factors,[2,3] bridging or the rapid equilibration of classical ions,[4–6] and perhaps even subtle stereoelectronic effects[7] have the potential to influence the stereochemistry of electrophilic additions to the carbon–carbon double bond of norbornene and related bicycloheptene derivatives.[8] In either a concerted or stepwise addition all of these factors could play a role in determining the direction of approach of the electrophilic reagent. Bridging or the equivalent equilibrating classical ions must be considered as possibly controlling the direction of nucleophilic attack for a stepwise addition involving a cationic intermediate. The configuration of any rearranged product can be considered in similar terms.

In any given system more than one of these factors may be operating in a reinforcing manner. The question of the degree of delocalization in the transition state and its role in determining the direction of attack by the halide ion in a hydrohalogenation has been considered.[1,2,9] *exo* attack of halide can occur even when delocalization is probably not very significant.[2] The present work considers further the importance, if any, of steric and torsional strain effects in controlling the stereochemistry of electrophilic additions to norbornene systems.

We have decided to investigate the bromination and deuterobromination of *anti*-7-bromobenzonorbornadiene (1) for several reasons. First of all it is known that the addition of bromine to benzonorbornadiene (2) proceeds with rearrangement to produce *exo*-5,-*anti*-7-dibromobenzonorbornene (3).[10] This enables one to examine certain 1,2 additions to the double bond of *anti*-7-bromobenzonorbornadiene (1) without being directly concerned with rearranged adducts. Thus in the hydrobromination of this *anti*-7-bromide 1, one should obtain the same cationic intermediate, excluding differences in solvation, as the one giving rise to the *exo*-5,*anti*-7-dibromide 3 from the bromination

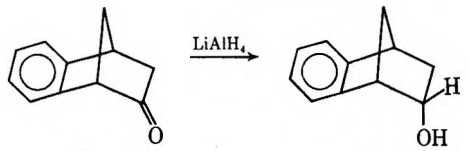


of benzonorbornadiene (2). Furthermore the olefin 1 is weighted sterically in favor of *endo* attack at C-5 and C-6, the bulky bromine at C-7 competing with the π electron cloud at C-2 and C-3 for steric approach control. The torsional strain factor[11] is also diminished in this system since the vinyl hydrogens at C-5 and C-6 are more nearly eclipsed, *ca.* 10–15°, with the bridgehead hydrogens as compared with the analogous dihedral angle of *ca.* 20° for norbornene.[12]

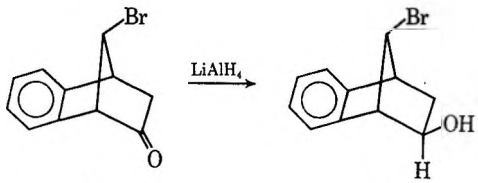
(1) H. C. Brown and K.-T. Liu, *J. Amer. Chem. Soc.*, **89**, 1525, 3898, 3900 (1967).
(2) R. Caple, H. W. Tan, and F. M. Hsu, *J. Org. Chem.*, **33**, 1542 (1968).
(3) M. J. S. Dewar and R. C. Fahey, *Angew. Chem. Intern. Ed. Engl.*, **3**, 245 (1964).
(4) S. J. Cristol and R. Caple, *J. Org. Chem.*, **31**, 2741 (1966).
(5) H. Kwart and J. L. Nyce, *J. Amer. Chem. Soc.*, **86**, 2601 (1964).
(6) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *ibid.*, **88**, 4922 (1966).
(7) C. W. Jefford and W. Wojnarowski, *Tetrahedron Lett.*, 193 (1968). Note Added in Proof.—The same conclusion regarding an electronic effect has recently been reported by T. T. Tidwell and T. G. Traylor, *J. Org. Chem.*, **33**, 2614 (1968).
(8) Hydride shifts can also affect product distribution. For example, see ref 6 and F. H. Dean, D. R. Marshall, E. W. Warnhoff, and F. L. M. Pattison, *Can. J. Chem.*, **45**, 2279 (1967).
(9) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 3901 (1967).
(10) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3727 (1967).
(11) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 701 (1967).
(12) These angles were estimated with aid of Dreiding stereomodels.

Results and Discussion

One piece of evidence that clearly indicates the bulky nature of the bromine in *anti*-7-bromobenzonorbornadiene (**1**) is the stereochemistry of the lithium aluminum hydride reduction of *anti*-7-bromo-5-benzonorbornenone (**4**). Whereas the reduction of 5-benzonorbornenone (**5**) selectively produced the *endo* alcohol (**6**),[13] the lithium aluminum hydride reduction of the bromo



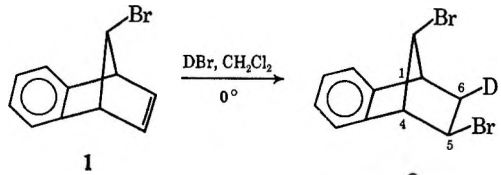
5 **6**



4 **7**

ketone **4** yielded the *exo* alcohol **7**. The bromo alcohol **7** was also obtained by the addition of the elements of hypobromous acid to benzonorbornadiene and has the characteristic nuclear magnetic resonance (nmr) spectrum for this type of disubstituted benzonorbornene[14] as discussed in the Experimental Section. A rearrangement is expected in the addition.[15-17]

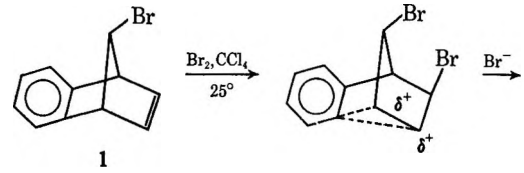
Analogous to some hydrochlorination results of Cristol and Nachtigall,[10] we have found that the addition of deuterium bromide to *anti*-7-bromobenzonorbornadiene (**1**) proceeded exclusively with *cis-exo* addition to produce *exo*-6-deuterio-*exo*-5,*anti*-7-dibromobenzonorbornene (**8**). The selective nature of this



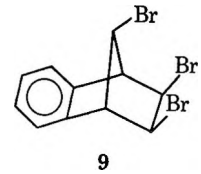
1 **8**

addition can readily be seen by comparing its nmr spectrum with that of authentic *exo*-5,*anti*-7-dibromobenzonorbornene (**3**).[14] The *endo* proton at C-6 in **3** occurs as an octet arising from J_{gem} = 13.1 cps, J_{cis} = 8.0 cps, and a long-range coupling with the proton at C-7 of about 1 cps. The *exo* proton at C-6 in **3** occurs as a doublet of triplets where, in addition to J_{gem}, J_{trans}, and $J_{1,6}$ = 4.1 cps. In the deuterated dibromide **8** the signal for the *exo* proton at C-6, δ 2.77,[18] clearly disappears, and the multiplet for the *endo* proton, δ 2.07, collapses to a doublet where the finer splitting is obscured and the peaks are broadened by the deuterium–hydrogen coupling, but where J_{gem} = 13.1 cps has distinctly vanished. These results are consistent with a stepwise[1,4,10] addition where the approach of the proton and bromide ion must be governed by factors other than those steric in origin.[10,19,20]

Somewhat more surprising is the *cis-exo* addition observed in the addition of bromine to *anti*-7-bromobenzonorbornadiene (**1**). The structure of the adduct, *anti*-7,*cis-exo*-5,6-tribromobenzonorbornene (**9**) is readily confirmed by its nmr spectrum. In addition



1



9

to the four aromatic protons only two narrow multiplets are observed.[21] A three-proton multiplet centered at δ 4.43 is observed with a width of 1.5 cps at the half-height for the isochronous protons on the carbons bearing bromine. The two chemically equivalent bridgehead protons produce a doublet, J = 1.2 cps, centered at δ 4.04.

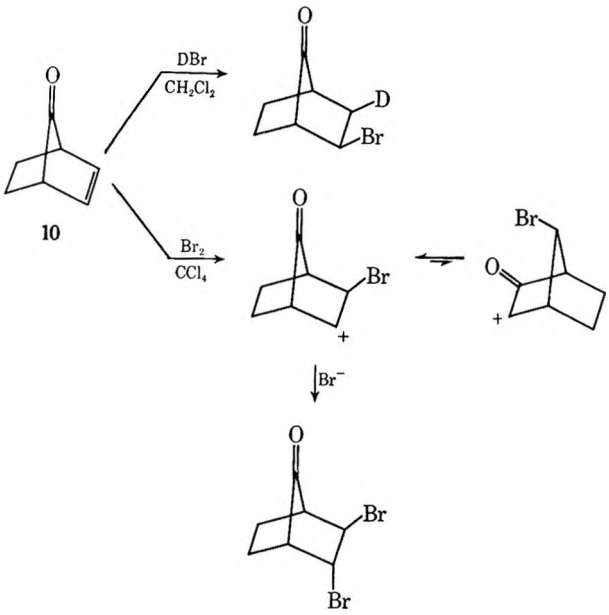
Our experimental results do not enable us to distinguish a rearranged product from an unrearranged adduct, but it appears essential to us that to account for this stereoselective *exo* nucleophilic attack on an intermediate cation one must assume the intervention of carbon bridging or a "windshield wiper effect."[22]

Where delocalization or rearrangement is not important, *trans* addition of molecular bromine can occur.[23,24] Probably the best example of this effect is the *trans* addition of bromine to 7-norbornenone (**10**). Whereas deuterium bromide added primarily *cis-exo* to this system,[2] bromine added to yield almost exclusively *trans*-2,3-dibromo-7-norbornanone (**11**). Apparently, when the delocalization or rapid migration of the σ electrons is not important, the product is determined by a bridged bromonium ion intermediate. In this case the rearranged cation would involve a juxtaposition of positive charges. Presumably it is the initial electrophilic attack that leads to the *exo* bromine as this preference has been noted elsewhere.[10,15,25] The structure of the dibromide **11** is readily confirmed by nmr analysis[21] as noted in the Experimental Section. See Scheme I.

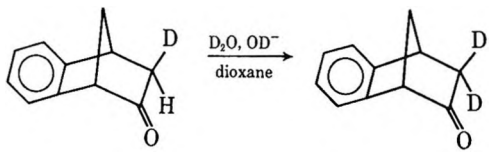
Torsional strain factors are probably not large enough to be significant here, especially in view of the weighted steric factor and the small dihedral angle between the bridgehead hydrogens and hydrogens on the

(13) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **75**, 422 (1953).
(14) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3738 (1967).
(15) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).
(16) J. Meinwald and G. A. Wiley, *J. Amer. Chem. Soc.*, **80**, 3667 (1958).
(17) L. H. Zalkow and A. C. Oehlschlager, *J. Org. Chem.*, **29**, 1625 (1964).
(18) Chemical shifts are in δ units (60 Mc) relative to tetramethylsilane.
(19) J. W. Wilt, G. Gutman, W. J. Ranus, Jr., and A. R. Zigman, *ibid.*, **32**, 893 (1967).
(20) G. W. Klumpp, A. H. Veefkind, W. L. deGraaf, and F. Bickelhaupt, *Ann.*, **706**, 47 (1967).
(21) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).
(22) H. C. Brown, Abstracts, the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p 20; "Non-Classical Intermediates," Organic Reaction Mechanisms Conference, Brookhaven, N. Y., Sept 1962.
(23) J. A. Berson and R. Swidler, *J. Amer. Chem. Soc.*, **76**, 4060 (1953).
(24) J. Mantecon, L. Cortes, E. Payo, and A. Salazar, *J. Org. Chem.*, **32**, 3796 (1967).
(25) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 4293 (1965), and references cited therein.

Scheme I



adjacent sp^2 carbons undergoing reaction. This expected leveling effect on torsional strain factors might possibly account for the enhanced rate of *endo* proton abstraction in the base-catalyzed enolate formation from 5-benzonorbornenone (**5**). By considering the extent of deuterium incorporation in **5** with the amount of exchange observed with an authentic sample of *exo*-6-deuterio-5-benzonorbornenone (**12**), we have concluded that the *endo* hydrogens exchange almost as rapidly as the *exo* hydrogens in this system[26] and selective monodeuteration is not possible. This is in contrast to norcamphor and norcamphor derivatives where selective *exo* monodeuteration is possible.[27] With dehydronorcamphor extensive dideuteration again occurs.[28]



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We tend to believe that for the polar addition of bromine to **1** a significant stereoelectronic factor is operating, and this factor accounts for the kinetic preference for the "regiospecific"[29] *exo* approach of the electrophilic bromine in spite of the hindered transition state resulting from this attack. It is possible that the energy difference responsible for this stereoelectronic factor is related to the ease of *exo* capture of the norbornyl cation compared with *endo* capture.[30] The lower energy of activation for *exo* approach of electrophilic bromine may arise from the extent of delocalization in the transition state. If this energy difference approaches the order of magnitude observed for the norbornyl cation,[30] it certainly would have to be considered as one of the major factors controlling the initial *exo* approach. Electrophilic attack from the *endo* side on **1** cannot so readily involve delocalization in the transition state if the electrophile is being complexed with the π orbital in the rate-determining step.[31] See Scheme II.

The subsequent *exo* nucleophilic attack by bromide ion on the cationic intermediate can best be accounted for in terms of the delocalized bridged intermediate.[32]

If such stereoelectronic factors do operate, they might also account for the *cis-exo* addition of deuterium bromide to **1**. Steric hindrance to approach in this case is not so large, however, as when the electrophile is bromine. Torsional factors perhaps cannot be ruled out entirely when the electrophile is a deuteron (and, by implication, a proton), but we believe that the stereoelectronic factor best accounts for the stereoselective *exo* approach.[33]

Experimental Section

Analytical.—Nuclear magnetic resonance spectra were obtained using a Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph A90-P3 instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were obtained with a Thomas–Hoover Uni-Melt apparatus and are uncorrected (taken in capillaries).

***anti*-7-Bromo-*exo*-5-benzonorbornenol (7).**—Benzonorbornadiene (**2**), 15.6 g (110 mmol), and N-bromosuccinimide (Arapahoe Chemicals, Inc.), 23.0 g (129 mmol), were dissolved in 125 ml of *t*-butyl alcohol and 180 ml of 1 *N* sulfuric acid. The solution was stirred at room temperature for 12 hr. The reaction solution was then added to 750 ml of water and extracted with three 150 ml-portions of methylene chloride. The extract was washed several times with a 10% sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated under vacuum to yield 23 g of a white solid. A small second spot which was not starting material could be detected by thin layer chromatography (tlc) over silica gel. The solid was recrystallized three times from hexane to yield 17.5 g (67%) of the pure solid, mp 95–96°. The nmr spectrum of the alcohol **7** is as expected.[14] The signal for the proton at C-7 occurs as a narrow multiplet, 3.5-cps width at half-height, at δ 4.08. The *endo* proton at C-5 occurs as a broad, complex multiplet centered at δ 3.88. The rearranged configuration is further established by the nmr spectrum of the corresponding ketone **4**.

Anal. Calcd for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64; Br, 33.42. Found: C, 55.04; H, 4.65; Br, 33.69.

***anti*-7-Bromo-5-benzonorbornenone (4).**—The oxidation of *anti*-7-bromo-*exo*-5-benzonorbornenol (**7**) to the corresponding ketone **4** was best accomplished using an Oppenauer oxidation. The alcohol **7**, 11.0 g (46 mmol), aluminum *t*-butoxide (Columbia Organic Chemicals Co., Inc.), 11 g, and *p*-benzoquinone, 12 g, were added to 300 ml of dry benzene. The black reaction mixture was refluxed with stirring for 12 hr; 5 g of additional aluminum *t*-butoxide was added; and the mixture was refluxed for another 3 hr. The cooled reaction mixture was then added to 500 ml of 3 *N* hydrochloric acid, and the reaction flask was washed thoroughly with benzene. The combined mixture was filtered with the aid of Celite. The benzene layer was removed and washed with three 250 ml-portions of 3 *N* hydrochloric acid,

(26) C. P. Wick, unpublished results of this laboratory.

(27) A. F. Thomas, R. A. Schneider, and J. Meinwald, *J. Amer. Chem. Soc.*, **89**, 68 (1967).

(28) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *Tetrahedron Lett.*, 4465 (1965). These authors offer an alternate explanation based on the relief of nonbonded repulsions to account for the *exo/endo* rates of exchange.

(29) A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968).

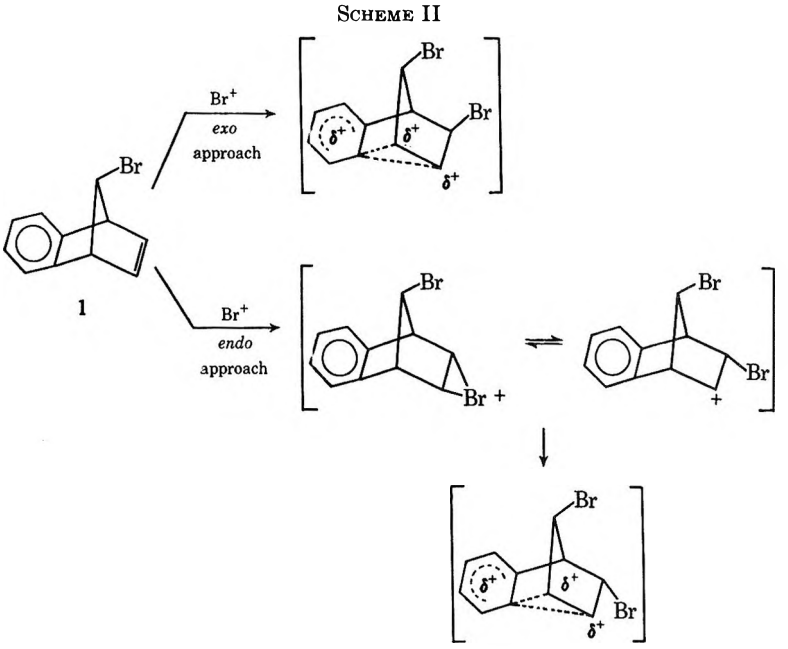
(30) H. L. Goering and C. B. Schewene, *ibid.*, **87**, 3516 (1965).

(31) J. E. Dubois and F. Garnier, *Chem. Commun.*, 241 (1968).

(32) (a) D. V. Braddon, G. A. Wiley, J. Dirlam, and S. Winstein, *J. Amer. Chem. Soc.* **90**, 1901 (1968); (b) H. Tanida, H. Ishitobi, and T. Irie, *ibid.*, **90**, 2688 (1968); (c) H. C. Brown and G. L. Tritle, *ibid.*, **90**, 2689 (1968).

(33) For recent reviews on electrophilic additions, see P. B. D. de la Mare and R. Boulton, "Electrophilic Additions to Unsaturated Systems," Elsevier Publishing Co., New York, N. Y., 1966, and B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms," John Wiley & Sons Ltd., London, 1965 and 1966.

SCHEME II



then with three 200 ml-portions of a 5% sodium hydroxide solution, and finally with water. The benzene extract was dried over anhydrous magnesium sulfate and removed under vacuum. A viscous yellow liquid remained which showed only one spot by tlc. Distillation under reduced pressure, bp 94–96° (0.02 mm), yielded 7.2 g (65%) of a colorless liquid. The distillate solidified upon standing to a crystalline mass. Recrystallization from cyclohexane yielded white crystals, mp 54.5–55.5°. The nmr spectrum of the ketone **4** is quite distinct. The signal for the proton at C-7 occurs as a narrow multiplet at δ 4.37. The *exo* proton at C-6 exists as a quartet, J_{gem} = 17.0 cps and $J_{1,6}$ = 3.8 cps, centered at δ 2.77. The *endo* proton at C-6 occurs as a quartet, J_{gem} = 17.0 cps and $J_{6,7}$ = 2.4 cps, centered at δ 1.83.

Anal. Calcd for $C_{11}H_9BrO$: C, 55.72; H, 3.83; Br, 33.70. Found: C, 55.51; H, 3.69; Br, 33.90.

Lithium Aluminum Hydride Reduction of 4.—A small sample of *anti*-7-bromo-5-benzonorbornenone (**4**) was reduced with lithium aluminum hydride in ethyl ether in a manner similar to that used for the reduction of 5-benzonorbornenone (**5**).[13] A near-quantitative yield of an alcohol was obtained that was identical in spectral and physical properties with those of an authentic sample of *anti*-7-bromo-*exo*-5-benzonorbornenol (**7**).

Hydrobromination of *anti*-7-Bromobenzonorbornadiene (1).—*anti*-7-Bromobenzonorbornadiene (**1**),[10] 1.0 g (4.5 mmol), was dissolved in 150 ml of reagent methylene chloride, and the solution was saturated with anhydrous hydrogen bromide at 0°. The reaction flask was tightly stoppered and allowed to stand at 0° in the dark for 25 hr. The excess hydrogen bromide and methylene chloride were removed by gentle warming and then under aspirator vacuum. Fresh methylene chloride was added, and the solution was dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and produced a near-quantitative yield of the dibromide **3**. Only one spot could be detected by tlc; its nmr spectrum was identical with that of an authentic sample of **3**.[10] Treatment with activated charcoal and recrystallization from ethanol produced white crystals, mp 78–79° (lit. mp 78–79.5[10] and 77–77.5°[15]).

Deuterobromination of *anti*-7-Bromobenzonorbornadiene (1). The addition of deuterium bromide was carried out as with the corresponding hydrobromination. The deuterium bromide was generated by the addition of deuterium oxide, 99.8% (Columbia Organic Chemicals Co., Inc.) to Eastman phosphorous tribromide. The deuterium bromide was trapped and distilled from a Dry Ice–acetone trap into a methylene chloride solution of **1**.

***anti*-7,*cis*-*exo*-5,6-Tribromobenzonorbornene (9).**—*anti*-7-Bromobenzonorbornadiene (**1**), 1.0 g (4.5 mmol), was dissolved in 5 ml of carbon tetrachloride, and the reaction flask was wrapped in aluminum foil. A 10% solution of bromine in carbon tetrachloride was added dropwise until the bromine color was maintained. The adduct immediately started to crystallize from the carbon tetrachloride solution. Removal of the solvent under vacuum gave a quantitative yield of a slightly yellow solid. Only one spot could be detected by tlc for this crude crystalline product. The adduct was recrystallized from benzene, mp 192–192.5°.

Anal. Calcd for $C_{11}H_9Br_3$: C, 34.68; H, 2.38; Br, 62.94. Found: C, 34.79; H, 2.38; Br, 62.73.

***trans*-2,3-Dibromo-7-norbornanone (11).**—7-Norbornenone (**10**),[34] 5.0 g (46 mmol), was dissolved in 11 ml of carbon tetrachloride and cooled in a salt–ice bath. To this solution was added dropwise a 40% solution of bromine in carbon tetrachloride at such a rate as to maintain the temperature below 0°. The addition of bromine was continued until a faint bromine color persisted. The solvent was removed under vacuum and the crude product examined by nmr spectroscopy. A very small amount of an unidentified product(s) was observable. A vpc analysis indicated about 10% of some impurity. The crude product was distilled, bp 140° (2 mm), and then the resulting low-melting solid "sublimed" six times at 100° (0.2 mm) to yield a clear solid, mp 52–54°. The nmr spectrum is quite conclusive.[21] The *exo* proton at C-2 occurs as broad multiplet centered at δ 4.73, whereas the *endo* hydrogen at C-3 occurs as a sharp doublet, $J_{2,3}$ = 2.6 cps, at δ 4.21.

Anal. Calcd for $C_7H_8Br_2O$: C, 31.37; H, 3.01; Br, 59.65. Found: C, 31.14; H, 2.81; Br, 59.44.

Registry No.—**1**, 7605-10-9; **4**, 17497-60-8; **7**, 17497-61-9; **9**, 17497-62-0; **11**, 17519-24-3.

Acknowledgments.—We are indebted to the Petroleum Research Fund of the American Chemical Society, Grant No. 1100-G1, and the Graduate School of the University of Minnesota for support of this work. One of us (C. S. I.) as a National Science Foundation Undergraduate Research Participant would like to thank the National Science Foundation.

(34) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

The Basicities of the Monoxides and Dioxides of *p*-Dimethylaminoazobenzene

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The three monoxides and two dioxides of *trans*-dimethylaminoazobenzene were synthesized, the assignments of various isomers were rechecked, and previous literature assignments were corrected. The basicities of these compounds were determined spectrophotometrically and potentiometrically. It was demonstrated that, in each compound, the first protonation occurs at the dimethylamino or oxidodimethylamino [$(CH_3)_2\overset{+}{N}O$] group in dilute acid, while protonation of the azo or azoxy group takes place only at fairly high concentration of sulfuric acid. The basicity data were analyzed by use of the Hammett equation, and the results were incorporated into previously established Hammett correlations. Estimates of the tautomeric equilibrium constants between the two first conjugate acids of each compound were obtained. The basicities of the same compounds in the first excited singlet states were estimated by use of the Förster cycle, and the tautomeric equilibrium constants in these states were derived. In several cases a reversal of the direction of the equilibrium between ground and excited states is demonstrated.

Derivatives of *p*-dimethylaminoazobenzene (DMAB, butter yellow) are of interest because of their well-known carcinogenic activity.[2] Previous papers from this laboratory have reported a considerable body of information concerning acid–base reactions of DMAB, of azoxybenzene, and of derivatives of both compounds.[3] The monoxides and dioxides of DMAB were first prepared by Anderson[4] and by Pentimalli;[5] polarographic reduction potentials on these were obtained and discussed by Costa and Puxeddu.[6] We have now undertaken a study of the basicities and of the electronic absorption spectra of the oxides of DMAB. In this study we were forced to reexamine the isomer assignments of the various products. We were further able to relate the basicities obtained in this work into the general framework of the acid–base reactions of azo- and azoxybenzene derivatives, as it has been developed in previous papers from this laboratory.[3,7] After this work was complete, there appeared a careful study of the various oxidation processes of DMAB and of the interrelation of the oxidation products.[8]

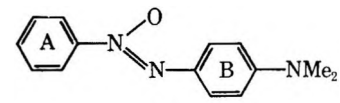
Results and Discussions

Syntheses and Isomer Assignments.—Oxidation of DMAB by perbenzoic acid in chloroform at reduced temperature yields *p*-phenylazo-N,N-dimethylaniline oxide [*p*-(oxido-N,N-dimethylamino)azobenzene] (**1**).[5,9] The *p*-dimethylaminoazoxy compounds, N,N-dimethyl-*p*-(phenyl-ONN-azoxy)aniline, the α isomer (**2**), and N,N-dimethyl-*p*-(phenyl-NNO-azoxy)aniline, the β isomer (**3**), were prepared by condensation of N-phenylhydroxylamine with N,N-dimethyl-*p*-nitrosoaniline in basic media and separated by column chromatography on neutral alumina.[4]

Oxidation of DMAB with hydrogen peroxide in glacial acetic acid at moderate temperatures yields a mixture of dioxides (and possibly other compounds). Column chromatography, in our hands, failed to yield pure products; however, one pure dioxide, mp 145°, was obtained by fractional crystallization of the reaction product from tetrahydrofurane. Oxidation under similar conditions of the monoxide of mp 121.5° yielded the other of the two oxides, mp 150°. These synthetic routes are summarized in Scheme I.

Anderson[4] originally assigned the monoxide of mp 122° to structure **2**, and the isomer of mp 126° to structure **3**, on the basis of uv absorption spectra. The spectral difference between the two compounds were quite small, and the argument is based on the assumption that all α and all β isomers show similar shifts of absorption bands, independent of the nature of the substituent present. The assumption does not seem *a priori* valid, and consequently Anderson's assignments are not convincing.

Pentimalli used Anderson's assignments of the monoxides. To confirm this assignment, he treated both compounds with bromine and found that under a standard set of very mild conditions only the compound of mp 122° was brominated. He concludes that this finding confirms Anderson's assignment of this compound as the β isomer (**3**). In our opinion, Pentimalli's



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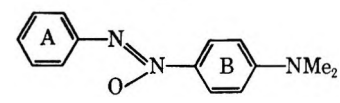

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bromination experiment, on the contrary, argues for the opposite assignment. Following the work of Angeli,[10] it may be assumed that a ring adjacent to the NO side of the azoxy group is very difficult to brominate. In other words, ring A of **2** and ring B of **3** may be as-

(1) U. S. Public Health Service Predoctoral Fellow.

(2) J. A. Miller and E. C. Miller, *Advan. Cancer Res.*, **1**, 339 (1953); J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Res.*, **17**, 387 (1957); *cf.* C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).

(3) (a) S. J. Yeh and H. H. Jaffé, *ibid.*, **81**, 3283 (1959); (b) C. S. Hahn and H. H. Jaffé, *ibid.*, **84**, 949 (1962); (c) M. Isaks and H. H. Jaffé, *ibid.*, **86**, 2209 (1964).

(4) A. Anderson, *J. Chem. Soc.*, 1722 (1952).

(5) L. Pentimalli, *Tetrahedron*, **5**, 27 (1959).

(6) G. Costa and A. Puxeddu, *Gazz. Chim. Ital.*, **89**, 1050 (1959).

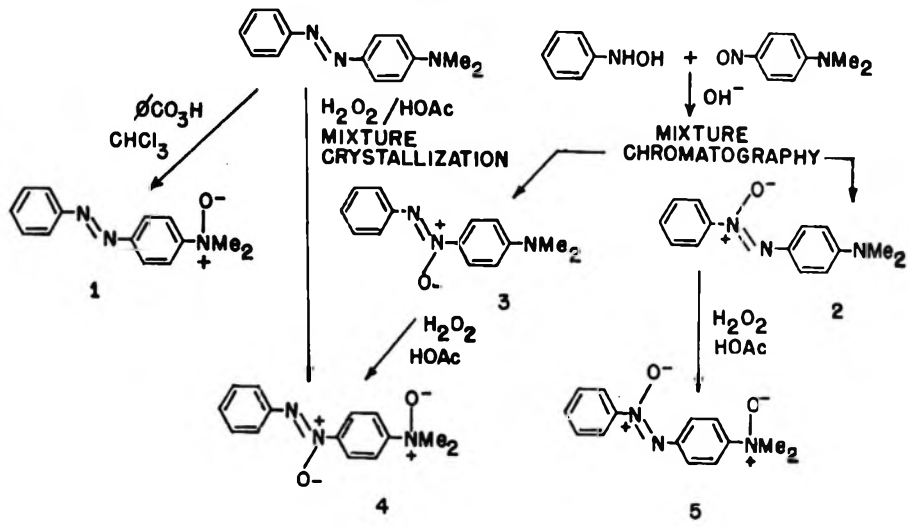
(7) (a) S. J. Yeh and H. H. Jaffé, *J. Amer. Chem. Soc.*, **81**, 3279 (1959); (b) J. H. Collins and H. H. Jaffé, *ibid.*, **84**, 4708 (1962).

(8) A. F. Douglas, P. H. Gore, and J. W. Hooper, *J. Chem. Soc.*, 674 (1967).

(9) International rules for nomenclature provide no name for the "dimethylamine oxide" [$(CH_3)_2\overset{+}{N}O$] group as a substituent, but require naming the compound as an amine oxide. Since, in this work, we will be interested in the effect of this group as a substituent on an aromatic compound, we propose to use the name N-oxido-N,N-dimethylamino, or simply oxidodimethylamino for this group. Upon protonation, the group $(CH_3)_2\overset{+}{N}OH$ is readily named N-hydroxy-N,N-dimethylammonio.

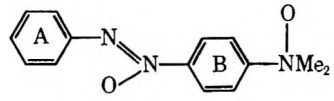
(10) A. Angeli, *Atti Accad. Naz. Lincei. Mem. Classe Sci. Fis. Mat. Nat. Sez. I.ª*, **24**, 1190 (1915).

SCHEME I



sumed to resist bromination. Ring B of 2 and ring A of **3** are similar, except for the presence of the strongly activating dimethylamino substituent in the former. Hence, if only one of the two compounds is brominated under a given set of conditions, we must conclude that this is 2.

Angeli studied the bromination of the oxidation product (by hydrogen peroxide in glacial acetic acid) of DMAB, to elucidate its structure, which should have been **4** or **5**. The brominated material was reduced



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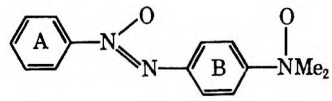

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with tin and hydrochloric acid, and benzoylated. The only brominated product isolated was benzoyl *p*-bromoaniline. This product can arise only from bromination of ring A of **4**, since ring A of **5** should not brominate. Thus, the oxidation product of DMAB, mp 145°, is **4**. The syntheses by Pentimalli of **4** and **5** from **3** and **2**, respectively, repeated in this work for **5** complete the stereochemistry and the relations between the compounds in Scheme I.

Finally, the interpretation of the basicities obtained in this work corroborate the assignments made here, as will be discussed below.

Unfortunately, the recent work of Douglas, Gore, and Hooper[8] is based on the Anderson–Pentimalli assignments. Consequently, many of the structures they give refer to the wrong isomer. It seems possible that the α–β rearrangements reported by these authors are only apparent because of the wrong assignments of isomers.

Basicities and Spectra.—The basicities of compounds **1–5** were determined and are expressed throughout as the pK_a of the conjugate acids. Each compound presents two separate and distinct pK's. In the cases of compounds **1**, **4**, and **5**, the pK corresponding to the first basicity (pK_2) produced no significant change in the uv absorption spectra, and consequently use had to be made of a titration method. All other pK's were determined spectrophotometrically. The results are summarized in Table I.

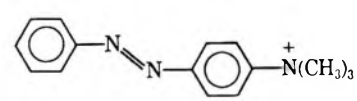
TABLE I

THE BASICITIES (AS pK_a's OF THE CONJUGATE ACIDS) OF THE OXIDES OF DMAB

No.	Compound	pK_{a2}[a]	pK_{a1}[a]
	p-Dimethylaminoazobenzene	2.96 ± 0.03	−5.34 ± 0.02
1	*p*-Oxidodimethylaminoazobenzene	4.11 ± 0.02	−4.65 ± 0.04
2	α-*p*-Dimethylaminoazoxybenzene	1.93 ± 0.05	−8.51[b]
3	β-*p*-Dimethylaminoazoxybenzene	2.62 ± 0.04	−8.02 ± 0.03
4	β-*p*-Oxidodimethylaminoazoxybenzene	4.03 ± 0.03	−8.00 ± 0.05
5	α-*p*-Oxidodimethylaminoazoxybenzene	3.71 ± 0.04	−8.41 ± 0.03

[a] Uncertainties given are standard deviations of at least five and usually more measurements. [b] Extrapolated value; see text.

Since all compounds have two basic centers, it is essential to identify the site of protonation in each step of basicity, *i.e.*, the structure of the conjugate acid. This is most easily done by a comparison of the uv absorption spectra of the compounds in solution of different acidity with each other and with certain reference compounds. All spectral data are summarized in Table II. The uv spectrum of **1** is extremely similar to the spectra of azobenzene and of the other azobenzene derivatives carrying a quaternized ammonio substituent, *e.g.*, N,N,N-trimethylammonioazobenzene, **6** (*cf.* Figure 1). This



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is, of course, due to the well-known fact that a quaternary ammonio substituent has no significant effect on the spectra of aromatic compounds in which it is substituted. Thus, the oxidodimethylamino group [$(CH_3)_2N\rightarrow O$] behaves as a quaternary ammonio group, which is not unexpected. The spectrum of the first conjugate acid of **1** again is almost identical with that of the free base (and with those of azobenzene and of **6**). This fact leads to the conclusion that the first protonation occurs completely at the oxidodimethyl-

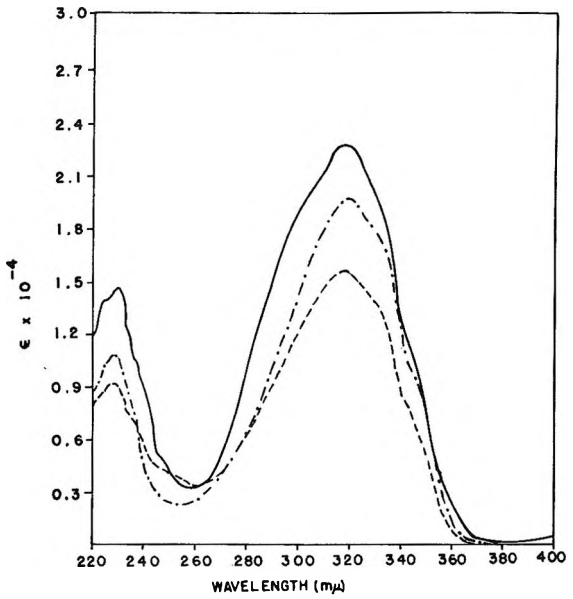


Figure 1.—Spectra of azobenzene (———), N,N,N-trimethylammonioazobenzene (– – – –), and *p*-phenylazo-N,N-dimethylaniline oxide (– · – · –).

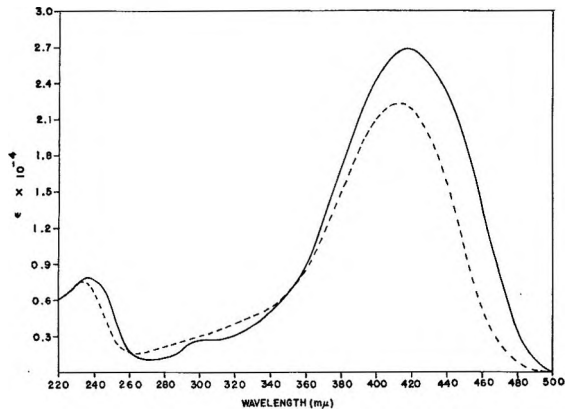


Figure 2.—Spectra of the first conjugate acid (BH^+) of azobenzene (———) and of the second conjugate acid (BH_2^{2+}) of *p*-phenylazo-N,N-dimethylaniline oxide (– – – –).

amino group (*i.e.*, at the N-oxido oxygen atom), and that the hydroxydimethylammonio group also behaves as a normal quaternary ammonio group.

In the second protonation of **1** (Figure 2), the spectrum changes drastically, giving a strong band at 420 mμ. This spectrum is almost identical with those of the conjugate acids of azobenzene and of **6**, and thus the second protonation of **1** occurs at the azo linkage.

The situation is quite similar for compounds **4** and **5**. The spectra of both compounds in 95% ethanol (325 and 320 mμ) resemble closely that of azoxybenzene (*cf.* Figure 3). Again the oxidodimethylamino group does not significantly affect the spectrum of the parent compound. The spectra of the first conjugate acids of **4** and **5** also closely approximate those of the free bases, again showing that protonation occurs at the oxidodimethylamino group exclusively. The spectra of the second conjugate acids of **4** and **5** (376 and 384 mμ) are shifted bathochromically relative to free base and first conjugate acid, and now resemble closely the spectrum of the first conjugate acid of azoxybenzene (Figure 4). Actually, the bathochromic shifts occuring upon protonation are 58 mμ for **4**, 59 mμ for **5**, and 62 mμ for azoxybenzene.

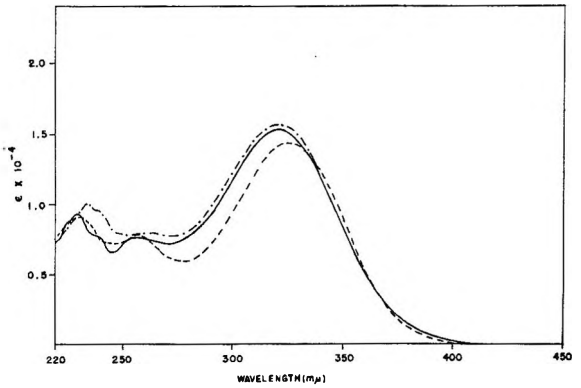


Figure 3.—Spectra of azoxybenzene (———), α-*p*-oxidodimethylaminoazoxybenzene (– – – –), and β-*p*-oxidodimethylaminoazoxybenzene (– · – · –).

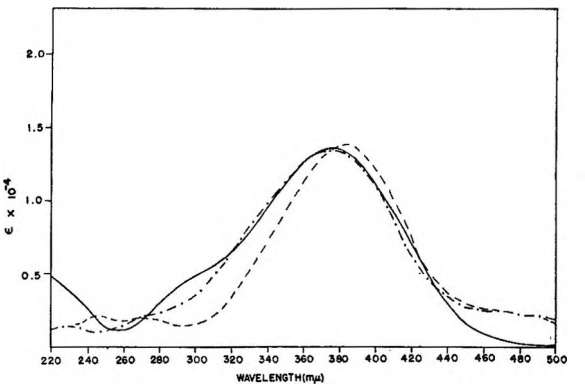


Figure 4.—Spectra of the first conjugate acid (BH^+) of azoxybenzene (———), of the second conjugate acid (BH_2^{2+}) of α-*p*-oxidodimethylaminoazoxybenzene (– – – –), and of the second conjugate acid (BH_2^{2+}) of β-*p*-oxidodimethylaminoazoxybenzene.

TABLE II
ULTRAVIOLET ABSORPTION SPECTRA OF AZOBENZENE, AZOXYBENZENE, OXIDIZED FORMS, AND ACID FORMS

		$^1B \leftarrow {}^1A$		$^1H \leftarrow {}^1A$		$^1W \leftarrow {}^1A$		$^1G \leftarrow {}^1A$	
No.	Compound	λ, mμ	ε × 10^{-4}	λ, mμ	ε × 10^{-4}	λ, mμ	ε × 10^{-4}	λ, mμ	ε × 10^{-4}
	Azobenzene	314	2.26	230	1.45	420	0.076		
	Azobenzene conjd acid	418	2.69	236	0.80	300	0.30		
	Azoxybenzene	322	1.54	235	0.92			260	0.78
	Azoxybenzene conjd acid	376	1.35	232	0.34			290	0.40
1	*p*-Phenylazo-N,N-dimethylaniline oxide	318	1.97	228	1.08	440	0.06		
	1st conjd acid	320	1.53	228	0.99				
	2nd conjd acid	413	2.24	234	0.75				
2	α-*p*-Dimethylamino-azoxybenzene	395	2.42	246	1.16			320 308	0.92
	1st conj acid	326	1.31	241	1.01			250	0.92
3	β-*p*-Dimethylamino-azoxybenzene	418	2.90	260	1.26				
	1st conjd acid	315	1.48	225	0.98			259	0.98
	2nd conjd acid	366	1.31						
4	β-*p*-Oxidodimethyl-aminoazoxy-benzene	322	1.60	230	0.91			261	0.80
	1st conjd acid	318	1.30	290	0.46				
	2nd conjd acid	376	1.33	230	0.14			272	0.20
5	α-*p*-Oxidodimethyl-aminoazoxy-benzene	327	1.44	234	1.01			256	0.80
	1st conjd acid	326	1.33	236	0.92				
	2nd conjd acid	383	1.38	246	0.20				

The spectra of compounds **2** and **3** in 95% ethanol are shown in Figure 5. They are considerably bathochromically shifted relative to azoxybenzene, owing to the

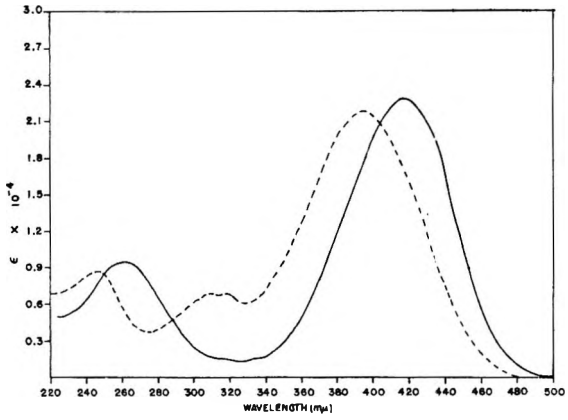


Figure 5.—Spectra of α- (- - - -) and β-p-dimethylaminoazoxybenzenes (———) in 95% ethanol

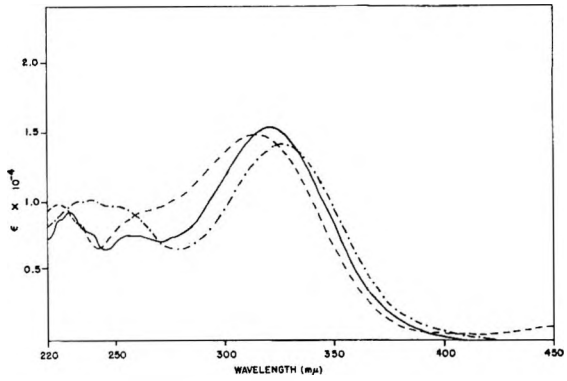


Figure 6.—Spectra of azoxybenzene (———), of the first conjugate acid (BH^+) of β-p-dimethylaminoazoxybenzene (- - - -), and of the first conjugate acid (BH^+) of α-p-dimethylaminoaxozybenzene (- · - · -).

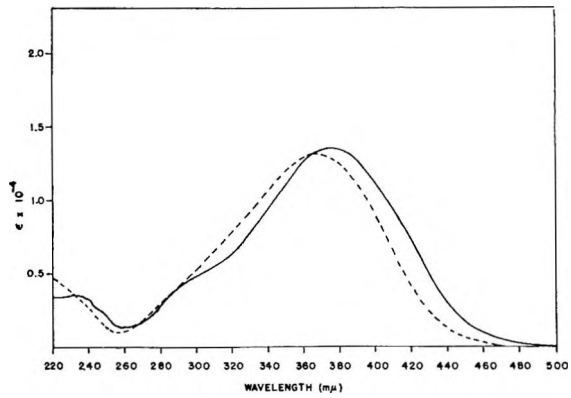


Figure 7.—Spectra of the first conjugate acid (BH^{2+}) of azoxybenzene (———) and of the second conjugate acid (BH_2^{2+}) of β-p-dimethylaminoazoxybenzene (- - - -).

effect of the free dimethylamino group. In slightly acidic solution, the spectra shift strongly hypsochromically and now closely resemble the spectrum of azoxybenzene (Figure 6) indicating that protonation has occurred on the dimethylamino group. The spectrum of the second conjugate acid of **3** (Figure 7) now closely resembles that of the conjugate acid of azoxybenzene. Compound **2** in strongly acidic solution was unstable and the spectrum of the second conjugate acid of **2** could not be observed. The second pK therefore could not be determined, and the value listed in Table I is a derived value as discussed below.

Thus we have seen that, in all of the compounds treated, the dimethylamino or oxidodimethylamino group protonates exclusively first, and the azo or azoxy group protonates at much higher acidity.

Application of the Hammett Equation.—Since we have previously examined the basicities of long series of azo and azoxy compounds, it is of interest to see how the new measurements reported fit in with the other material.

First, compound **1**, in its second protonation, is an azobenzene substituted by a hydroxydimethylammonio group. From $\rho = 2.20$ and $pK_0 = -2.90$[7a] we calculate a σ of 0.795 for this group. Further estimates of this same constant may be obtained from the second protonation of **4** and **5** and ρ values for protonation of azoxy compounds,[3b] $\rho_\beta = 1.735$, $\rho_\alpha = 2.508$, and $pK_0 = -6.45$, leading to 0.90 and 0.795, respectively. ρ_β is the least certain of the ρ values used, and its standard deviation exceeds 10% of its absolute value; consequently the value of 0.90 for *o*-hydroxydimethylammonio is least reliable, and the other two values agree fortuitously well. We may accept a value of about 0.80 for this constant. This is not significantly different from the σ values for other quarternary ammonio groups: *p*-NMe_3^+, 0.82; *p*-$NHMe_2^+$, 0.82. The second protonation of compound **3** provides an estimate of σ (*p*-$NHMe_2^+$), again +0.90 and again a little higher than expected since it uses the same low ρ_β of 1.735. This type of argument now permits us to calculate pK_1 of **2**, which was experimentally unaccessible. Using $\rho_\alpha = 2.508$, $pK_0 = -6.45$, and σ (*p*-$NHMe_2^+$) = −0.82 gives p$K_1 = -8.51$.

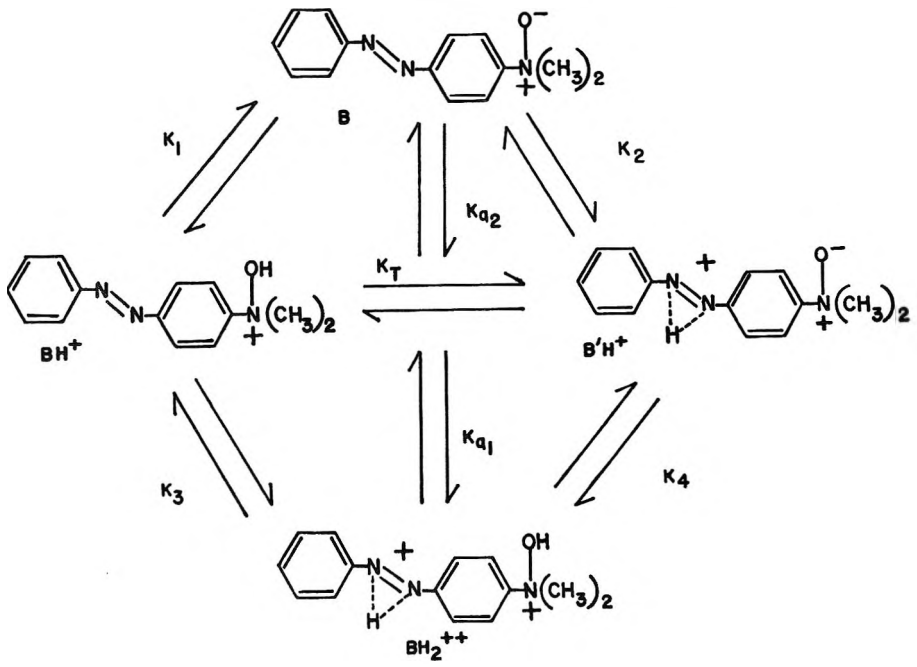
The σ values calculated for the *p*-hydroxydimethylammonio group in the preceding paragraph provide corrobatory evidence for the isomer assignment above. If the assignment were reversed, in accordance with the suggestions of Anderson and Pentimalli, σ values of 0.63 and 1.13 would result; the lack of agreement of these values with one another and with the value of 0.795 obtained from **1** strongly suggest that their assignment is inconsistent.

It now seems of interest to attempt to apply the Hammett equation to the protonation of the dimethylamino group (compounds **2** and **3**) and the oxidodimethylamino group (compounds **1**, **4**, and **5**). Unfortunately, very little information is available on substituent effects on the basicity of dimethylaniline oxide. From the pK's of **2** and **3**, together with the known application of the Hammett equation to dimethylanilines, we can calculate σ values for *p*-phenylazoxy-ONN-**2**, and *p*-phenylazoxy-NNO-**3**. The values so obtained are 0.78 and 0.56, respectively.

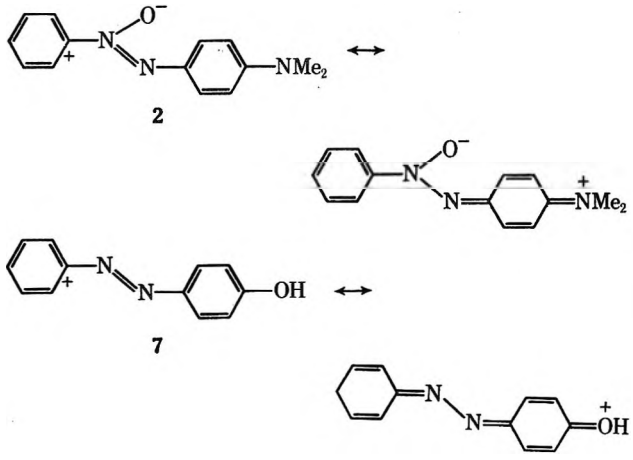
For the *p*-phenylazo group, Hammett originally reported a σ^- value of 0.64. The data of Yeh and Jaffé[11] on phenylazophenols lead to a value of 0.70.[11] Application of the values so obtained to the basicities of the substituted dimethylaniline oxides is not straightforward. The values given above are σ^- values. In *p*-phenylazophenol, **7**, and in **2**, quinoid resonance structures may be expected to make significant contributions, more so in **2** than in **7**, because a charge separa-

(11) S. J. Yeh and H. H. Jaffé, *J. Amer. Chem. Soc.*, **81**, 3287 (1959).

SCHEME II



tion exists in any form of 2, but not in the "normal" form of 7. No such resonance can be written for 3, and consequently the σ^- and σ values should be the same.



According to the data for the pK_2 of 1, 4, and 5 in Table I, σ (p-C_6H_5–NN) > σ (p-C_6H_5–NNO) > σ (p-C_6H_5–ONN), although all values are very close. Unfortunately, the aniline oxides are not very sensitive to substituent effects, and any further refinement of these arguments must await carefully collected data on some other reaction series, preferably one which is more sensitive to substituent effects.

Tautomeric Equilibria.—Although we have concluded above from spectroscopic evidence that, in each compound, the first protonation occurs at the dimethylamino or oxidodimethylamino group, it is of interest to attempt to obtain estimates of the equilibrium constants for the equilibria between the two tautomers of the first conjugate acid of the compounds under investigation. The equilibrium is shown in Scheme II. In this scheme we will call the ammonium or hydroxyammonium form BH^+, the azonium or azoxonium form $B'H^+$; K_{a1} and K_{a2} are our measured basicities. The seven equilibrium constants in this scheme are interrelated, and only three are independent. The desired K_t can be obtained from any one of several relations, *e.g.*,

$$K_t = [B'H^+]/[BH^+] = K_1/K_2 = K_4/K_3 \quad (1)$$

$$K_1K_3 = K_2K_4 \quad (2)$$

As a working hypothesis, we will assume that

$$K_{a1} = K_3,\ K_{a2} = K_1 \quad (3)$$

and test this hypothesis later. The K_2 for 1, 4, and 5 is the azo or azoxy protonation of an azo- or azoxybenzene bearing an oxidodimethylamino substituent. Assuming the σ value for this substituent to be about equal to that of other quaternary ammonio groups, we may estimate these K_2 values as given in Table III. The values of K_4 cannot readily be estimated independently, since they involve protonation of the oxidodimethylamino group, about which virtually no information is available, as discussed above, and hence were estimated from eq 2.

TABLE III

pK AND K_t VALUES FOR EQUILIBRIUM SCHEME

No.	Compound	pK_1	pK_2	pK_3	pK_4	K_t
	p-Dimethylaminoazobenzene	4.42	5.27	-4.43	-5.21	7.08
1	p-Oxidodimethylaminoazobenzene	4.11	-4.80	-4.65	4.26	1.23×10^{-9}
2	α-p-Dimethylaminoazoxybenzene	1.93	-2.19	-8.47	-4.35	7.59×10^{-5}
3	β-p-Dimethylaminoazoxybenzene	2.62	-6.07	-8.02	$+0.67$	2.04×10^{-9}
4	β-p-Oxidodimethylaminoazoxybenzene	4.03	-7.87	-8.00	$+3.90$	1.26×10^{-12}
5	α-p-Oxidodimethylaminoazoxybenzene	3.71	-8.51	-8.41	$+3.81$	6.03×10^{-13}

From the K_2 and K_4 values so obtained, we can now readily calculate K_t, as listed in Table III. These values are seen to be rather extreme. We can now reassess our approximation made in eq 3. Using

$$K_{a2} = \frac{[B][H^+]}{([BH^+] + [B'H^+])} = \frac{[B][H^+]}{[BH^+](1 + K_t)} = \frac{K_1}{1 + K_t}$$

since the K_t values which we find are very small with respect to 1, eq 3 is verified. Thus the data obtained here are consistent with the spectroscopic findings. Of course, the K_t values are extremely crude, and not much significance should be attached to them except for the order of magnitude.

Equilibrium Constants in Singlet Excited State.—It has been demonstrated in recent years that excited-state equilibrium constants, pK^*'s, can be obtained for acid–base reactions.[12] The simplest method for obtaining such data is through application of the Förster cycle[13] to the absorption spectra of the conjugate acid–base pair. Using this method, pK_1^* and pK_3^* were determined for the compounds in this study. The requisite spectroscopic data are taken from Table II. Azo- and azoxybenzene are included for comparison. (pK_1^* values could not be calculated for α-*p*-dimethylaminoazoxybenzene since no ground-state pK_{a1} and no spectroscopic information on the second conjugate acid is available.)

Since the Förster cycle depends on spectroscopic data for the various chemical species involved in the equilibrium scheme (Scheme II), pK^*'s estimated actually refer to the individual partial equilibrium constants, not to the directly observable pK_a's. Thus, for compounds **1**, **4**, and **5**, where the first protonation step in the ground state is, to an excellent approximation, expressed purely as K_1, the insensitivity of the uv spectra leads to K_1^* values equal to the ground-state values. Upon second protonation of these compounds, which in the ground state corresponds to K_3, a strong bathochromic shift is observed, which leads to the K_3^* values reported in Table IV.

TABLE IV
CALCULATIONS OF pK_{a1}^* AND pK_{a2}^*

No.	Compound	pK_3^* ΔpK_a	pK_{a2}	pK_3^*	pK_1^* ΔpK_a	pK_{a1}	pK_1^*
	Azobenzene				16.6	−2.9	13.7
	Azoxybenzene				10.5	−6.5	4.1
1	*p*-Oxidodimethylaminoazobenzene	0.0	4.1	4.1	14.8	−4.7	10.2
2	α-*p*-Dimethylaminoazoxybenzene	−13.0	1.9	−11.1			
3	β-*p*-Dimethylaminoazoxybenzene	−18.2	2.6	−15.6	10.7	−8.0	2.7
4	β-*p*-Oxidodimethylaminoazoxybenzene	0.0	4.0	4.0	10.0	−8.0	2.0
5	α-*p*-Oxidodimethylaminoazoxybenzene	0.0	3.7	3.7	9.8	−8.4	1.4

In the ground state we were able to equate pK_{a1} with pK_3 and pK_{a2} with pK_1. If we attempt to do the same in the excited state, we are led to the contradictory finding that the first pK of the second conjugate acid in these compounds is larger than the second pK. The most probable cause for this reversal may be a change in sign of pK_t between ground and excited states. Thus we must try to estimate K_t^*. To do so, estimation of K_2^* and/or K_4^* would be sufficient.

For compound **1**, K_4^* of the equilibrium scheme (II) refers to protonation of the amino oxide group. It has been shown that this reaction yields identical pK values for ground and excited states and consequently pK_4^* = pK_4. Using eq 1 and 2, pK_2^* = +10.42, $K_t^* = 2.04 \times 10^6$. From these data it is seen that, in the excited state, *p*-oxidodimethylaminoazobenzene protonates first virtually exclusively at the azo group, and only at higher acidity at the oxidodimethylamino group, while the order is just the reverse in the ground state.

For compounds **4** and **5**, again it can be presumed that pK_4 = pK_4^*, values for pK_2^* and K_t^* can be determined as above, and similar conclusions are drawn.

In contrast to the findings for the last three compounds, for α- (**2**) and β-*p*-dimethylaminoazoxybenzene (**3**), a considerable change in basicity occurs between the ground and excited state for both the first and second ionization constant.

It has already been shown that initial protonation of both isomers occurs at the dimethylamino group. Since the unshared electron pair on the nitrogen atom of this group is in conjugation with the aromatic portion of the molecule, the electron distribution about the nitrogen atom will be directly affected by the transition.

Since K_{a1}^* is not known for the α isomer, K_t^* cannot be determined. However, for the β isomer, K_t^* value can be calculated through use of the Hammett equation and the equilibrium scheme (II). It is seen that K_2^* represents protonation of the azoxy group in the system under investigation. An evaluation of excited-state acidity constants for a series of β-azoxybenzenes and determination of the pK^*–σ relationship for this series of compounds is given later in this paper. From these data, $\rho^* = 1.97$, $\log K_0^* = -2.86$, σ [N(CH$_3$)$_2$] = −0.83, and $\log K_2^* = -4.50$; $K_t^* = 1.20 \times 10^{20}$.

Since the first protonation of all of our compounds in the ground state occurs on the dimethylammonio or oxidodimethylammonio group, at the time of second protonation we deal with azo and azoxy compounds bearing the nonconjugated, purely inductive substituents dimethylammonio and hydroxydimethylammonio. Consequently the values of ΔpK_3 obtained for compound **1** should resemble ΔpK_a for azobenzene, and ΔpK_3 for the other compounds should resemble ΔpK_a for azoxybenzene. These similarities are well borne out by the data in Table IV.

The tremendous change in the equilibrium upon excitation of the azo and azoxy compounds in this study is aptly shown by comparison of K_t values in Tables III and V. The equilibrium between the two forms of the conjugate acids shifts from the ammonium or hydroxyammonium form in the ground state to the hydroxyazonium or azonium form in the excited state for **1** and **3**. For compounds **4** and **5**, although the equilibrium is not shifted, the change in K_t is still quite large.

TABLE V
pK^* AND K_t^* FOR THE EQUILIBRIUM SCHEME

No.	Compound	pK_1^*	pK_2^*	pK_3^*	pK_4^*	K_t^*
1	*p*-Oxidodimethylaminoazobenzene	4.1	9.8	10.1	3.8	2.0×10^6
3	β-*p*-Dimethylaminoazoxybenzene	−15.6	+4.5	2.7	−17.4	1.2×10^{20}
4	β-*p*-Oxidodimethylaminoazoxybenzene	4.0	2.1	2.0	3.9	1.3×10^{-4}
5	α-*p*-Oxidodimethylaminoazoxybenzene	3.7	1.3	1.4	3.8	3.8×10^{-4}
	p-Dimethylaminoazobenzene	−9.6	7.8	10.8	−15.6	2.0×10^{26}

(12) (a) H. H. Jaffé, D. L. Beveridge, and H. L. Jones, *J. Amer. Chem. Soc.*, **86**, 2932 (1964); (b) W. Bartok, P. J. Lucchesi, and N. S. Snider, *ibid.*, **84**, 1842 (1962); (c) J. C. Haylock, S. F. Mason, and B. E. Smith, *ibid.*, **85**, 4897 (1963).

(13) (a) T. Förster, *Z. Elektrochem.*, **54**, 42 (1950); (b) A. Weller, *Progr. Reaction Kinetics*, **1**, 189 (1961); (c) E. L. Wehry and L. B. Rogers in "Fluorescence and Phosphorescence," D. M. Hercules, Ed., Interscience Publishers, New York, N. Y., 1966, pp 125–140.

TABLE VI

CALCULATION OF pK^* FOR MONOSUBSTITUTED AZOBENZENES

Designation	Substituent	B λ[a]	B ν[b]	BH+ λ[a]	BH+ ν[b]	Δν[b]	ΔpK	pK$_1$	pK$_1$*	σ	σ+	σ−
a	H	314	318	419	239	79	16.6	−2.90	13.7	0		
b	4-OC_2H_5	348	287	468	214	73	15.2	−1.28	13.9	−0.24	−0.778	
c	4-OCH_3	348	287	469	213	74	15.4	−1.36	14.0	−0.268	−0.778	
d	4-CH_3	332	301	438	228	73	15.2	−2.35	12.8	−0.170	−0.311	
e	3-CH_3	322	311	420	238	73	15.2	−2.70	12.5	−0.069		
f	4-Br	328	305	440	227	78	16.2	−3.47	12.8	+0.232	+0.150	
g	3-Br	322	311	420	238	73	15.2	−3.83	11.4	+0.391		
h	4-$COCH_3$	328	305	420	238	67	13.9	−3.98	10.0	+0.502		+0.874
i	4-CN	326	307	418	239	68	14.1	−4.52	9.6	+0.660		+1.000
j	3-NO_2	316	316	412	243	73	15.2	−4.63	10.6	+0.710		
k	4-NO_2	334	299	420	238	61	12.7	−4.70	8.0	+0.778		+1.27
l	4-$N^+OH(CH_3)_2$	318	314	412	243	71	14.8	−4.65	10.1	+0.795		
m	4-OH	346	289	460	217	72	15.0	−1.02	14.0	−0.37	−0.92	

[a] Millimicrons. [b] Reciprocal centimeters × 10^{-2}.

TABLE VII

CALCULATION OF pK^* FOR MONOSUBSTITUTED AZOXYBENZENES

Designation	Substituent	B λ[a]	B ν[b]	BH+ λ[a]	BH+ ν[b]	Δν[b]	ΔpK	pK$_1$	pK$_1$*	σ	σ+	σ−
						α Isomer						
a	H	322	311	383	262	49	10.3	−6.45	3.8	0		
b	$-CH_3$	340	294	394	254	40	8.4	−6.04	2.4	−0.170	−0.311	
c	$-OCH_3$	360	277	442	226	51	10.7	−6.10	4.6	−0.268	−0.778	
d	$-OC_2H_5$	358	279	425	234	45	9.4	−6.04	3.3	−0.24	−0.778	
e	$-NO_2$	356	281	372	269	12	2.5	−9.83	−7.3	+0.778		+1.27
f	−Br	334	299	394	254	45	9.4	−7.01	2.4	+0.232	+0.150	
g	$-N^+OH(CH_3)_2$	326	307	385	260	47	9.9	−8.41	1.5	+0.795		
						β Isomer						
h	$-CH_3$	344	291	394	254	37	7.8	−6.16	1.6	−0.170	−0.311	
i	$-OCH_3$	364	275	450	222	53	11.1	−6.15	5.0	−0.268	−0.778	
j	−Cl	332	301	405	247	54	11.2	−6.96	4.3	+0.227	+0.114	
k	−Br	336	297	390	256	41	8.5	−6.94	2.6	+0.232	+0.150	
l	$-N^+OH(CH_3)_2$	318	314	376	266	48	10.0	−8.00	2.0	+0.795		
m	$-N^+H(CH_3)_2$	315	317	375	270	47	9.8	−8.02	1.8	+0.820		

[a] Millimicrons. [b] Reciprocal centimeters × 10^{-2}.

The results of these calculations are subject to a considerable amount of error. Use of the Förster cycle involves a number of assumptions and therefore, only approximate results can be obtained. In determining pK^*'s the λ_{max} was taken from the absorption spectra of compounds under study; the absorption bands, in many instances, are broad; and values of λ_{max} may be uncertain by several millimicrons. Some pK's were estimated on the basis of the Hammett equation with approximate values for substituent effects. However, the differences in K_t between ground and excited states are so large that even errors of a power of ten or more would not invalidate the qualitative conclusions drawn.

Application of the Hammett Equation to the Excited-State Equilibria.—Considerable work has been done in this laboratory over the past few years in the application of the Hammett equation to evaluate substituent effects on the ionization constant of the conjugate acid of azo- and azoxybenzenes and in its application to excited-state pK's. We have extended this work in an attempt to fit the data obtained in this work into pK^*–σ correlations.

Jaffé and Jones,[14] in an exhaustive literature survey of series of compounds for which excited-state pK values had been determined, have obtained fair results in the correlation, with exalted σ values usually required; this work included the azo and azoxy series.

These two series were reexamined with the inclusion of data for compounds from this study. Table VI gives all calculations for the azobenzene series.

The best fit of pK^* *vs.* σ was obtained when σ values were used in place of σ^+ values for electron-donating groups and σ^- values were used for electron-withdrawing substituents. This conclusion is just the contrary of the finding of Yeh and Jaffé,[7a] who have shown in the ground state that σ^+ and normal σ values were required. These data indicate that in the ground state the azo group acts as an electron-withdrawing group, while in the excited state the group behaves as an electron donor. A similar behavior has also been noted in the ground states of *cis*-azobenzenes.[15]

For the azoxybenzene series a plot of pK^* *vs.* σ was made using data from this study combined with those of Hahn and Jaffé.[3b] Results of the calculations are given in Table VII.

Although the points are more scattered than those for the azobenzene series, the correlation still is significant. The use of σ and σ^- substituent values give a better fit than use of σ^+ in the azoxybenzenes examined, in agreement with the fit demonstrated with azobenzenes. Sta-

(14) H. H. Jaffé and H. L. Jones, *J. Org. Chem.*, **30**, 964 (1965).

(15) J. H. Collins and H. H. Jaffé, *J. Amer. Chem. Soc.*, **84**, 4708 (1962).

tistical data for the correlations found are given in Table VIII.

TABLE VIII

REACTION CONSTANTS FOR pK* FOR MONOSUBSTITUTED AZO- AND AZOXYBENZENES

	Azobenzenes		Azoxybenzenes	
			α isomer	β isomer
	σ^-	$\sigma^\pm$	σ^-	σ^-
ρ^* [a]	3.42	2.54	5.15	1.97
r [b]	0.983	0.973	0.803	0.516
s [c]	0.389	0.479	2.41	1.46
s_0 [d]	0.206	0.189	1.56	0.853
Log K_0* [e]	−12.93	−12.19	−0.001	−2.86
n [f]	13	13	6	6

[a] The reaction constant in the excited state. [b] The correlation coefficient. [c] The standard deviation of the data. [d] The standard deviation of the reaction constant. [e] The intercept with the $\sigma = 0$ axis. [f] The number of points in the regression line.

neutralized with dilute NaOH, and the product extracted with chloroform. The solvent was evaporated, and the resulting material was recrystallized from dry THF and dried *in vacuo* over P_2O_5.

Elemental analysis and melting points of these compounds are given in Table IX.

pK Measurements.—Values for pK_a for compounds **2** and **3** were determined spectrophotometrically[16] using a standard NaOAc–HCl buffer. Spectra in neutral and acid solutions were recorded using a Cary Model 11 spectrophotometer. Titration curves at selected wavelengths (ϵ *vs.* pH) were determined using a Beckman Model DU quartz spectrophotometer.

For compounds **1**, **4**, and **5**, it was found that formation of the conjugate acid did not result in a significant change in the uv spectra. The acid solution was added in a stepwise manner to a solution of base of accurately known concentration. The pH of the solution was measured using a Beckman Zeromatic pH meter after each addition of acid. The pK was determined from the relationship

$$pK_a = pH + \log\left[\frac{C_{HA} - [H^+]}{(C_B + C_{HCl}) + [H^+]}\right]$$

TABLE IX

ANALYSES AND MELTING POINTS OF MONOXIDES AND DIOXIDES OF *p*-DIMETHYLAMINOAZOBENZENE

Compound	Mp found	Lit. mp	% C		% H		% N	
			Calcd	Found	Calcd	Found	Calcd	Found
p-Oxidodimethylaminoazobenzene	145	126–127	69.68	70.16[a]	6.27	6.31	17.42	17.27
α-*p*-Dimethylaminoazoxybenzene	121–121.5	121.5	69.68	69.81	6.27	6.36	17.42	17.49
β-*p*-Dimethylaminoazoxybenzene	126–126.5	126.2–126.6	69.68	69.61	6.27	6.54	17.42	17.59
β-*p*-Oxidodimethylaminoazoxybenzene	145–145.5	125–126	65.35	65.61[a]	5.88	6.06	16.34	16.83
α-*p*-Oxidodimethylaminoazoxybenzene	150	117–118	65.35	65.30	5.88	5.93	16.34	16.26

[a] Values corrected for H_2O by Karl Fisher.

Experimental Section

Compounds.—*p*-Phenylazo-N,N-dimethylaniline oxide (**1**) was prepared by oxidation of *p*-dimethylaminoazobenzene (DMAB) with an equimolar amount of freshly prepared perbenzoic acid at reduced temperature.[5] Neutralization of the reaction mixture with Na_2CO_3 yielded a solid, orange product. The compound was recrystallized from THF, which had been distilled over $LiAlH_4$, and dried *in vacuo* over P_2O_5.

α- and β-*p*-dimethylaminoazoxybenzene were prepared through the condensation of N-phenylhydroxylamine with N,N-dimethyl-*p*-nitrosoaniline (at a 2:1 mole ratio) in a slightly basic medium.[4] N,N-Dimethyl-*p*-nitrosoaniline was obtained from Eastman Kodak and was recrystallized from petroleum ether: mp 84.5–85°. N-Phenylhydroxylamine was prepared by the reduction of nitrobenzene with aqueous ammonium chloride and zinc dust. The product was recrystallized from ethyl ether, rapidly dried *in vacuo*, and used immediately.

Initial separation of the desired compounds from tars in the reaction products was accomplished by recrystallization from *n*-heptane. Isomers were separated on a 1 × 15 in. column of neutral Al_2O_3 using benzene as the solvent. With benzene as the eluent a light orange fraction was recovered. The benzene was removed *in vacuo*, and the yellow needles of α-*p*-dimethylaminoazoxybenzene (**2**) that formed were recrystallized to a constant melting point from dry THF and dried *in vacuo* over P_2O_5.

The dark orange fraction was rechromatographed using 98% benzene–2% ether solution as the eluent. Two small fractions were rapidly eluted while the last large band yielded orange crystals which were recrystallized from dry THF and dried *in vacuo* over P_2O_5. These crystals were identified as β-*p*-dimethylaminoazoxybenzene (**3**).

β-*p*-Oxidodimethylaminoazoxybenzene (**4**) was prepared by treating DMAB with 34% H_2O_2 in glacial acetic acid at 40°.[5] The reaction was continued until the color of the reaction mixture changed from dark red to yellow. Treatment of the solution with dilute sulfuric acid and ice yielded a product as orange leaves. The solid material was recovered and dissolved in a Na_2CO_3 solution. When cooled to 0°, yellow crystals formed. The product was recrystallized from dry THF and dried *in vacuo* under P_2O_5.

α-*p*-Oxidodimethylaminoazoxybenzene (**5**) was prepared by treating α-*p*-dimethylaminoazoxybenzene with 34% H_2O_2 at 40° for 48 hr in glacial acetic acid.[5] The reaction mixture was

The pK_{a1}'s of all compounds were determined in mixtures of aqueous H_2SO_4 and 20% ethanol, using the H_0 acidity scale of Jaffé and Gardner[17] and Yeh and Jaffé.[18]

In the presence of concentrated sulfuric acid, azoxybenzenes undergo the Wallach rearrangement, resulting in the formation of the corresponding hydroxyazo compounds. The following method of sample preparation was used to reduce to a minimum the heat evolved in making up a solution of the organic base in sulfuric acid and the consequent Wallach rearrangement. The acid solution (40 ml) was pipetted into a 50-ml volumetric flask. Ethanol was slowly added to the acid solution, with cooling, up to the neck of the flask, leaving 2–3 ml to be added to the mark. The acid–alcohol solution was chilled to a predetermined temperature, and 2 ml of a stock solution of the base was pipetted into the chilled solution with constant agitation and then brought to the mark with alcohol. The heat of mixing of the base solution and alcohol brought the temperature of the solution to 25 ± 0.1°. Absorption at selected wavelengths was measured using a Beckman Model DU quartz spectrophotometer; pK_{a1}'s were calculated from the resulting titration curves (ϵ *vs.* H_0).

It was not possible to determine the pK_a of α-*p*-dimethylaminoazoxybenzene experimentally. This compound was very unstable in the presence of solutions of 90–100% sulfuric acid, and all uv spectra obtained on solutions in this acid region showed considerable concentration of rearrangement product.

Registry No.—**1**, 2747-31-1; **2**, 13921-71-6; **3**, 3291-89-2; **4**, 14135-50-3; **5**, 13921-67-0; Table VI—a, 103-33-3; b, 7466-38-8; c, 2396-60-3; d, 949-87-1; e, 17478-66-9; f, 4418-84-2; g, 4171-34-0; h, 4827-16-1; i, 1837-93-0; j, 4827-19-4; k, 2491-52-3; l, 17478-72-7; m, 1689-82-3; Table VII—a, 495-48-7; b, 17310-79-1; c, 17478-75-0; d, 17478-76-1; e, 4504-08-9; f, 16054-48-1; g, 17478-37-4; h, 17310-78-0; i, 17478-80-7; j, 17478-82-9; k, 16109-68-5; l, 17478-38-5; m, 17476-14-7.

(16) L. A. Flexser, L. P. Hammett, and A. Dingwall, *J. Amer. Chem. Soc.*, **57**, 2103 (1935).
(17) H. H. Jaffé and R. W. Gardner, *ibid.*, **80**, 319 (1958).
(18) S. J. Yeh and H. H. Jaffé, *ibid.*, **81**, 3274 (1959).

A Palladium-Catalyzed Synthesis of Benzyl Esters from Methylbenzenes

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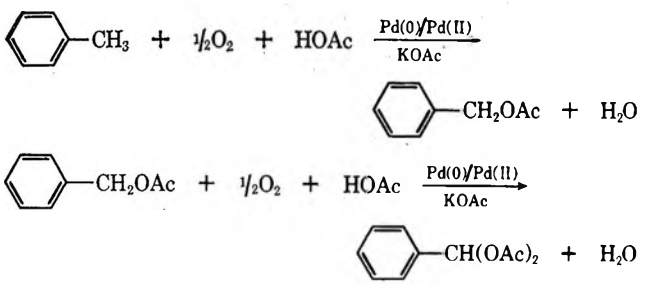
Benzyl esters are produced catalytically at moderate temperatures from methylbenzenes in a liquid phase process employing a homogeneous palladium–stannous acetate catalyst and air (1 atm). Toluene in acetic acid gives benzyl acetate. At high conversions, the secondary oxidation product, benzylidene diacetate, is formed. Other methylbenzenes, *e.g.*, mesitylene, durene, and hexamethylbenzene, give similar oxidation products. Xylenes undergo a selective diacetoxylation reaction in acetic acid, giving α,α'-diacetates in preference to α,α-diacetates.

The catalytic, liquid phase process described herein is an outgrowth of the stoichiometric oxidation of toluene by palladium(II) acetate in acetic acid.[1] The process proceeds at moderate temperatures and pressures with a palladium–stannous acetate catalyst in a carboxylic acid. Air is the ultimate oxidant. The high conversions obtainable from this selective and efficient process make it the method of choice for preparing many benzyl esters from methylbenzenes.

A limited number of metallic oxidants have been used to oxidize methylbenzenes to benzyl esters in carboxylic acids. The best known of these reagents is lead tetraacetate, which gives moderate yields.[2] Several workers have reported the use of ceric salts.[3] Chromic acid in acetic anhydride has yielded benzyl esters in some cases,[4] but further oxidation to benzoyl derivatives is the usual course of the reaction. The stoichiometric oxidation of toluene to benzyl acetate by palladium(II) salts has been reported.[5]

Results and Discussion

In the simplest form of the process, a methylbenzene is dissolved in a carboxylic acid containing a palladium(II) acylate and an alkali metal carboxylate. The solution is stirred at 100° for several hours while air is blown through the reaction flask. A benzyl monoester is efficiently produced. At high conversions small amounts of benzyl diesters are produced. For example, the reaction of toluene is as shown below. Subsequent oxidation of the diacetate is negligible.



In its simplest form, the process is efficient, but not very productive (Figure 1). The palladium metal formed in the reaction is deposited as a mirror which is difficult to oxidize. The addition of a high surface material, such as charcoal (Figure 1), alumina, silica, etc., substantially increases the rate of oxidation by dispersing the palladium metal.

Remarkably, tin salts, such as stannous acetate, increase the rate of benzylic oxidation about 90 times that of the base case (Figure 1 and Table I). To a lesser degree, triphenylphosphine and triethyl phosphite also increase the benzylic oxidation rate.

TABLE I

EFFECT OF CHARCOAL AND COCATALYSTS ON THE OXIDATION OF TOLUENE AT 100°

Expt[a]	Additive	Moles of $C_6H_5CH_2OAc$/mole of Pd
1	None	0.68
2	Charcoal	6.3
3	$Sn(OAc)_2$	64
4	$Sn(OAc)_2$ and charcoal	96
5	$(C_6H_5)_3P$	31
6	$(C_2H_5O)_3P$	12

[a] Experiments 1–5 were carried out in solutions of 8.0 mol of acetic acid, 1.2 mol of toluene, 1.1 mol of potassium acetate, and 0.008 mol of palladium(II) acetate for 6 hr while air was blown through the flask at a rate of 500 ml/min. Experiment 6 contained the same ratios, but half the amounts of reactants.

If the catalyst is charged as a mixture of palladium(II) acetate, stannous acetate, and charcoal, optimum benzylic oxidation rates result (Figure 1). The fastest rate observed under these conditions was 0.360 mol/(l. hr). This rate may be limited by the mass transfer of oxygen. Faster rates may be possible at higher oxygen partial pressures.

Comparable oxidation rates are obtained by generating the palladium oxidant from 5% palladium(0) on charcoal with air (Figure 1).

Several alkylaromatics were oxidized using the most productive catalyst system described above (Table II).

Reactions of toluenes bearing substituents such as nitro, chloro, and acetoxy on the ring are very slow. With a methoxy group present on the ring, benzylic oxidation competes with nuclear oxidation.

When alkylaromatics with side chains greater than methyl are oxidized, undesirable side reactions occur. The benzylic oxidation product, α-methylbenzyl acetate, is formed from ethylbenzene in low yield, along

(1) D. R. Bryant, J. E. McKeon, and B. C. Ream, *Tetrahedron Lett.*, 3371 (1968).

(2) R. Criegee in "Oxidation in Organic Chemistry," Vol. 5, part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, p 312.

(3) (a) C. M. Selwitz and E. R. Tucci, U. S. Patents 3,349,117 and 3,346,622 (1967); (b) W. S. Trahanovsky and L. B. Young, *J. Org. Chem.*, **31**, 2033 (1966).

(4) (a) T. Nishimura, *Org. Syn.*, **36**, 58 (1956); (b) S. V. Lieberman and R. Connor, *ibid.*, **18**, 61 (1938); (c) W. Triebs and H. Schmidt, *Ber.*, **61**, 459 (1928).

(5) (a) J. M. Davidson and C. Triggs, *Chem. Ind.* (London), 457 (1966). (b) After this manuscript was submitted for publication, J. M. Davidson and C. Triggs [*J. Chem. Soc.*, 1324, 1331 (1968)] expanded their original report. (c) In German Patent 1,262,992, Farbenfabriken Bayer AG discloses the preparation of benzyl acetate from toluene, acetic acid, and oxygen, in the presence of a supported catalyst apparently containing reduced palladium.

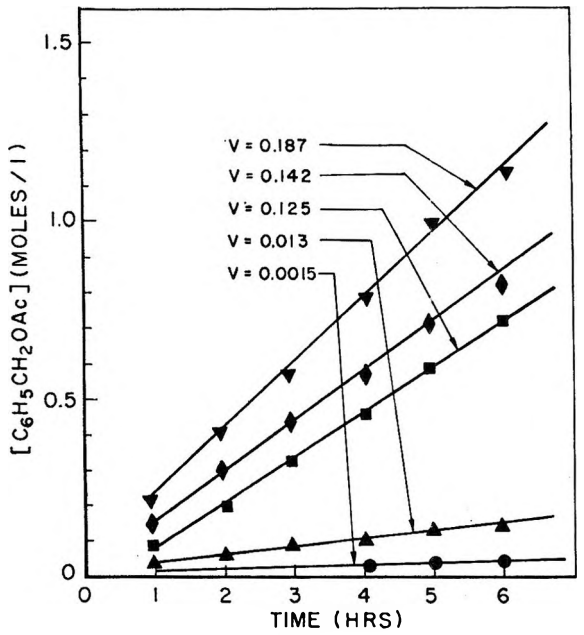


Figure 1.—Effect of catalyst composition on rate of benzyl acetate formation. Reactions contained 8.04 mol of HOAc, 1.10 mol of KOAc, 1.0 mol of toluene, and ●, 0.008 mol of $Pd(OAc)_2$; ▲, 0.008 mol of $Pd(OAc)_2$ and 33.6 g of charcoal; ■, 0.008 mol of $Pd(OAc)_2$ and 0.06 mol of $Sn(OAc)_2$; ◆, 0.008 mol of 5% Pd on charcoal and 0.06 mol of $Sn(OAc)_2$; ▼, 0.008 mol of $Pd(OAc)_2$, 0.06 mol of $Sn(OAc)_2$, and 33.6 g of charcoal. The first hour is excluded because the steady-state $Pd(OAc)_2$ concentration had not yet been established. V = rate in mol/(l. hr).

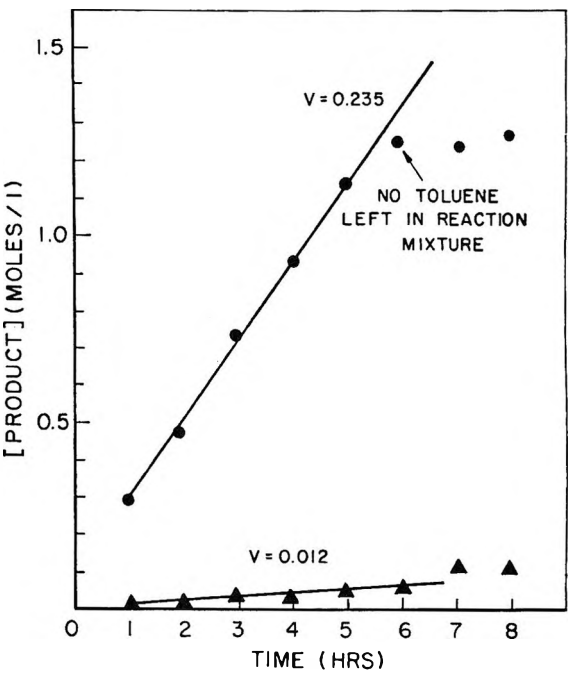


Figure 3.—Complete conversion of toluene: ●, $C_6H_5CH_2OAc$; ▲, $C_6H_5CH(OAc)_2$. Reactants: 8.04 mol of HOAc, 1.1 mol of KOAc, 1.0 mol of toluene, 0.016 mol of $Pd(OAc)_2$, 0.06 mol of $Sn(OAc)_2$, and 33.6 g of charcoal. The first hour is excluded because the steady-state $Pd(OAc)_2$ concentration had not been established. V = rate in mol/(l. hr).

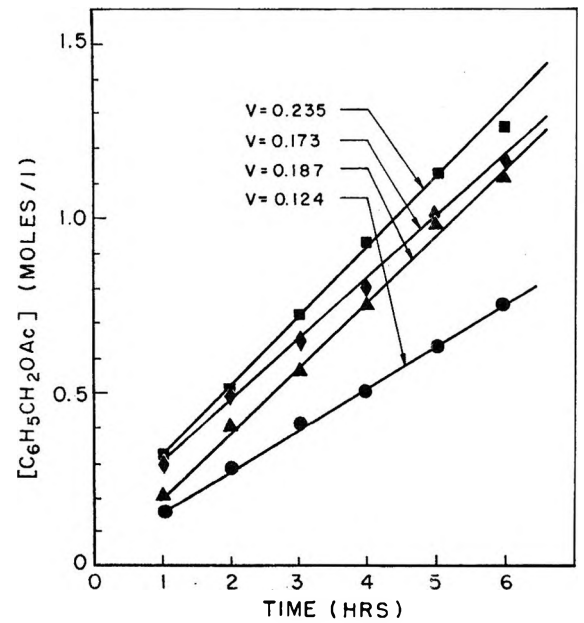


Figure 2.—Effect of $[Pd(OAc)_2]$ on rate of benzyl acetate formation: ●, 0.004 mol; ▲, 0.008 mol; ■, 0.016 mol; ◆, 0.032 mol of $Pd(OAc)_2$. Other reactants: 8.04 mol of HOAc, 1.10 mol of KOAc, 1.0 mol of toluene, 0.06 mol of $Sn(OAc)_2$, and 9.33 g of charcoal/0.004 mol of $Pd(OAc)_2$. The first hour is excluded because the steady-state $Pd(OAc)_2$ concentration had not yet been established. V = rate in mol/(l. hr).

with a comparable quantity of several other products (Table II). A similar product mixture can be obtained from styrene under the same oxidation conditions. Tetralin and indane give results similar to those obtained with ethylbenzene.

The oxidation of toluene in acetic acid was studied in the most detail. Benzyl acetate is the major product at moderate conversions. Benzylidene diacetate becomes an important product at high conversions and can be made the principal product by employing longer reaction times. Some benzaldehyde is formed from thermal decomposition[6] and hydrolysis of benzylidene diacetate. Only a trace (0.2%) of benzoic acid is formed, even at complete conversion of toluene.

Pure benzyl acetate is oxidized three times more slowly than toluene under comparable conditions. In the presence of toluene, benzyl acetate is oxidized up to 20 times more slowly. This might mean that toluene forms a stronger complex with the catalyst than does benzyl acetate.

The rate of benzyl acetate formation depends on palladium(II) acetate at low concentrations (Figure 2). At high concentrations, other factors limit the rate of oxidation. The availability of oxygen at atmospheric pressure may be important in this respect.

Figure 3 shows the profile of a reaction which was continued until no toluene remained. Of the toluene, 80 mol % was converted into a 15:1 mixture of benzyl acetate and benzylidene diacetate, and 20% was lost by entrainment. With properly designed equipment, complete oxidation is achieved.

In the catalytic reaction (Figure 3), formation of a palladium–toluene complex is not the rate-controlling step of the reaction since the rate is independent of the toluene concentration.

Xylene oxidations are more complex than that of toluene. In addition to mono- and diacetates, tri- and

(6) N. A. D. Parlee, J. C. Arnell, and C. C. Coffin, *Can. J. Res.*, **18B**, 223 (1940).

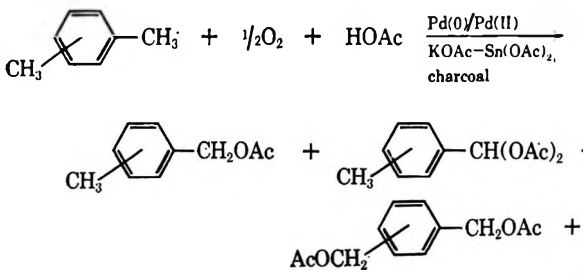
TABLE II[a]

BENZYLIC OXIDATIONS OF ALKYLAROMATICS WITH A PALLADIUM CATALYST AND AIR AT 100°

Alkylaromatic	Acid	Time, hr	% conversion of alkylaromatic into products[b]	Products	% of product mixture[c]
Toluene	Acetic	9	79.7	C_6H_5CHO	6.7 (9.1)
				$C_6H_5CH_2OAc$	91.4 (89.4)
				$C_6H_5CH(OAc)_2$	1.9 (1.1)
				$C_6H_5CO_2H$	... (0.4)
Toluene[d]	Propionic	6	22.3	C_6H_5CHO	0.6
				$C_6H_5CH_2OAc$	2.0
				$C_6H_5CH_2O_2CC_2H_5$	92.0
				$C_6H_5CH(O_2CC_2H_5)_2$	5.4
p-Xylene	Acetic	8	50.6	*p*-$CH_3C_6H_4CHO$	Trace
				p-$CH_3C_6H_4CH_2OAc$	58.0
				p-$CH_3C_6H_4CH(OAc)_2$	4.7
				p-$C_6H_4(CH_2OAc)_2$	37.3
o-Xylene	Acetic	24	38.2	*o*-$CH_3C_6H_4CH_2OAc$	57.4
				o-$CH_3C_6H_4CH(OAc)_2$	4.6
				o-$C_6H_4(CH_2OAc)_2$	38.0
m-Xylene	Acetic	24	43.5	*m*-$CH_3C_6H_4CHO$	10.0
				m-$CH_3C_6H_4CH_2OAc$	33.1
				m-$CH_3C_6H_4CH(OAc)_2$	6.9
				m-$C_6H_4(CH_2OAc)_2$	50.0
Mesitylene	Acetic	24	8.0	3,5-$(CH_3)_2C_6H_3CH_2OAc$	62.5
				20 minor unidentified products	37.5
Durene	Acetic	96	(28.0)	2,4,5-$(CH_3)_3C_6H_2CH_2OAc$	... (98.9)
				2,4,5-$(CH_3)_3C_6H_2CO_2H$	... (1.1)
Hexamethylbenzene	Acetic	96	(21.9)	2,3,4,5,6-$(CH_3)_5C_6CH_2OAc$	... (100.0)
Hexamethylbenzene	Propionic[e]	96	(26.5)	2,3,4,5,6-$(CH_3)_5C_6CH_2O_2CC_2H_5$	... (100.0)
Ethylbenzene	Acetic	25	8.3	$C_6H_5CH{=}CH_2$	13.6
				$C_6H_5CH(OAc)CH_3$	39.0
				$C_6H_5(CH_2)_2OAc$	13.2
				cis-$C_6H_5CH{=}CHOAc$	13.2
				trans-$C_6H_5CH{=}CHOAc$	16.7
				$C_6H_5CH_2CHO$	1.4
				$C_6H_5COCH_3$	2.9

[a] All experiments were carried out in solutions of 1.1 mol of alkali metal carboxylate in 8.0 mol of the corresponding carboxylic acid, with air being blown through the flask at a rate of 500 ml/min. In reactions using acetic acid, the catalyst was charged as a mixture of $Pd(OAc)_2$, $Sn(OAc)_2$, and charcoal. In reactions using propionic acid, the catalyst was charged as a mixture of 5% Pd on charcoal and $Sn(OAc)_2$. Ratio of $Sn(OAc)_2$:Pd was 3.75:1; the amount of alkylaromatic ranged from 0.15 to 1.0 mol. [b] This figure represents the amount of alkylaromatic oxidized. In the case of toluene, 15–20% of the starting material was lost by entrainment in the air flow. Entrainment also caused loss of starting material in the xylene reactions. The numbers in this column in parentheses were determined from isolated material; all others were determined by glpc after addition of an internal standard. [c] Numbers in parentheses are based on isolated material, while the others were determined by glpc, using an internal standard. [d] The benzyl acetate formed in this reaction results from the $Sn(OAc)_2$ present in the catalyst. [e] Reaction temperature was 145°, and $Sn(OAc)_2$:$Pd(OAc)_2$ ratio was 7.5:1.

tetraacetates, as well as aldehydes resulting from decomposition of α,α-diacetates, are possible.



The major products are the methylbenzyl acetates (Table II). Further oxidation of the monoacetates gives α,α'-diacetates in preference to α,α-diacetates. *p*-Xylene shows a higher selectivity toward the α,α'-diacetate than the other isomers. The selective diacetoxylation reaction forms the basis of a novel route to xylylene derivatives which will be discussed in greater detail in a separate paper. Under the conditions reported in Table II, only traces of tri- and tetraacetates are formed.

Methylbenzenes with greater than two methyl groups are also oxidized by this process, but reaction rates are slower than those obtained with toluene and the xylenes, *i.e.*, toluene > *p*-xylene > *o*- and *m*-xylene > mesitylene > durene > hexamethylbenzene. The formation of the monoesters of durene and hexamethylbenzene, though slow, is very selective. Increased reaction rates might be attainable by using higher reaction temperatures and greater partial pressures of oxygen.

Progress has been made in identifying the unexpectedly complex interactions involved in the mechanism of this oxidation process. Our results cannot be adequately described here; we hope to describe them in detail in the near future.

Experimental Section

I. Typical Rate Determination.—To an appropriately sized flask, fitted with a thermometer, a stirrer, a high-capacity condenser, and a sampling port equipped with a rubber septum for removal of liquid samples by hypodermic syringe, were charged 482.0 g (8.04 mol) of acetic acid, 107.9 g (1.10 mol) of potassium acetate, 109.3 g (1.20 mol) of toluene, 14.2 g (0.06 mol) of stan-

nous acetate, and 1.8 g (0.008 mol) of palladium(II) acetate. The resulting mixture was stirred at 100° while air was blown over its surface at a flow rate of 500 ml/min.

Periodically, a 3-ml aliquot was removed and *n*-butyrophenone, the internal standard, was added. Glpc analyses were carried out on a 9.5 ft × 0.25 in. aluminum column, packed with 10% trimer acid on a Teflon-6 support, at 172° and a helium flow of 70 ml/min.

Anal. Time (hr) for $C_6H_5CH_2OAc$ (mol/l.) by glpc: 1, 0.075; 2, 0.216; 3, 0.331; 4, 0.461; 5, 0.598; and 6, 0.720.

Rate with $(C_6H_5)_3P$ Present.—The procedure described under I was followed using 15.7 g (0.06 mol) of $(C_6H_5)_3P$ instead of stannous acetate. The final sample represents an 18.5% yield, based on toluene.

Anal. Time (hr) for $C_6H_5CH_2OAc$ (mol/l.) by glpc: 1, 0.000; 2, 0.056; 3, 0.133; 4, 0.209; 5, 0.276; and 6, 0.352.

Rate with $(EtO)_3P$ Present.—The procedure described under I was followed using 4.9 g (0.03 mol) of triethyl phosphite instead of stannous acetate and halving the amounts of the other reactants. The final sample represents a 7.0% yield, based on toluene.

Anal. Time (hr) for $C_6H_5CH_2OAc$ (mol/l.) by glpc: 3, 0.107; and 6, 0.153.

II. Preparative Reactions. General Procedures.—Melting and boiling points are uncorrected. All yields are based on alkylbenzene charged. The reactants were charged to an appropriately sized flask, fitted with a stirrer, a condenser, a thermometer, and an air-inlet tube. The reaction mixture was stirred at 100° for the specified time, while air was blown over its surface at a rate of 500 ml/min.

The cooled reaction mixture was filtered through diatomaceous silica. The filtrate was diluted with an equal volume of water and extracted with 1:1 Et_2O–pentane. The extracts were combined, washed successively with a saturated $NaHCO_3$ solution, water, and a saturated NaCl solution, then dried ($MgSO_4$). The products were isolated by distillation, sublimation, or column chromatography, as noted.

To determine if carboxylic acids were present, the aqueous layers were combined, acidified, and extracted with benzene. The extracts were dried ($MgSO_4$), concentrated, and treated with BF_3–MeOH reagent[7] to obtain the methyl esters for glpc analysis.

III. Oxidation of Toluene in Acetic Acid.—A charge of 482.0 g (8.04 mol) of acetic acid, 107.9 g (1.10 mol) of potassium acetate, 92.0 g (1.00 mol) of toluene, 14.2 g (0.06 mol) of stannous acetate, 3.6 g (0.016 mol) of palladium(II) acetate, and 33.6 g of charcoal was stirred at 100° for 9 hr. After the usual work-up, distillation gave 66.0 g of a liquid, bp 103–105° (20 mm) [lit.[8] bp 222–223° (760 mm)], containing 4.5 g (4.2%) of benzaldehyde and 61.5 g (41.0%) of benzyl acetate.

Benzaldehyde was identified by its 2,4-dinitrophenylhydrazone, mp 233–235° (lit.[9] mp 237°). A purified sample of benzyl acetate had the correct ir spectrum.

Trituration of the distillation residue (4.9 g) with petroleum ether (bp 60–70°) gave 1.3 g of crude solid. Recrystallization gave 1.0 g (0.5%) of benzylidene diacetate, mp 44–45° (lit.[10] mp 43.5–44°), identified by its ir and nmr spectra.

Acidification of the aqueous layers, followed by extraction and esterification, gave 0.28 g of methyl benzoate, which corresponds to a 0.2% yield (based on toluene).

Oxidation of *p*-Xylene in Acetic Acid.—The procedure described under III was followed using 106.0 g (1.0 mol) of *p*-xylene instead of toluene. After 8 hr, the usual work-up gave (by glpc) [compound, wt (g), % yield] *p*-xylene, 0.2, 0.2; *p*-tolualdehyde, trace, ...; *p*-methylbenzyl acetate, 54.2, 33; *p*-methylbenzylidene diacetate, 4.4, 1.9; and *p*-xylylene diacetate, 34.8, 15.7.

Distillation gave 44.3 g (27.0%) of *p*-methylbenzyl acetate, bp 170–174° (200 mm) [lit.[8] bp 227–230° (760 mm)], identified by its ir spectrum.

The pot residue (41.6 g) solidified upon cooling. Crystallization from petroleum ether (bp 60–70°) afforded 23.1 g (10.4%) of *p*-xylylene diacetate, mp 49–51° (lit.[11] mp 45–49°), identified by its ir and nmr spectra.

p-Tolualdehyde and *p*-methylbenzylidene diacetate were identified by their glpc retention times. No carboxylic acids were found by the usual procedure.

Oxidation of Durene in Acetic Acid.—The procedure described under III was followed using 50.0 g (0.36 mol) of durene instead of toluene. After 4 days, the reaction mixture was worked up, and 20.6 g (41.2% recovery) of durene, mp 77.5–79.5° (lit.[12] mp 79–80°), was obtained by sublimation. Distillation of the sublimation residue gave 19.1 g (27.7%) of 2,4,5-trimethylbenzyl acetate: bp 95° (1 mm) [lit.[13] bp 141–150° (9 mm)]; ir (neat) 5.77 (ester C=O) and 8.10 μ (acetate); nmr ($CDCl_3$) δ 5.04 ppm ($ArCH_2OAc$).

Acidification of the aqueous layers gave 0.2 g (0.34%) of 2,4,5-trimethylbenzoic acid, mp 154–156° (lit.[14] mp 150°).

Oxidation of Hexamethylbenzene in Acetic Acid.—The procedure described under III was followed using 25.0 g (0.15 mol) of hexamethylbenzene instead of toluene and a reaction time of 4 days. After the usual work-up, the residue was chromatographed in 2-g portions on 100 g of 28–200 mesh silica gel. Elution with petroleum ether (bp 60–70°) gave 7.4 g (32.6% recovery) of hexamethylbenzene, mp 164–165° (lit.[15] 165–166°); elution with chloroform gave 7.0 g (21.9%) of 2,3,4,5,6-pentamethylbenzyl acetate, recrystallized from methylcyclohexane, mp 82–84° (lit.[16] mp 83–85°), identified by its ir and nmr spectra.

Oxidation of Ethylbenzene in Acetic Acid.—The procedure described under III was followed using 106.0 g (1.00 mol) of ethylbenzene instead of toluene. After 25 hr the usual work-up gave (by glpc) 17.6 g (16.6% recovery) of ethylbenzene and [compound, wt (g), % yield] styrene (I), 1.67, 1.6; α-methylbenzyl acetate (II), 4.81, 2.9; β-phenylethyl acetate (III), 1.62, 1.0; *cis*-styryl acetate (IV), 1.63, 1.1; *trans*-styryl acetate (V), 2.06, 1.3; phenylacetaldehyde (VI), 0.16, 0.1; acetophenone (VII), 0.36, 0.3; and two unknowns (1.54 g).

Compounds I–V were isolated by preparative glpc and identified by their ir spectra. Compounds VI and VII were identified by their glpc retention times.

IV. Oxidation of *o*-Xylene in Acetic Acid.—A charge of 482.0 g (8.04 mol) of acetic acid, 106.0 g (1.0 mol) of *o*-xylene, 107.9 g (1.10 mol) of potassium acetate, 28.4 g (0.12 mol) of stannous acetate, 7.2 g (0.032 mol) of palladium(II) acetate, and 33.6 g of charcoal was stirred at 100° for 24 hr. The usual work-up gave (by glpc) [compound, wt (g), % yield] *o*-xylene, 1.6, 1.5; *o*-methylbenzyl acetate, 40.5, 24.7; *o*-methylbenzylidene diacetate, 3.2, 1.4; and *o*-xylylene diacetate, 26.8, 12.1.

Fractionation gave 33.9 g (22.6%) of *o*-methylbenzyl acetate, bp 94° (5 mm) [lit.[17] bp 119–121° (15 mm)], and 24.4 g (11.0%) of *o*-xylylene diacetate, bp 151° (5 mm), which crystallized on standing. Recrystallization from petroleum ether (bp 30–60°) gave a white powder, mp 33.5–34.5° (lit.[18] mp 35–36°). The products were identified by their ir and nmr spectra.

Oxidation of *m*-Xylene in Acetic Acid.—The procedure described under IV was followed using 106.0 g (1.0 mol) of *m*-xylene instead of *o*-xylene. The usual work-up gave (by glpc) [compound, wt (g), % yield] *m*-tolualdehyde, 8.0, 6.8; *m*-methylbenzyl acetate, 26.5, 16.2; *m*-methylbenzylidene diacetate, 5.6, 2.5; and *m*-xylylene diacetate, 40.0, 18.0.

Fractionation yielded 22.3 g (13.6%) of *m*-methylbenzyl acetate, bp 94° (5 mm) [lit.[19] bp 226° (760 mm)], and 36.3 g (16.4%) of *m*-xylylene diacetate, bp 158° (5 mm).

m-Tolualdehyde and *m*-methylbenzylidene diacetate were identified by their glpc retention times. *m*-Methylbenzyl acetate and *m*-xylylene diacetate were identified by their ir and nmr spectra.

m-Xylylene diacetate was prepared independently from *m*-xylylene glycol and acetyl chloride and had bp 154° (5 mm); ir (neat) 5.87 (ester C=O) and 8.12 μ (acetate); nmr ($CDCl_3$)

(7) L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33** (3), 363 (1961).

(8) G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 3943 (1954).

(9) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1956, p 283.

(10) E. H. Man, J. J. Sanderson, and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 847 (1950).

(11) R. W. Murray and A. M. Trazzolo, *J. Org. Chem.*, **29**, 1268 (1964).

(12) H. H. Stechl, *Ber.*, **97**, 2681 (1964).

(13) L. I. Smith and C. W. MacMullen, *J. Amer. Chem. Soc.*, **58**, 629 (1936).

(14) W. H. Mills, *J. Chem. Soc.*, 2192 (1912).

(15) N. M. Cullinane, S. J. Chard, and C. W. C. Dawkins, *Org. Syn.*, **35**, 73 (1955).

(16) L. Summers, *J. Amer. Chem. Soc.*, **76**, 3481 (1954).

(17) K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

(18) J. Entel, C. H. Ruof, and H. C. Howard, *ibid.*, **74**, 441 (1952).

(19) B. Radziszewski and P. Wispek, *Ber.*, **15**, 1747 (1882).

δ 1.97 (s, 6, CH_3CO—), 5.03 (s, 4, $ArCH_2O$—), and 7.25 ppm (m, 4, aromatic).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.9; H, 6.4. Found: C, 65.1; H, 6.5.

Oxidation of Mesitylene in Acetic Acid.—The procedure described under IV was followed using 60.0 g (0.50 mol) of mesitylene instead of *o*-xylene and half of the amounts of the other reactants. After the usual work-up, distillation gave 25.0 g (41.6% recovery) of mesitylene and 4.5 g (5.0% based on mesitylene charged) of 3,5-dimethylbenzyl acetate, bp 154° (35 mm) [lit.[20] bp 99–105° (4 mm)], identified by its ir spectrum. The pot residue (2.7 g) contained 20 unknown peaks by glpc.

V. Oxidation of Toluene in Propionic Acid.—A charge of 250.0 g (3.34 mol) of propionic acid, 36.8 g (0.46 mol) of lithium propionate, 36.8 g (0.40 mol) of toluene, 7.1 g (0.03 mol) of stannous acetate, and 17.2 g (0.008 mol) of 5% palladium on charcoal was stirred at 100° for 6 hr. The usual work-up gave (by glpc) [compound, wt (g), % yield] toluene, 4.8, 13.0; benzaldehyde, 0.1, 0.2; benzyl acetate, 0.3, 0.5; benzyl propionate, 13.7, 20.8; and benzylidene dipropionate, 0.8, 0.8.

Distillation gave 11.3 g (17.3%) of pure benzyl propionate, bp 87–88° (1 mm) [lit.[21] bp 222° (760 mm)], identified by its ir spectrum. The other products were identified by their glpc retention times.

VI. Oxidation of Hexamethylbenzene in Propionic Acid.—A charge of 592.0 g (8.00 mol) of propionic acid, 88.0 g (1.10 mol) of lithium propionate, 36.6 g (0.226 mol) of hexamethylbenzene, 28.4 g (0.12 mol) of stannous acetate, and 34.4 g (0.016 mol) of 5% palladium on charcoal was stirred at 145° for 4 days. After the usual work-up, 17.8 g (48.6% recovery) of hexamethylbenzene was obtained by sublimation. Distillation of the sublimation residue gave 14.1 g (26.5%) of 2,3,4,5,6-pentamethylbenzyl propionate, bp 170° (5 mm). The distillate solidified on standing and after crystallization from petroleum ether (bp 60–70°) had mp 78–79°; ir (KBr) 5.80 (ester C=O) and 8.40 μ (propionate); nmr ($CDCl_3$) δ 1.14 (t, 3, J = 7.5 Hz, $CH_3CH_2CO_2$—), 2.24 (m, 17, $CH_3CH_2CO_2$— and $ArCH_3$), and 5.29 ppm (s, 2, $ArCH_2O$—).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.9; H, 9.5. Found: C, 77.2; H, 9.8.

(20) S. D. Ross, M. Finkelstein, and R. C. Peterson, *J. Amer. Chem. Soc.* **86**, 4139 (1964).

(21) I. M. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. 5, Oxford University Press, New York, N. Y., 1965, p 2786.

Registry No.—Toluene, 108-88-3; *p*-xylene, 106-42-3; *o*-xylene, 95-47-6; *m*-xylene, 108-38-3; mesitylene, 108-67-8; durene, 95-93-2; hexamethylbenzene, 87-85-4; ethylbenzene, 100-41-4; $Pd(OAc)_2$, 3375-31-3; $Sn(OAc)_2$, 638-39-1; $(C_6H_5)_3P$, 603-35-0; $(C_2H_5O)_3P$, 122-52-1; $C_6H_5CH_2OAc$, 140-11-4; *m*-xylylene diacetate, 17604-82-9; 2,3,4,5,6-pentamethylbenzyl propionate, 17604-83-0.

Acknowledgment.—We wish to thank Mr. John R. Morrison for his excellent technical assistance in the development of these procedures.

The Photorearrangements of 2,4-Disubstituted Phenyl Esters[1-3]

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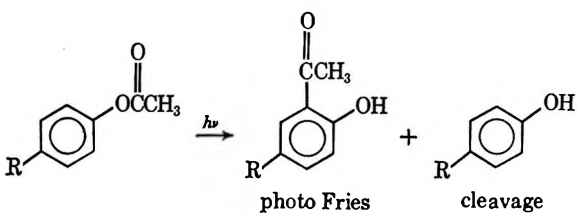
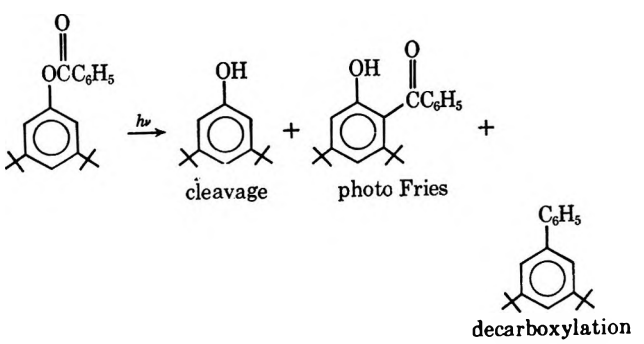
Various 2- and 2,4-disubstituted phenyl esters have been irradiated by ultraviolet light, and the products have been isolated and characterized. The relative large numbers of products obtained (up to six) showed that at least five different reactions were taking place: (1) photo Fries rearrangements resulting in *o*-hydroxyacetophenones, (2) photo Fries rearrangements in which methoxy groups were displaced resulting in *o*- and *p*-hydroxyacetophenones, (3) cleavage reactions resulting in phenols and in one case benzaldehyde, (4) decarboxylation reactions resulting in methylbenzene and biphenyl compounds, and (5) phototransposition of the ring carbon atoms resulting in rearranged methylbenzene and biphenyl compounds. Mechanisms for the various reactions are discussed.

The photochemical reactions of aryl esters have drawn considerable interest in recent years.[4-8] The photo Fries rearrangement of these esters to yield



hydroxyaceto- and hydroxybenzophenone was first reported by Anderson and Reese[4] and Kobsa.[5] Along with the photo Fries, these workers also observed a considerable amount of cleavage products. More recently some attention has been given to the mechanisms of this reaction.[6,7]

With sterically hindered aryl esters, the normal photo Fries and cleavage reactions are accompanied by decarboxylation[8] and, in some cases, decarbonylation[8d] reactions. For example, the photolysis of 3,5-di-*t*-butylphenyl benzoate gave 3,5-di-*t*-butylbiphenyl



(1) Supported by the Research Division, Brigham Young University, and the United Fund of Utah County.

(2) Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer purchased under the National Science Foundation Grant GP-6837.

(3) Presented in part by E. L. Loveridge at the student section of the Pacific Northwest Regional American Chemical Society Meeting, Richland, Wash., June 1967.

(4) (a) J. C. Anderson and C. B. Reese, *Proc. Chem. Soc.*, 217 (1960); (b) J. C. Anderson and D. B. Reese, *J. Chem. Soc.*, 1781 (1963).

(5) H. Kobsa, *J. Org. Chem.*, **27**, 2293 (1962).

(6) G. M. Coppinger and E. R. Bell, *J. Phys. Chem.*, **70**, 3479 (1966).

(7) M. R. Sandner and D. J. Trecker, *J. Amer. Chem. Soc.*, **89**, 5725 (1967).

(8) (a) R. A. Finnegan and A. W. Hagen, *Tetrahedron Lett.*, 365 (1963); (b) R. A. Finnegan and J. J. Mattice, *Tetrahedron*, **21**, 1015 (1965); (c) R. A. Finnegan and D. Knutson, *Chem. Ind.* (London), 1837 (1965); (d) R. A. Finnegan and D. Knutson, *J. Amer. Chem. Soc.*, **89**, 1970 (1967).

TABLE I

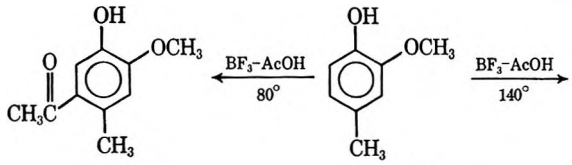
THE PHOTOREARRANGEMENTS OF VARIOUS SUBSTITUTED PHENYL ACETATES

Run	Substituent[a]	Solvent[b]	Time, hr	Recovered ester, %	Yields of products, %[c] II	III	IV	V	VI	VII
1	Ia	B	4	52	7	0	17	48	14	14
2[d]	Ib	B	4	2	10	0	8	55	13	8
3[e]	Ib	E	4	10	Trace[f]	0	20	61	11	4
4	Ic	B	4	3	15	4	19	56	6	0
5	Ic	E	8	0	Trace[f]	0	24	68	8	0
6[g]	Ic	H	4	90	16	5	18	55	6	0
7	Id	B	4	3	34	3[h]	8	54	0	0

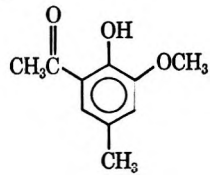
[a] Two grams of substrate in 150 ml of solvent. [b] B = benzene; E = ethanol; H = hexane. [c] Products were analyzed and isolated by vpc and characterized by spectroscopy. [d] A 6% yield of another product was observed. This material could not be isolated since the peak was too close to Ib. [e] A 4% yield of another product was observed. This material could not be isolated since the peak was too close to Ib. [f] Vapor phase chromatogram shows a trace amount of material believed to be this product. [g] Same vpc as run 4. [h] Not isolated, but believed to be this product.

in addition to 3,5-di-*t*-butylphenol and 2-hydroxy-4,6-di-*t*-butylbenzophenone.[8c] It was this competition of reactions as well as the unusual thermal Fries rearrangements of the 2,3-disubstituted phenyl esters that prompted us to undertake this study.

The thermal Fries reaction of the 2,4-disubstituted phenyl esters has been reported to give rearrangements of both the *ortho* and the *meta* positions.[9,10] Indeed, the acylation of 2-methoxy-4-methylphenol (creosol) with carboxylic acids in the presence of boron trifluoride, which involves a Fries rearrangement,[11] gave both *ortho* and *meta* isomers.[10] At ordinary temperatures (80° and below) only the *meta* isomer was formed, while at elevated temperatures (140° and above) only the *ortho* isomer was obtained.[10] Presumably the intermediate creosyl acetate cleaves heterolytically at ordinary temperatures to give the acyl carbonium ion which substitutes to the most active *meta* position (*meta* to the original ester group, but *ortho,para* to methyl and methoxy groups). At elevated temperatures, a homolytic cleavage occurs yielding an acyl radical which adds to the *ortho* position.



creosol



At the outset of this study, we expected to find only *ortho* rearrangement, cleavage, and decarboxylation-type reactions taking place. Not only products from these reactions were formed, but also products from the phototransposition of carbon atoms on the benzene ring[12] and *ortho* and *para* Fries rearrangements in which a methoxy group was displaced. At no time was a *meta*-rearranged product isolated.[13]

(9) A. Ballio and L. Almuante, *Ric. Sci.*, **21**, 85 (1951).

(10) P. Da Re and L. Cimatoribus, *J. Org. Chem.*, **26**, 3650 (1961).

(11) K. Kindler, H. Oelschlager, and P. Henrich, *Arch. Pharm.*, **287**, 210 (1954).

(12) See L. Kaplan, K. E. Wilzbach, W. G. Brown, and S. S. Yang, *J. Amer. Chem. Soc.*, **87**, 675 (1965), and other papers of this series.

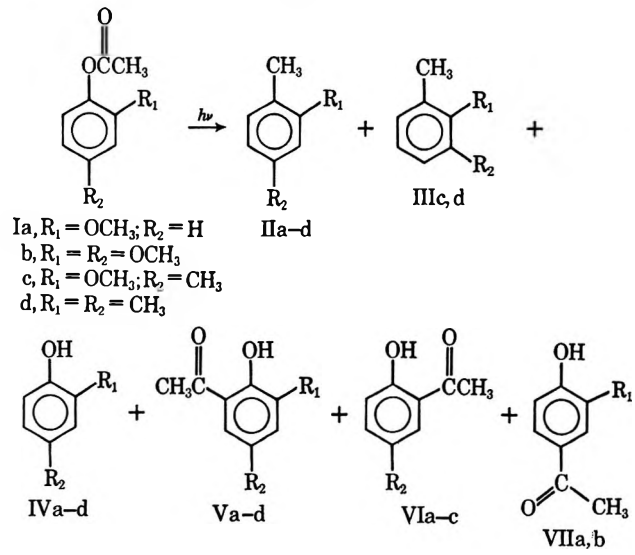
(13) This result was not surprising as others had also reported that the *meta*-rearranged product was not formed.[4,5]

Results and Discussion

All the esters used in this study were purchased or prepared from the corresponding phenols. After the esters were dissolved in the appropriate solvent, the solutions were saturated with nitrogen and irradiated through quartz. The reaction products were analyzed and isolated by means of vapor phase chromatography (vpc). The products were characterized by infrared (ir) and nuclear magnetic resonance (nmr) spectroscopy and by elemental or mass spectrometric analysis (see Experimental Section).

In many cases the ir spectrum of the product compound was found to be the same as that found in the Sadtler series of spectra. In some of these cases, further analysis was not carried out. A general reaction scheme for the acetates can be written as shown in Scheme I. As shown in Table I, not all of

SCHEME I



these products are formed in every reaction. Products VI and VII were not formed in those cases where methyl groups occupied the *ortho* and/or *para* positions (runs 4–7). Also, little of product II and none of product III were observed when the substrates were irradiated in ethanol. No *meta*-rearranged product was isolated in any of these reactions even at low temperatures (−25 to 30°).[13]

2-Methoxy-4-methylphenyl benzoate gave similar results (Scheme II, Table II).

Scheme II

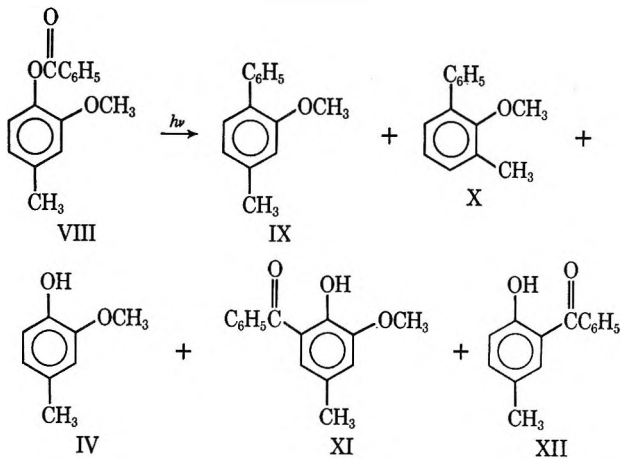


Table II

Photorearrangement of 2-Methoxy-4-methyl Benzoate[a]

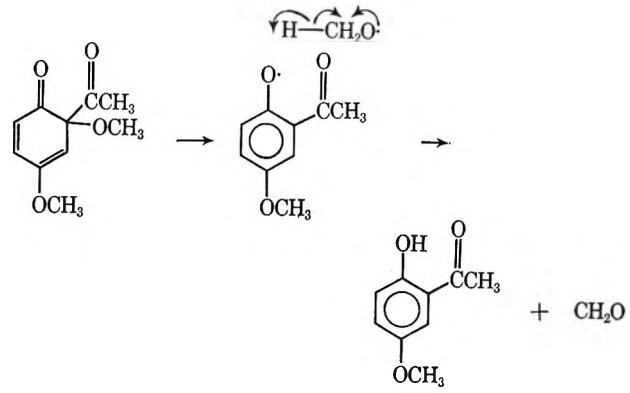
Run	Solvent[b]	Time, hr	Recovered ester, %	Yields of products, %[c] IX	X	IVc	XI	XII
8[d]	B	4	14	27	8	16	40	6
9[e]	E	4	22	2	0	25	63	7

[a] Two grams of substrate in 150 ml of solvent. [b] B = benzene; E = ethanol. [c] Products were analyzed and isolated by vpc and characterized by spectroscopy. [d] Benzaldehyde (3%) was also isolated. [e] Another unidentified product (3%) was present.

The displacement of a methoxy group during the photo Fries rearrangement has not previously been reported. To our knowledge, this reaction does not take place in the thermal Fries rearrangement.[14] Indeed, the thermal reaction with the 2,4-dimethoxy- and 2-methoxy-4-methylphenyl acetates did not result in a loss of a methoxy group but gave *ortho* and *meta* rearrangements as reported above.[9,10,15]

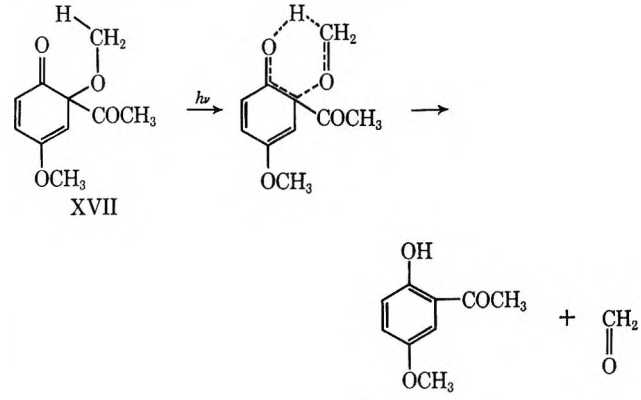
The displacement of a methoxy group probably takes place much like that reported by Kobsa for the rearrangement of 4-*t*-butyl-2,6-dichlorophenyl acetate. In that case a loss of chlorine was observed.[5] An over-all mechanism for the photo Fries reaction in these systems is proposed in Scheme III. There is some evidence to support this mechanism. The fact that no *meta*-rearranged product forms suggest that no heterolytic cleavage of the C–O bond occurs. Furthermore, the quantum yield of the photo Fries rearrangement is not affected by wide variations of solvent viscosity, and the presence of oxygen does not alter the product yield.[7] The intermediate XIII, XIV, or XV must, therefore, be a tightly bound neutral species. This may be a photoactivated charge-transfer complex,[6,7] a bridged diradical with neutral charge,[4b,7] or very tightly held radical fragments as suggested by Sandner and Trecker.[7] As seen in Tables I and II, most of the reaction proceeds along path 1 to the unoccupied *ortho* position. This is probably due to steric hindrance. The occupied *ortho* position is more susceptable to rearrangement than the occupied *para* position (runs 2 and 3), probably because the *ortho* is closer to the attacking acyl group.

The fate of the departing methoxy group is not known. It is quite likely that the group would leave as a radical and could be the source of hydrogen necessary to complete the reaction. Thus, a small amount of formaldehyde would be produced. This possibility is under further study. It is likely that the

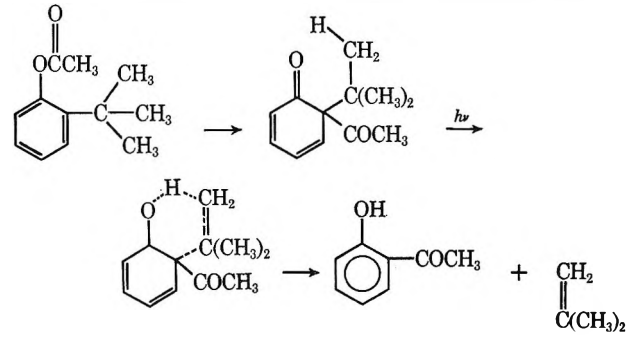


formaldehyde contributes to the polymer that is always observed in these reactions.

The *o*-methoxy group could possibly be cleaved by a secondary photochemical reaction of the dienone intermediate XVII.[16] This would follow the well-known Norrish type-II cleavage.[17] This possibility



was examined by preparing and irradiating *o*-*t*-butylphenyl acetate. If a Norrish type-II cleavage of a dienone intermediate (similar to XVI, XVII, or XVIII) is operative, then some 2-hydroxyacetophenone should be present. None of this latter product was observed.



Only normal *ortho*- and *para*-rearrangement products were isolated. Thus intermediates like XVII are probably not undergoing secondary photochemical reactions.

Intermediates XIII, XIV, and XV could be involved in the formation of phenolic materials. In this case

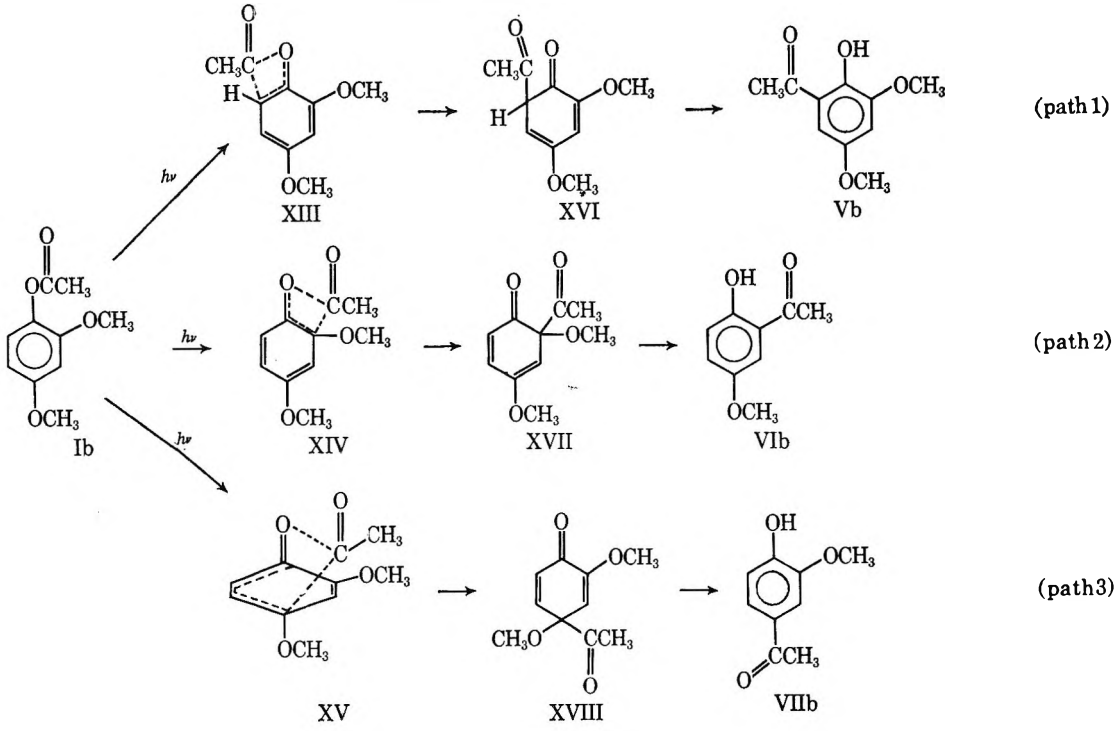
(14) For a review, see A. Gerecs in "Friedel–Crafts and Related Reactions," Vol. III, part I, G. A. Olah, Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, p 499.

(15) A. Ballio, *Gazz. Chim. Ital.*, **79**, 924 (1949).

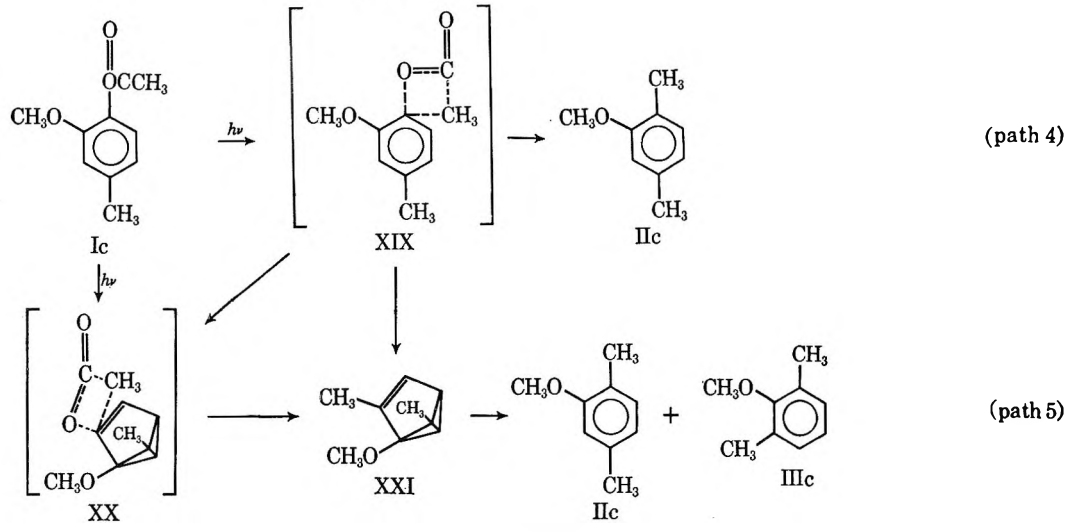
(16) This possibility was suggested by one of the referees.

(17) See J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, p 382.

SCHEME III



SCHEME IV



the tightly bound species could separate into an aryloxy and an acyl radical. The fate of the acyl radical has been the subject of numerous conjectures. These radicals are no doubt responsible in part for the polymer produced in these reactions. They can also lead to aldehydes[5] as shown by the isolation of 3% benzaldehyde in run 8 (Table III). The small amounts of acetaldehyde that would be formed in the acetate reaction would be lost either during the reaction or upon work-up.

The decarboxylation reactions show a marked dependence on the solvent. Essentially no product (II) was formed in alcohol. The reasons for this solvent dependence are not fully understood.[13] Since radical reactions generally show little or no dependence on the polarity of the solvent, this may mean that there is more polar character to these reactions than previously thought. At any rate a meaningful explanation must await a more detailed study of this reaction.[8d] We were somewhat surprised to find no decarbonylation products (1,2,4-trimethoxybenzene in the case of substrate Ib) present in the reaction mixtures. It has been proposed that the decarbonylation reaction occurs because carbon monoxide separates prior to the diffusion of the aryloxy and acyl radicals from the solvent cage.[8d] In our system the steric requirements of the *o*-methoxy (or methyl) group may force the forming radicals to separate more rapidly. Thus the radicals would be out of the cage before carbon monoxide could separate.

Phototransposition of carbon atoms on the benzene ring[12] was observed by the isolation of 2,6-dimethylanisole (IIIc in run 4) and 2-methoxy-3-methylbiphenyl (X in run 8). 1,2,3-Trimethylbenzene (IIId in run 7) may also have been formed; however, not enough was present to isolate and characterize. No

(18) Finnegan and Knutson[8d] have also observed a solvent dependence in the decarboxylation reaction.

Table III
A List of Reaction Products

Run	Fraction	Compound	Yield, %[a]	Remarks
1	1	IIa	7	Ir same as Sadtler 28945; nmr δ m 7.1 (4), s 4.02 (3), s 2.35 (3)
	2	IVa	17	Ir and nmr same as an authentic sample
	3	VIa	14	Ir and nmr same as an authentic sample
	4	Ia	52	Ir and nmr same as an authentic sample
	5	Va[b]	48	Ir band at 1640 cm^{-1}; nmr δ s 12.2 (1), m 7.0 (3), s 3.85 (3), s 2.57 (3)
	6	VIIa	14	Ir same as Sadtler 19571; nmr δ s 7.45 (1), m 6.9 (2), s 5.93 (1), s 3.95 (3), s 2.44 (3)
2	1	IIb	10	Ir same as Sadtler 24448; nmr δ m 6.9 (1), m 6.25 (2), s 3.78 (3), s 3.72 (3), s 2.10 (3)
	2	IVb	8	Ir and nmr same as authentic sample
	3	VIb[b]	13	Ir same as Sadtler 32461; nmr δ s 11.6 (1), m 7.0 (3), s 3.78 (3), s 2.59 (3)
	4	VIIb[b]	8	Ir same as Sadtler 19571; nmr δ s 7.54 (1), m 6.9 (2), s 5.93 (1), s 3.95 (3), s 2.44 (3)
	5	Ib	2	Ir and nmr same as authentic sample
	6	Vb[b]	55	Ir band at 1635 cm^{-1}; nmr δ s 11.7 (1), s 6.61 (2), s 3.83 (3), s 3.73 (3), s 2.56 (3)
	7		6	Could not be separated from fraction 6
4	1	IIIc	4	Ir same as Sadtler 18712
	2	IIc	15	Ir same as Sadtler 19397; nmr δ m 6.7 (3), s 3.72 (3), s 2.29 (3), s 2.13 (3)
	3	IVc	19	Ir and nmr same as authentic sample
	4	VIc[b]	6	Ir same as Sadtler 20306; nmr δ s 11.8 (1), m 7.0 (3), s 2.54 (3), s 2.28 (3)
	5	Ic	3	Ir and nmr same as authentic sample
	6	Vc[b]	56	Ir has band at 1640 cm^{-1}; nmr δ s 12.0 (1), s 7.02 (1), s 6.78 (1), s 3.78 (3), s 2.50 (3), s 2.23 (3)
7	1	IId	34	Ir same as Sadtler 1038
	2	Unknown	3	Possibly 1,2,3-trimethylbenzene
	3	IVd	8	Ir and nmr same as authentic sample
	4	Id	4	Ir and nmr same as authentic sample
	5	Vd[b]	54	Ir has band at 1626 cm^{-1}; nmr δ s 12.2 (1), s 7.14 (1), 2 6.97 (1), s 2.41 (3), s 2.18 (3), s 2.11 (3)
8	1		3	Vpc retention time same as benzaldehyde; ir and mp, after oxidation, same as benzoic acid; ir and nmr same as authentic sample
	2	IVc	16	Ir and nmr same as authentic sample
	3	X	8	Ir bands at 1590, 1465, 1410, 1260, 1215, 1100, 1070 d, 1010, 805, 787, 760, 748, 695 cm^{-1}; mass spectrum showed parent peak at mass 198.
	4	IX	27	Ir bands at 1600, 1580, 1500, 1478, 1455, 1395, 1285, 1250, 1188, 1160, 1130, 1070, 1035, 1005, 920, 845, 810, 765, 725, 695 cm^{-1}; nmr δ m 8.4 (6), m 7.86 (2), s 4.26 (3), s 2.70 (3); mass spectrum showed a parent peak at mass 198
	5	XII[b]	6	Ir same as Sadtler 29391
	6	VIII	14	Ir and nmr same as authentic sample
	7	XI[b]	40	Ir has band at 1610 cm^{-1}; nmr δ s 13.1 (1), m 8.77 (5), m 8.05 (2), s 4.51 (3), s 2.63 (3)
	8	Unknown	3	Not isolated

[a] Esters of Ia, Ib, Ic, Id, and VIII are recovered starting materials. All others are percentage of total products. [b] Acceptable analytical data (±0.3) were obtained on these compounds.

phototransposition products were observed in the 2,4-dimethoxyphenyl acetate reaction (run 2). In previous studies of these types of reactions, only the rearrangement of alkyl groups was reported.[12]

The phototransposition reaction is believed to occur during the course of the decarboxylation reaction. This suposition is based on two facts. First, no Fries-rearranged products were observed in which the ring substituents had "migrated." This indicates that the transposition did not take place on the starting materials before they reacted. Second, the prolonged irradiation of 2-methoxy-4-methyl acetate (run 4 for 24 hr) failed to change the ratio of 2,5-dimethylanisole (IIc) to 2,6-dimethylanisole (IIIc). This indicates that the transposition did not take place after the formation of IIc. The phototransposition reaction has been reported to involve a benzvalene intermediate.[12,19] This intermediate then could be involved in our methyl "migration" reaction. There is good evidence for decarboxylation intermediate XIX since a concerted decarboxylation process has been demonstrated using optically active esters.[8d] Whether this intermediate XIX rearranges to the benzvalene compound XXI or a benzvalene is formed directly from the starting esters is not readily apparent from our results. If it can be assumed that the benzvalene XXI aromatizes to compounds IIc and IIIc with equal probability, then about 25% of the decarboxylation product IIc is obtained through path 5 (see Scheme IV).

Experimental Section

Materials and Apparatus.—Many of the chemicals used in this study were purchased and used as received: 2-methoxyphenylacetate (Ia), 2,4-dimethylphenol (IVd), 2-methoxy-4-methyl-

(19) Benzvalene was recently isolated in the photolysis of benzene: K. E. Wilzback, J. S. Ritscher, and L. Kaplan, *J. Amer. Chem. Soc.*, **89**, 1031 (1967).

phenol (creosol) (IVc), *m*-dimethoxybenzene, and N-methylformanilide from Eastman Kodak and acetyl chloride, benzoyl chloride, and pyridine from J. T. Baker. 2,4-Dimethylphenyl acetate (Id) was generously supplied to us by Professor W. J. Horton. An Aerograph 202 B temperature-programmed vapor phase chromatograph was used to analyze and separate all photochemical products. All ir spectra were obtained on Beckman IR-8 or IR-7 spectrophotometers. The nmr spectra were taken on a Varian A-60A spectrometer.[2] Ultraviolet irradiations were carried out using a Hanovia quartz immersion reactor inserted into the reaction solution. A Hanovia 450-W medium-pressure lamp was used in all experiments.

Preparation of Starting Materials. Acetate Esters.—2,4-Dimethoxyphenol (IVb) was prepared by the peracetic acid oxidation of 2,4-dimethoxybenzaldehyde.[20] The latter compound was prepared by the procedure of Sommers, Michaels, and Weston from *m*-dimethoxybenzene.[21] The oxidation was carried out using 5.17 g of 90% hydrogen peroxide in 100 ml of glacial acetic acid added to 22.0 g (0.16 mol) of 2,4-dimethoxybenzaldehyde in 200 ml of glacial acetic acid to give phenol IVb (60% yield), bp 110–112° (1 mm).[20] The ir spectrum of a purified (vpc) sample contained a strong hydroxy band at 3220 cm^{-1}; the nmr spectrum exhibited the following peaks, δ m 6.5 (3), s 4.75 (1), s 3.8 (3), and s 3.6 (3).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.50. Found: C, 61.99; H, 6.79.

2,4-Dimethoxyphenyl acetate (Ib) was prepared by mixing equal molar amounts of crude 2,4-dimethoxyphenol and acetyl chloride in pyridine. After standing for 1 hr, the reaction mixture was added to water, and the aqueous mixture was extracted with ether. The ether extracts were washed with dilute aqueous acid and then dilute sodium bicarbonate solution and dried over anhydrous calcium chloride. After distillation, the product acetate [yield 75%, bp 97–98° (1 mm)] was found to contain a small amount of 2,4-dimethoxybenzaldehyde. The aldehyde was effectively removed by stirring an ether solution of acetate Ib overnight with aqueous sodium bisulfite. An analytical sample was isolated by vpc. The ir spectrum contained a band at 1755 cm^{-1}; the nmr spectrum exhibited the following peaks, δ m 6.6 (3), s 3.66 (3), s 3.61 (3), and s 2.14 (3).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.18; H, 6.13.

2-Methoxy-4-methylphenyl acetate (Ic) was prepared by the above procedure to give an 80% yield: bp 77–79° (1 mm); $n^{25}D$ 1.5070. A band at 1755 cm^{-1} was observed in the ir spectrum, and the nmr spectrum had the following peaks, δ m 6.7 (3), s 3.06 (3), s 2.22 (3), and s 2.12 (3).

(20) R. I. Meltzer and J. Doczi, *J. Amer. Chem. Soc.*, **72**, 4988 (1950).

(21) A. H. Sommers, R. I. Michaels, Jr., and A. W. Weston, *ibid.*, **72**, 5546 (1952).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.59; H, 6.71. Found: C, 66.63; H, 6.67.

Benzoate Esters.—2-Methoxy-4-methylphenyl benzoate (VIII) was prepared by mixing equal molar amounts of 2-methoxy-4-methylphenol and benzoyl chloride in pyridine. The resulting reaction mixture was treated as reported above for the acetates yielding a solid product, mp 74–75°. The ir spectrum exhibited a band at 1725 cm^{-1}, and the nmr spectrum had the following peaks, δ m 6.5–8.3 (8), s 3.65 (3), and s 2.28 (3).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.40; H, 5.82. Found: C, 74.45; H, 5.99.

2-Methyl-4-methoxy-5-hydroxyacetophenone (Nonphotochemical *meta*-Rearranged Product).—The procedure of Da Re and Cimatoribus[10] was used to prepare this compound using creosol, acetic acid, and boron trifluoride, mp 124–126° (lit. mp 129–130°).[10] The ir spectrum contained bands at 3100 and 1650 cm^{-1}, and the nmr spectrum had peaks at δ s 8.45 (1), m 7.80 (1), s 6.59 (1), s 4.58 (3), and d 2.83 (6).

Irradiation Reactions.—The substrate (about 2 g) was dissolved in 150 ml of the appropriate solvent. The solution was placed in a reactor into which the quartz immersion well was fitted. A small stream of nitrogen was sparged into the bottom of the reactor 30 min before the reaction was started and continued throughout the duration of the reaction. Upon completion of the irradiation, the solvent was removed under vacuum (30–40 mm), and the remaining oil was subjected to vpc analysis using SE-30 on Chromosorb W and programming the temperature from 100 to 250° or 285°. Yields were calculated from the relative peak areas. Pure samples of the products were collected for analysis. The results are shown in Tables I and II. Table III contains a detailed list of products in runs 1, 2, 4, 7, and 8. Run 3 gave the same results as run 2 except only a trace amount of fraction 1 and different relative amounts of fractions 2, 3, 4, 5, and 7 were obtained (see Table I). Runs 5 and 6 gave the same compounds as run 4 but in different yields. Run 9 gave the same products as run 8 except in different yields.

Registry No.—Ib, 7203-46-5; Ic, 879-67-4; IVb, 13330-65-9; Va, 703-98-0; Vb, 17605-00-4; Vc, 7452-85-9; Vd, 1198-66-9; VIII, 17605-03-7; IX, 17603-90-6; X, 17603-91-7; XI, 17603-92-8.

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Aralkyl Hydrodisulfides.[1] IX. The Reaction with Tertiary Arsines

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The reaction of triphenylarsine with benzyl or benzhydryl hydrodisulfide and of triethylarsine with benzhydryl hydrodisulfide occurs only on sulfhydryl sulfur atom yielding the corresponding trisubstituted arsine sulfide and thiol. Benzyl hydrodisulfide is attacked competitively on sulfenyl and sulfhydryl sulfur atoms by triethylarsine and gives triethylarsine sulfide, α-toluenethiol, dibenzyl trisulfide, and hydrogen sulfide. The products resulted from sulfenyl sulfur attack by the arsine are different from those by tertiary phosphines or trisubstituted phosphites. The mechanism of sulfenyl sulfur attack by the arsine was confirmed by using benzyl hydrodisulfide, of which the sulfenyl sulfur was labeled with ^{35}S, and compared with that by phosphine or phosphite. A correction was made on the latter mechanism.

Previous works[2-4] have shown that aralkyl hydrodisulfide, when attacked by tertiary phosphine (or trisubstituted phosphite) on the sulfenyl sulfur atom, gives phosphine sulfide (or O,O,O-trisubstituted phosphorothionate), hydrogen sulfide, the corresponding disulfide, and hydrocarbon, and that, when attacked on the sulfhydryl sulfur, it yields phosphine sulfide (or the phosphorothionate) and thiol. In the present work benzyl or benzhydryl hydrodisulfide was allowed to react with tertiary (triethyl or triphenyl)arsine, in order to check whether or not the arsine behaves similarly to the phosphorus compound.

Results and Discussion

In a stream of nitrogen a tertiary arsine in ether was added at room temperature to an aralkyl hydrodisulfide in the same solvent. Although the reaction seemed to proceed at once, the mixture was kept standing for 20 hr under an atmosphere of nitrogen to complete the reaction. The variety and amounts of the products are summarized in Table I. The results in Table I indicate that triphenylarsine yielded the corresponding arsine sulfide and thiol, but triethylarsine gave the same products only when treated with benzhydryl hydrodisulfide.

TABLE I
REACTION OF ARALKYL HYDRODISULFIDES WITH TERTIARY ARSINES

Expt no.	Reactants, mmol				Products, mmol			
	R	RSSH	R′	AsR′₃	R′₃AsS	RSH	RS₂R	H₂S
1	$C_6H_5CH_2$	10[a]	C_2H_5	11[a]	7.2	9.0	0.5	0.7
2	$(C_6H_5)_2CH$	10[a]	C_2H_5	11[a]	7.0	8.7		
3	$C_6H_5CH_2$	10	C_6H_5	11	7.9	9.8		
4	$(C_6H_5)_2CH$	10	C_6H_5	11	8.9	9.8		

[a] See Experimental Section.

Previous works[2-4] have confirmed that the sulfhydryl sulfur attack by trivalent phosphorus compounds yields the phosphine sulfide (or phosphorothionate) and the thiol. By analogy with the above reaction, the sequence with a tertiary arsine can be written by replacing PR'_3 [or $P(OR')_3$] with AsR'_3. However, the variety and amounts of the products in expt 1 are different from those of the reaction with triethylphosphine or triethyl phosphite, which are again

$$RSSH + AsR'_3 \longrightarrow [RS]^-\left[\begin{matrix}SH\\|\\AsR'_3\end{matrix}\right]^+ \longrightarrow RSH + SAsR'_3 \quad (1)$$

cited from previous works and indicated in Table II. The prominent distinction between expt 1 in Table I and the results in Table II is that arsine yields a small amount each of dibenzyl trisulfide and hydrogen sulfide, an almost quantitative amount of the thiol, no hydrocarbon, and no dibenzyl disulfide. All of our efforts to find toluene in the present products by using gas chromatography or nmr method proved fruitless. From the viewpoint of material balance the nearly quantitative yield of the thiol in expt 1, Table I, may result at least from the expense of toluene in Table II. Nucleophilic attack of arsine on alternative sulfenyl sulfur which is similar to attack of trivalent phosphorus compounds may interpret the formation of the present results. As mentioned in our previous papers[2-4] two quite equivalent sequences (eq 2 and 3) could be applied to sulfenyl sulfur attack

$$RSSH + PR'_3 \longrightarrow [R]^-\left[\begin{matrix}SSH\\|\\PR'_3\end{matrix}\right]^+ \longrightarrow RH + R'_3P^+SS^- \text{ and further steps} \quad (2)$$

$$RSSH + PR'_3 \longrightarrow \left[\begin{matrix}RS\\|\\PR'_3\end{matrix}\right]^+[SH]^- \text{ and further steps} \quad (3)$$

of phosphorus compounds, where R′ signified C_2H_5, C_6H_5, OC_2H_5, and OC_6H_5. The sequence in eq 2 should be abandoned only for the reason that arsine did not give toluene. The similar sequence in eq 4–7 can be adopted for the present case. However, intermediate I should give RSH by the splitting of the S–As bond as indicated in eq 6 in contrast to the

$$RSSH + AsR'_3 \longrightarrow \left[\begin{matrix}RS\\|\\AsR'_3\end{matrix}\right]^+[SH]^- \quad (4)$$

$$HS^- + RSSH \longrightarrow H_2S + [RSS]^- \quad (5)$$

$$[RSAsR'_3]^+ + RSSH \longrightarrow \left[\begin{matrix}RSAs{-}SSR\\\|\quad\quad|\\R'_3\ \ H\end{matrix}\right]^+ \longrightarrow \underset{\text{I}}{} \quad RSH + [R'_3AsSSR]^+ \quad (6)$$

previous results that the similar intermediate containing phosphorus gave RH by the splitting of the R–S bond. The formation of the remaining products,

(1) Part VIII: S. Kawamura, T. Kitao, T. Nakabayashi, T. Horii, and J. Tsurugi, *J. Org. Chem.*, **33**, 1179 (1968).
(2) J. Tsurugi, T. Nakabayashi, and T. Ishihara, *ibid.*, **30**, 2707 (1965).
(3) T. Nakabayashi, S. Kawamura, T. Kitao, and J. Tsurugi, *ibid.*, **31**, 861 (1966).
(4) T. Nakabayashi, J. Tsurugi, S. Kawamura, T. Kitao, M. Ui and M. Nose, *ibid.*, **31**, 4174 (1966).

TABLE II

REACTION OF BENZYL HYDRODISULFIDE (RSSH, 10 mmol) WITH TRIVALENT PHOSPHORUS COMPOUNDS CITED FROM PREVIOUS WORKS[a,b]

Expt no.	Table	Part no.	Reactants	Products, mmol: Pentavalent P compounds	RSH	RS_2R	H_2S	RH
4	I	III[a]	$(C_2H_5)_3P$	$(C_2H_5)_3PS$, 9.7	3.7	1.7	2.5	1.3
1	I	VII[b]	$(C_2H_5O)_3P$	$(C_2H_5O)_3PS$, 9.5	3.7	1.2	2.7	1.4

[a] See ref 2. [b] See ref 4.

TABLE III

SPECIFIC ACTIVITIES OF THE REACTION PRODUCTS OF BENZYL HYDRODISULFIDE-[^{35}S] WITH TRIETHYLARSINE

Products	Chemical forms for counting analysis	Specific activities (*A*) of standards, cpm/mg	Specific activities (*B*) of the products or those derived from the products, cpm/mg	$B/A \times 100$[a]
$(C_2H_5)_3AsS$	$(C_2H_5)_3AsS$	26,254	0	0
$C_6H_5CH_2SH$	$(C_6H_5CH_2)_2S_2$	43,823	41,232	94.1
$(C_6H_5CH_2)_2S_3$	$(C_6H_5CH_2)_2S_2$	43,823	41,476	94.9
H_2S	$(C_6H_5)_3PS$	17,415	0	0

[a] Indicates the per cent distribution of radioactive sulfur to total sulfur in the products.

dibenzyl trisulfide and the arsine sulfide, can be explained by interaction of $[R'_3AsSSR]^+$ (eq 6) and $[RSS]^-$ (eq 5). The sequence in eq 4–7 for the present

$$[R'_3AsSSR]^+ + [RSS]^- \longrightarrow R'_3AsS + RSSSR \quad (7)$$

reaction will be confirmed by using benzyl hydrodisulfide labeled with ^{35}S.

Reaction with ^{35}S-Labeled Benzyl Hydrodisulfide.—Benzyl hydrodisulfide-[^{35}S] ($C_6H_5CH_2{}^{35}SSH$), the sulfenyl sulfur of which was specifically labeled with ^{35}S, was allowed to react with triethylarsine under the same conditions as for nonlabeled compound. The results are shown in Table III, where specific activities of radiochemically pure products and those of the corresponding standard compounds are indicated. The latter compounds were prepared from the same radioactive species as was the benzyl hydrodisulfide-[^{35}S]. Table III indicates that the sulfur atom of the thiol and sulfur atoms attached to benzyl group of the trisulfide arise from the sulfenyl sulfur, and that triethylarsine sulfide and hydrogen sulfide arise only from the sulfhydryl sulfur of the hydrodisulfide. All of these results can be explained by the sequences given in eq 1 and 4–7 if the symbol RSSH in the above equations was replaced with $R^{35}SSH$. On the contrary, in our previous works[3,4] was observed clearly the distribution of ^{35}S in the phosphine sulfide or phosphorothionate. The activity of the compound must result from R–S bond splitting of the intermediate as indicated in eq 8,

$$[R^{35}SPR'_3]^+ + R^{35}SSH \longrightarrow \left[R{-}{}^{35}SP(R'_3)H{-}S^{35}SR\right]^+ \longrightarrow RH + {}^{35}SPR'_3 + [R^{35}SS]^+ \quad (8)$$

which follows steps similar to eq 4 and 5 cited above. Otherwise the activity of the compound cannot be explained. The conclusion of the present paper is that, when the arsine and trivalent phosphorus compound attack the sulfenyl sulfur of the hydrodisulfide, both give a similar intermediate, each which, in turn, leads to the different products as indicated in eq 6 and 8.

Connection with Analogous Reaction.—The next problem to be solved is to elucidate the reason why the arsine gave dibenzyl trisulfide, whereas phosphine or phosphite gave the disulfide. The formation of dibenzyl disulfide was previously[2–4] assumed to result from the recombination of the anion RSS^- and the cation RSS^+, and then desulfuration of the tetrasulfide to the disulfide by the phosphine present in the reaction system. Analogy to the reaction with the arsine makes the previously assumed mechanism doubtful. Therefore, the reaction was reexamined here by using nmr spectroscopy. Triphenylphosphine and about an equimolar amount of benzyl hydrodisulfide, both in carbon tetrachloride, were mixed in an nmr test tube. Immediately after mixing, neither tetrasulfide nor disulfide was detected; only signals of the trisulfide were observed. Only 2 days later, signals of the disulfide appeared together with those of the trisulfide.

A supplementary nmr experiment shows that desulfuration of dibenzyl tetrasulfide to disulfide by triphenylphosphine took 24 hr at room temperature. Another experiment, run under the same conditions as those reported in the previous paper,[2] showed the following result. Within 1 hr after mixing both triphenylphosphine and benzyl hydrodisulfide in ether, the triphenylphosphine sulfide that precipitated was filtered, and the solvent was replaced with carbon tetrachloride. The nmr spectra identified dibenzyl trisulfide but no tetrasulfide or disulfide. All nmr evidence suggests that the precursory product should be the trisulfide, the formation of which can be written as follows by the analogy with the sequence for the arsine. The cation RSS^+ produced in eq 8 interacts again with the phosphine to yield $[R'_3PSSR]^+$, which is quite analogous to the cation $[R'_3AsSSR]^+$ in eq 7. This step and the succeeding ones indicated in eq 9–11 will take the place of those reported in our previous works.[2–4] The results of activity measurements carried out in our previous works[3,4] do not contradict the reaction sequence cited above.

$$RSS^+ + R'_3P \longrightarrow [RSSPR'_3]^+ \quad (9)$$

$$[RSSPR'_3]^+ + RSS^- \longrightarrow R'_3PS + RSSSR \quad (10)$$

$$RSSSR + R'_3P \longrightarrow RSSR + R'_3PS \quad (11)$$

It seems necessary here to summarize the reaction mechanisms of aralkyl hydrodisulfide with the nucleophile, the phosphine, the phosphite, or the arsine. The nucleophilic attack on sulfhydryl sulfur yields phosphine sulfide, phosphorothionate, or arsine sulfide and arylalkanethiol *via* eq 1. The attack on sulfenyl sulfur proceeds *via* eq 4 and 5 and then produces the intermediate I. The intermediate I containing phos-

phorus splits at the R–S bond (by eq 8) and the succeeding steps are given in eq 9–11. On the other hand the intermediate I containing arsenic splits at the S–As bond by eq 6 and yields the end products *via* eq 7. Desulfuration efficiency by triethylarsine may be inferior to that by the corresponding phosphine or phosphite because dibenzyl trisulfide remains among the other products. Therefore, the arsine can be said to have weaker thiophilicity than phosphine or phosphite. Previous works reported that in the absence of steric hindrance sulfenyl sulfur of hydrodisulfide was preferably attacked by nucleophiles. The present results, on the other hand, indicate the preferential attack on sulfhydryl sulfur by the arsine and suggest that the arsine suffers more steric hindrance than phosphine or phosphite.

Experimental Section

Materials.—Nonlabeled benzyl and benzhydryl hydrodisulfide,[6] and ^{35}S-labeled benzyl hydrodisulfide[3] were prepared and purified by the method reported elsewhere. Triphenyl-[6] and triethylarsines[7] as starting materials, triphenylarsine sulfide[8] and triethylarsine sulfide[9] as authentic materials, and also ^{35}S-labeled triethylarsine sulfide[9] as a standard for counting analysis were prepared by the methods in the literature. Nonlabeled dibenzyl di- and trisulfides[5] and dibenzhydryl disulfide[5] as authentic materials and ^{35}S-labeled dibenzyl disulfide[3] as a radioactive standard were prepared by the method described elsewhere.

Identification and Estimation of the Nonradioactive Reaction Products.—The products and their derivatives which melted above room temperature were identified by mixture melting point with authentic specimens. Hydrogen sulfide evolved during the reaction was determined by the method reported elsewhere.[2] Analysis of the polysulfides mixture was accomplished satisfactorily by using nmr spectroscopy.[1,10] We found in the present research that the nmr technique was also feasible for the products containing thiol in addition to the polysulfide mixture. The nmr spectra of all samples were taken on JNM 3H-60 spectrometer (60 Mc) with tetramethylsilane as the internal standard. τ values of authentic specimens at low concentrations (*ca.* 7%) in carbon tetrachloride were as follows: $C_6H_5CH_2SH$, 8.49 (–SH, triplet) and 6.39 (–CH_2–, doublet); $(C_6H_5CH_2)_2S_2$, 6.49; $(C_6H_5CH_2)_2S_3$, 6.02; $(C_6H_5CH_2)_2S_4$, 5.89; $(C_6H_5CH_2)_2S_5$, 5.85; $(C_6H_5)_2CHSH$, 7.95 (–SH, doublet); and 4.66 (–CH–, doublet).

Chemical shifts of each component in arbitrary concentrations were, of course, slightly different from the above values. For identification, authentic compounds were added to the solution of products and the corresponding peaks were carefully examined. Amounts of the components were determined by comparison of the respective integral values with that of tetrachloroethane (τ *ca.* 5.9) as another internal standard for integral purpose only.

The Reaction of Nonlabeled Aralkyl Hydrodisulfides.—To an ethereal solution of the hydrodisulfide in a flask described elsewhere[2] was added dropwise a solution of the arsine in ether in a stream of nitrogen. For the reaction with triethylarsine, 40 mmol of the hydrodisulfide and 44 mmol of the arsine were used for manipulating convenience, and the results were calculated as described in Table I. Because of easy oxidizability of triethylarsine, its solution was syringed into the flask through a rubber stopper instead of a dropping funnel.[2] The mixture was kept under a gentle stream of nitrogen for 20 hr at room temperature to complete the reaction. Throughout the reaction no evolution of hydrogen sulfide was observed except for the reaction of benzyl hydrodisulfide with triethylarsine. White crystals separated from the solution were collected, weighed, recrystallized from ethanol, and identified as triphenylarsine sulfide, mp and mmp 162°, and triethylarsine sulfide, mp 119°. The arsine sulfides could be estimated nearly quantitatively owing to their low solubility in ether. However, *t*-arsine sulfide has slightly higher solubility and, therefore, gives slightly less yield than *t*-phosphine sulfide.[2,3] Similarly triethylarsine sulfide seems to have slightly higher solubility than triphenylarsine sulfide. The ethereal solution filtered from the arsine sulfide was diluted with ether to 100 ml. The succeeding procedure is described separately for the individual reactions.

A.—For the reaction of hydrodisulfides with triphenylarsine, an aliquot (10 ml) of the solution was titrated with a kerosene solution of cupric oleate,[2,4] which was found in a preliminary experiment to be inert to triphenylarsine. For further identification of the thiol, an ethanolic iodine solution was added to the remaining portion (90 ml) of the ethereal solution. The solution was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, white crystals were recrystallized from the benzene–ethanol mixture and found to be the corresponding disulfide.

B.—For benzhydryl hydrodisulfide with triethylarsine, which was found to interact with cupric oleate, the solvent of an aliquot (50 ml) of the ethereal solution was replaced with carbon tetrachloride. The thiol was determined by nmr spectroscopy from the carbon tetrachloride solution and identified from the remaining portion of ethereal solution by method A.

C.—For benzyl hydrodisulfide with triethylarsine, an aliquot (50 ml) of the ethereal solution was used for nmr spectral identification and determination of α-toluenethiol and dibenzyl trisulfide. The remaining portion of the ethereal solution was used for further identification of the thiol by the method described in A.

Procedure for Benzyl Hydrodisulfide-[^{35}S] with Triethylarsine.—Benzyl hydrodisulfide-[^{35}S] (20 mmol) was allowed to react with triethylarsine (22 mmol) under the same conditions as for the nonradioactive compound. Radioactive thiol (after its conversion into the corresponding disulfide), dibenzyl trisulfide (after desulfuration to the corresponding disulfide by potassium cyanide), and nonradioactive triethylarsine sulfide (as such) were isolated and identified, respectively. Hydrogen sulfide absorbed in iodine solution was released as elementary sulfur and converted into triphenylphosphine sulfide.[3] The products were recrystallized to respective constant activities and subjected to counting analysis by the method reported elsewhere.[3,4]

Reexamination of the Reaction Products of Benzyl Hydrodisulfide with Triphenylphosphine.—The products from the reaction of benzyl hydrodisulfide with triphenylphosphine were studied again by the nmr method to find if it can be assumed that dibenzyl tetrasulfide is the intermediate compound leading to dibenzyl disulfide.

The reaction was carried out under the same condition as described in the previous experiment,[2] but, after 1 hr, crystals of triphenylphosphine sulfide that separated from the solution were filtered, and ether was quickly evaporated under reduced pressure. To the oily residue was added an appropriate amount of carbon tetrachloride, and then the nmr spectrum was recorded. In the spectrum, the methylene signal of dibenzyl trisulfide was observed but no signal dibenzyl tetrasulfide appeared. Dibenzyl trisulfide was identified by adding the authentic specimen and by confirmation of no splitting and increase in height of the peak of the trisulfide. When the authentic tetrasulfide was added, another peak corresponding to the tetrasulfide was found in the separated position from the trisulfide.

Registry No.—Triphenylarsine, 603-32-7; triethylarsine, 617-75-4; benzyl hydrodisulfide, 3492-66-8; benzhydryl hydrodisulfide, 3492-67-9; benzyl hydrodisulfide-[^{35}S], 6379-78-8.

(5) J. Tsurugi and T. Nakabayashi, *J. Org. Chem.*, **24**, 807 (1959).
(6) R. L. Shriner and C. N. Wolf, *Org. Syn.*, **30**, 95 (1950).
(7) R. R. Renshaw and C. E. Holm, *J. Amer. Chem. Soc.*, **42**, 1468 (1920).
(8) F. Zuckerkandl and M. Sinai, *Chem. Ber.*, **54**, 2485 (1921).
(9) H. Landolt, *Ann.*, **89**, 326 (1854).
(10) D. Grant and J. R. Wazer, *J. Amer. Chem. Soc.*, **86**, 1450, 3012 (1964).

The Acid-Catalyzed Hydrolysis of 2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane and Tetramethylethylene Glycol Acetals of Aromatic and Aliphatic Aldehydes

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The rates of hydrolysis of several *para*-substituted benzaldehyde acetals of ethanol, ethylene glycol, and tetramethylethylene glycol have been measured in H_2O at 30°. The tetramethylethylene glycol acetals all hydrolyze very slowly in comparison with the other types of acetals. For example, 2-(*p*-methoxyphenyl-4,4,5,5-tetramethyl-1,3-dioxolane has a second-order rate constant 40,000 times less than that for *p*-methoxybenzaldehyde diethyl acetal. The rates of hydrolysis of 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes are also much slower in 50% dioxane–H_2O than those of the corresponding diethyl acetals or 1,3-dioxolanes, and the sensitivity of the rate to inductive effects is less ($\rho^* = -2.2$). The ΔS^* for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in aqueous HCl is −15.8 eu. Substitution of a methyl group at the reaction center slows the hydrolysis of tetramethylethylene glycol acetals greatly; 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane hydrolyzes 540 times more slowly than the corresponding benzaldehyde derivative. Thus, this data in conjunction with data previously reported points strongly to the participation of water in the hydrolysis of the 4,4,5,5-tetramethyl-1,3-dioxolanes with the most likely possibility involving an A2 mechanism.

There is little doubt that the acid-catalyzed hydrolysis of acetals generally involves preequilibrium protonation of the substrate followed by a unimolecular rate-determining decomposition to an alcohol and a resonance-stabilized carbonium ion.[1] It has recently been found in this laboratory, however, that the hydrolysis of certain 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in water proceeds in a manner markedly different from that of normal acetals.[2] The application of various mechanistic criteria gave evidence which pointed consistently to a mechanism involving solvent participation in the rate-determining step. If water is actively involved in the transition state then possible mechanisms would involve either partially rate-determining protonation by hydronium ion or nucleophilic assistance by water in an A2-type reaction. The A2 mechanism was preferred[2] in view of the extreme slowness of the reactions in comparison with those of analogous diethyl and ethylene glycol acetals of substituted benzaldehydes previously studied in 50% dioxane–H_2O;[3,4] the D_2O solvent isotope effect ($k_{D_2O}/k_{H_2O} = 2.4$) indicated that proton transfer was essentially complete, and the magnitude of the slope of a plot of log $k_{obsd} + H_0$ *vs.* log a_{H_2O} was 1.9. Capon and Thacker[5] recently presented similar data for the hydrolysis of methyl furanosides which can be interpreted in terms of an A2 mechanism, although other possibilities were also considered.

It would be expected that replacement of the hydrogen at the acetal carbon by an alkyl group would markedly reduce the rate if attack by solvent was occurring at that position. The rate of hydrolysis of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane has accordingly been measured and has been found to be extremely slow in comparison with that for the corresponding benzaldehyde derivative.

It would appear likely that the differences in behavior between tetramethylethylene glycol acetals and ethylene glycol or diethyl acetals are produced by steric inhibition of the normal A1 reaction by the presence of methyl groups at the 4 and 5 positions of the 1,3-dioxolane ring, thus allowing other mechanisms to become observable. It was therefore of importance to assess the influence of the 2 substituent on these reactions. Accordingly the rates of hydrolysis have been measured for a series of acetals where the 2 substituent is alkyl rather than aryl.

Experimental Section

Materials.—The acetals of substituted benzaldehydes were those previously reported.[2,3] Acetals of aliphatic aldehydes were prepared by the same methods. 2-Propyl-4,4,5,5-tetramethyl-1,3-dioxolane boiled at 77–78° at 28.7 mm, $n^{22}D$ 1.4235. *Anal.* Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.54; H, 11.82. 2-(β-Chloroethyl)-4,4,5,5-tetramethyl-1,3-dioxolane boiled at 74–75° at 4.8 mm, $n^{25.5}D$ 1.4370. *Anal.* Calcd for $C_9H_{17}ClO_2$: C, 56.10; H, 8.89; Cl, 18.40. Found: C, 56.17; H, 8.95; Cl, 18.22. 2-(β-Phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane boiled at 113° at 3.5 mm, $n^{24}D$ 1.4925. *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.85; H, 9.34. The sodium salt of 2-(β-carboxyethyl)-4,4,5,5-tetramethyl-1,3-dioxolane was prepared from the corresponding methyl ester (bp 81–84° at 1.9 mm, $n^{25}D$ 1.4380) by a procedure previously described.[6] The salt was recrystallized from an ethanol–ether mixture. *Anal.* Calcd for $C_{10}H_{17}O_4Na$: C, 53.56; H, 7.64. Found: C, 53.65; H, 7.41. 2-Propyl-1,3-dioxolane boiled at 134–140°, $n^{23}D$ 1.4498 (lit.[7] bp 130–135°). Butyraldehyde diethyl acetal had bp 59–60° at 33 mm, $n^{24}D$ 1.3975 (lit.[8] bp 143–144°).

2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane was prepared by a ketal interchange method. Equivalent amounts of acetophenone, ethyl orthoformate, and tetramethylethylene glycol were allowed to stand for 12 hr in the presence of a trace of *p*-toluenesulfonic acid. Ethanol was then slowly distilled from the reaction mixture. When all of the ethanol had been removed the residue was taken up in benzene and washed with 0.1 *M* NaOH solution. The benzene extract was dried over sodium sulfate. The benzene was then evaporated, and the liquid residue was distilled. The product boiled at 77–78° at 1.2 mm, $n^{24}D$ 1.4890. *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.41; H, 9.27.

Dioxane was purified by the method of Fieser.[9] Acetonitrile

(1) For the evidence which has led to this mechanism and the pertinent references, see E. H. Cordes in "Progress in Physical Organic Chemistry," Vol. 4, A. Streitwieser, Jr., and R. W. Taft, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 1.

(2) T. H. Fife, *J. Amer. Chem. Soc.*, **89**, 3228 (1967).

(3) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).

(4) T. H. Fife and Lily Hagopian, *ibid.*, **31**, 1772 (1966).

(5) B. Capon and D. Thacker, *J. Chem. Soc., B.*, 185 (1967).

(6) T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 271 (1965).

(7) M. J. Astle, J. A. Zaslowesky, and P. G. Lafytis, *Ind. Eng. Chem.*, **46**, 787 (1954).

(8) S. M. McElvain, R. L. Clarke, and G. D. Jones, *J. Amer. Chem. Soc.*, **64**, 1966 (1942).

(9) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.

was Eastman Kodak Spectrograde and was further purified by twice distilling it from P_2O_5 and once from K_2CO_3.

Kinetic Measurements.—The equipment and procedures were the same as previously employed.[2,3] The rates were measured spectrophotometrically on a Zeiss PMQ11 spectrophotometer by following the appearance of the aldehyde or ketone product. The acetals were dissolved in dioxane, and the rates were initiated by adding 1 drop of this solution to 3.5 ml of acidic solution in the cuvette with a calibrated dropping pipet and vigorous stirring. The cuvette was then stoppered tightly with a Teflon stopper. At the conclusion of each reaction the ultraviolet spectrum of the solution was found to be identical with that of the appropriate aldehyde. For rate measurements in the presence of various salts the acetals were dissolved in acetonitrile, and 1 drop was added to the solution in the cuvette.

Results

The rates of hydrolysis of several *para*-substituted benzaldehyde acetals of ethanol, ethylene glycol, and tetramethylethylene glycol have been measured in aqueous solutions at 30°. The data are reported in Table I. It can be seen that the tetramethylethylene glycol acetals hydrolyze in each case much more slowly than the corresponding ethylene glycol or diethyl acetal. Replacing the hydrogen at the acetal carbon by a methyl group in the case of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane further reduces the rate by a factor of 540 compared with 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane.

TABLE I

RATES OF HYDROLYSIS OF SUBSTITUTED BENZALDEHYDE ACETALS OF ETHANOL, ETHYLENE GLYCOL, AND TETRAMETHYLETHYLENE GLYCOL IN H_2O AT 30°

Acetal	pH	k_{obsd}, min^{-1}	k_H,[a] l. mol^{-1} min^{-1}	k_{rel}[b]
(a) 2-(*p*-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane[c]	1.0[d]	0.400	4.00	1.0
(b) 2-(*p*-Methoxyphenyl)-1,3-dioxolane	3.07[e]	3.50	4,113	1,030
(c) *p*-Methoxybenzaldehyde diethyl acetal	5.25[f]	0.901	160,000	40,000
(d) 2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane[c]	1.0[d]	0.0739	0.739	1.0
(e) 2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	0[g]	0.00137	0.00137	0.00185
(f) 2-Phenyl-1,3-dioxolane	3.07[e]	0.215	252.6	342
(g) Benzaldehyde diethyl acetal	3.55[h]	3.81	13,510	18,280

[a] k_{obsd}/a_H. [b] Relative rate ratios within each series where the *para* substituent is the same for all compounds. [c] Data from ref 2. [d] 0.1 *M* HCl. [e] HCl solution, μ = 0.1 *M* with KCl. [f] Acetate buffer; buffer catalysis was not observed; μ = 0.1. [g] 1.0 *M* HCl. [h] Formate buffer; buffer catalysis was not observed; μ = 0.1.

A series of 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes was studied in 50% dioxane–H_2O. The rates of hydrolysis are presented in Table II. The 2-propyl derivative hydrolyzes much more slowly than the ethylene glycol or diethyl acetal, but the effect of methyl group substitution in the 1,3-dioxolane ring is less marked than when the substituent at the 2 position is substituted phenyl. The four tetramethylethylene glycol acetals studied gave a linear plot of log k_{obsd} at one acid concentration *vs.* σ^*, the Taft substituent constant,[10] shown in Figure 1 with a slope, ρ^*, of −2.2.

The smaller relative rate differences for the 2-alkyl compared with the 2-aryl derivatives are at least partly due to the change in solvent from H_2O to 50% dioxane–H_2O. In Table III are given rate constants and relative rate ratios for hydrolysis of the various benzaldehyde acetals in 50% dioxane–H_2O. It can be seen that the differences in rate are less pronounced in 50% dioxane–H_2O than in H_2O. This is due to the organic solvent mixture having a smaller rate-retarding effect on the hydrolysis of the tetramethylethylene glycol acetal.

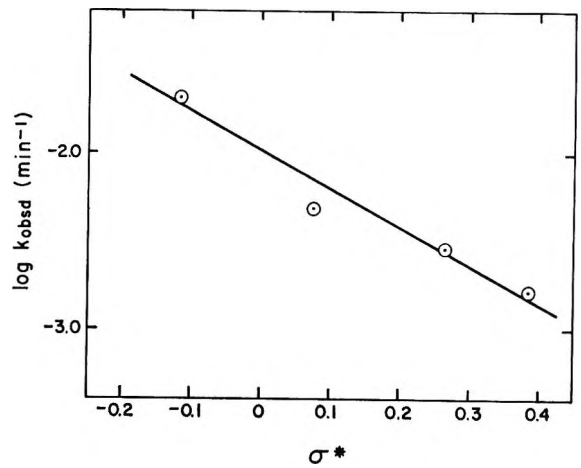


Figure 1.—Plot of log k_{obsd} *vs.* σ^* for hydrolysis of 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes in 50% dioxane–H_2O at 30° and pH 0.30.

TABLE II

RATES OF HYDROLYSIS OF ACETALS OF ALIPHATIC ALDEHYDES IN 50% DIOXANE–H_2O AT 30°

Acetal	σ^* [a]	pH	k_{obsd}, min^{-1}	k_H,[b] l. mol^{-1} min^{-1}	k_{rel}
(a) Butyraldehyde diethyl acetal		2.37	0.122	28.5	695.1
(b) 2-Propyl-1,3-dioxolane		0.30[c]	0.289	0.578	14.1
(c) 2-Propyl-4,4,5,5-tetramethyl-1,3-dioxolane	−0.115	0.30[c]	0.0207	0.041	1.0
(d) 2-(β-Phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane	0.08	0.30[c]	0.00483	0.0097	
(e) 2-(β-Carboxyethyl)-4,4,5,5-tetramethyl-1,3-dioxolane	0.265[d]	0.30[c]	0.0026	0.0052	
(f) 2-(β-Chloroethyl)-4,4,5,5-tetramethyl-1,3-dioxolane	0.385	0.30[c]	0.00166	0.0033	

[a] Reference 10. [b] k_{obsd}/a_H. [c] 1.0 *M* HCl–dioxane (v/v). [d] A σ^* of +2.94 was reported for the undissociated carboxyl group,[10] but T. C. Bruice and D. Piszkiewicz [*J. Amer. Chem. Soc.*, 89, 3568 (1967)] found that a value of +2.08 gave a better fit to their data. Therefore, the value of σ^* employed in the present study was 2.08/(2.8)^2 since Taft[10] recommended 2.8 as the factor for attenuation of the inductive effect per methylene group interposed between the substituent and the reaction center.

TABLE III

RATE CONSTANTS FOR HYDROLYSIS OF ACETALS IN 50% DIOXANE–H_2O (v/v) AT 30°

Compound	pH	k_{obsd}, min^{-1}	k_H, l. mol^{-1} min^{-1}	k_{rel}
Benzaldehyde diethyl acetal[a]	4.12	0.0549	723.3	4465
2-Phenyl-1,3-dioxolane[a]	2.36	0.111	25.4	157
2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane	0.30[b]	0.0812	0.162	1.0
2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	*c*	0.00124	0.0005	0.003

[a] Reference 3. [b] 1.0 *M* HCl–dioxane (v/v). [c] 4.80 *M* HCl–dioxane (v/v).

(10) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 556.

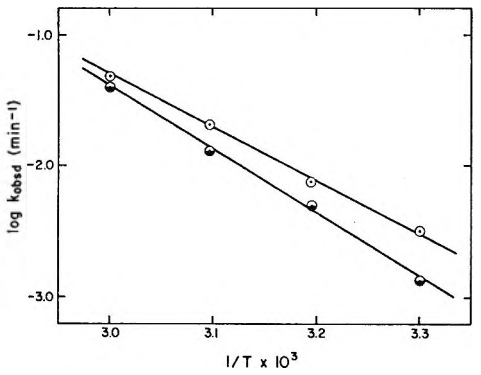


Figure 2.—Plot of log k_{obsd} *vs.* $^1/_T$° *K* for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in 0.1 *M* HCl, ⊙, and 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane in 1.0 *M* HCl, ◒.

The hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in 0.1 *M* HCl and the hydrolysis of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane in 1.0 *M* HCl was studied as a function of temperature. Rates were determined at 30, 40, 50, and 60° (±0.1). Rates were measured in triplicate at each temperature with an average deviation of less than 2% in each case. The rate constants are given in Table IV, and plots of

TABLE IV

RATE CONSTANTS (k_{obsd}, min^{-1}) FOR HYDROLYSIS OF 2-(*p*-NITROPHENYL)-4,4,5,5-TETRAMETHYL-1,3-DIOXOLANE IN 0.1 *M* HCl AND 2-PHENYL-2,4,4,5,5-PENTAMETHYL-1,3-DIOXOLANE IN 1.0 *M* HCl AT VARIOUS TEMPERATURES

Compound	Temp, °C	k_{obsd}, min^{-1}
2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane	30	0.0032
	40	0.0076
	50	0.0207
	60	0.0490
2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	30	0.00137
	40	0.00505
	50	0.0132
	60	0.0394

log k_{obsd} *vs.* $^1/_T$ are shown in Figure 2. Activation parameters were determined and are reported in Table V. The errors reported in ΔH^* and ΔS^* were calculated from the standard error of the plot of ln k_{obsd} *vs.* $^1/_T$. A highly negative value of ΔS^* (−15.8 eu) was found for the *p*-nitro derivative.

TABLE V

ACTIVATION PARAMETERS FOR HYDROLYSIS OF TETRAMETHYLETHYLENE GLYCOL ACETALS IN H_2O

Compound	ΔH^*, kcal/mol	ΔS^*, eu[a]
2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane[b]	16.1 ± 0.5	−14.2 ± 1.7
2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane	17.5 ± 0.3	−15.8 ± 0.9
2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	21.6 ± 0.4	−8.6 ± 1.2

[a] Calculated at 30° with the rate constant having the units of l. mol^{-1} sec^{-1}. [b] Reference 2.

In Table VI rate constants are given for hydrolysis of the acetals in aqueous HCl with various salts added. High concentrations of iodide ion in 0.01 *M* HCl increase the rate of hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane to a greater extent than equal concentrations of the less nucleophilic chloride or perchlorate ion, but the magnitude of the effect is fairly small. From the similarity of the rate constants with added chloride, bromide, or perchlorate ion it would appear that these ions are influencing the reaction primarily by an ionic strength effect.

Discussion

The tetramethylethylene glycol acetal of *p*-methoxybenzaldehyde hydrolyzes in water approximately 1030 times more slowly than the corresponding ethylene glycol derivative and 40,000 times more slowly than the corresponding diethyl acetal. The relative rate ratios are less for the unsubstituted compound, but it can be seen in Table I that introduction of methyl groups into the 4 and 5 positions of the 1,3-dioxolane ring has still resulted in an extremely large rate retardation. These rate differences are also found when the substituent at the 2 position is alkyl rather than aryl, although the effects are less pronounced. From the data in Table II it can be seen that 2-propyl-4,4,5,5-tetramethyl-1,3-dioxolane hydrolyzes 695 times more slowly than the corresponding diethyl acetal in 50% dioxane–H_2O. The large rate differences observed with the *p*-methoxyphenyl derivatives are due in part to the fact that the *p*-methoxy group enhances the rate of hydrolysis of the diethyl acetal by resonance interaction with the incipient carbonium ion in the transition state,[3] whereas such a facilitating effect is absent in the case of the tetramethylethylene glycol acetal.[2] Still, other factors must also be of great importance as evidenced by the relatively slow rates of hydrolysis of the 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes.

A plot of the logarithms of the rate constants for hydrolysis of the 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes *vs.* σ, the Hammett substituent constant,[11] was found to be linear[2] with a ρ of −2.0 in contrast to the marked upward curvature found for *para*-substituted benzaldehyde diethyl acetals and ethylene glycol acetals;[3] by employing *meta* substituents ρ was found to be −3.35 for hydrolysis of those compounds.[3] The linearity of the relationship with σ in the case of the tetramethylethylene glycol acetals and the less negative value of ρ compared with that for diethyl acetals indicated that the transition state had much less carbonium ion character. Nucleophilic attack by solvent at the reaction center would also result in a more positive value of ρ.

When the substituent at the 2 position is alkyl, the sensitivity of the reaction to polar effects is also considerably smaller with the tetramethylethylene glycol acetals. The ρ^* of −2.2 is much less negative than the value of −3.60 found for hydrolysis of diethyl acetals in 50% dioxane–H_2O.[12] The smaller sensitivity to inductive effects with the 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes is similar to that found in the substituted benzaldehyde series and also indicates that the transition state for hydrolysis of these tetramethylethylene glycol acetals of aliphatic aldehydes has less carbonium

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(12) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 5590 (1955).

TABLE VI

RATE CONSTANTS (min^{-1}) FOR HYDROLYSIS OF ACETALS IN HCl SOLUTIONS CONTAINING VARIOUS SALTS AT 0.2 *M*

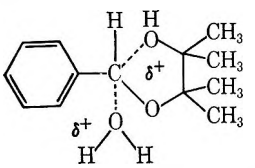
Acetal	HCl	$NaClO_4$	NaCl	NaBr	NaSCN	NaI
2-(*p*-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane[a]	0.1 *M*					
	0.400[b]	0.469	0.451	0.469	0.497	0.490
	0.01 *M*					
	0.0419					0.0475[c]
		0.0469	0.0460			0.0530
		0.0539[d]	0.0499[d]			0.0649[d]
	0.1 *M*					
2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane[e]	0.0207	0.0214	0.0216	0.0224	0.0241	

[a] Data obtained at 30°. [b] Data from ref 2. [c] 0.01 *M* HCl, 0.1 *M* NaI. [d] 0.01 *M* HCl, 0.4 *M* salt. [e] Data obtained at 50°.

ion character than in the cases of the corresponding diethyl acetals. The 2-propyl derivative, however, does hydrolyze four times more slowly than 2-phenyl in 50% dioxane–H_2O. This result can best be explained on the basis of resonance effects by the phenyl substituent,[12] and shows that the acetal carbon must still have at least some positive charge in the transition state. However, the small rate difference of 4 can be contrasted with the factors of 25 and 44 for hydrolysis of the butyraldehyde and benzaldehyde diethyl and ethylene glycol acetals.

Other pronounced differences in hydrolytic behavior were also found between the various types of substituted benzaldehyde acetals,[2] and general acid catalysis was observed in the hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in formic acid buffers. These differences pointed strongly to a change in mechanism due to methyl substitution in the 1,3-dioxolane ring with the most likely possibility being an A2 reaction involving attack of water on the protonated acetal.

The large rate decrease (540 times) produced by replacing the hydrogen at the acetal carbon by a methyl group in 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane strongly suggests that attack by solvent is taking place at that position during hydrolysis of the acetals as in mechanism 1. Acetophenone diethyl ketal hydrolyzes faster than benzaldehyde diethyl acetal, the reaction proceeding by an A1 mechanism.[4] 2-Phenyl-2-methyl-1,3-dioxolane does hydrolyze more slowly than 2-phenyl-1,3-dioxolane but only by a factor of 5.[4] Thus, in terms of an A1 mechanism it would be expected that methyl group substitution at the reaction center would accelerate the reaction since polar effects of the methyl group would stabilize an intermediate carbonium ion or, perhaps since a 1,3-dioxolane ring is opening, the rate would be only slightly reduced. It might also reasonably be expected that the methyl group would facilitate the rate if partially rate-determining proton transfer to oxygen from hydronium ion was occurring as in the hydrolysis of ortho esters.[13] Since the reaction center probably does bear some positive charge in the transition state it is likely that bond breaking is proceeding to a greater extent than bond making with solvent, in mechanism 1.



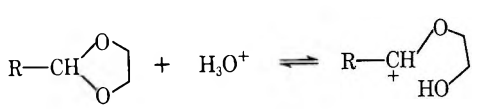
(1)

(13) C. A. Bunton and R. H. DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965).

The ΔS^* of −15.8 eu found in this study for the hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane is further evidence for the involvement of solvent in the rate-determining step. Positive entropies of activation have been observed in numerous instances for reactions involving unimolecular decomposition of a protonated intermediate, while reactions in which solvent participates should have ΔS^* values that are highly negative.[14,15] A value of −15.8 eu is clearly more in accord with solvent involvement than with a unimolecular rate-determining step. It is of interest that ΔS^* becomes more negative as electron withdrawal by the *para* substituent becomes greater.

The ΔS^* of −8.6 eu for hydrolysis of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane is similar to that observed for ethylene glycol acetals and ketals.[3,4] The transition state for hydrolysis of that compound may therefore have considerably more unimolecular character than is the case with the other tetramethylethylene glycol acetals. This would be reasonable since the presence of the methyl group would strongly inhibit nucleophilic attack. If this is indeed the case then a semiquantitative assessment of the ability of the tetramethyl-1,3-dioxolane ring system to inhibit A1 hydrolysis with aromatic derivatives is possible since the second-order rate constant for hydrolysis of the tetramethylethylene glycol derivative of acetophenone is 10^7 times less than that of benzaldehyde diethyl acetal. Acetophenone diethyl ketal was not sufficiently soluble in H_2O for accurate measurement of its rate of hydrolysis in that solvent, but in 50% dioxane–H_2O it was found to hydrolyze 33 times faster than benzaldehyde diethyl acetal.[4] Therefore, if the reasonable assumption is made that the ratio of the rate constants would be approximately the same in H_2O, then 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane is 3×10^8 times less reactive than acetophenone diethyl ketal.

Capon and Thacker[5] suggested that the slightly negative ΔS^* values for hydrolysis of 2-substituted 1,3-dioxolanes[3] and furanosides[5] might result from reversibility of an initial ring-opening step so that $k_{obsd} = k_2K$, where K is the equilibrium constant for ring



(2)

opening and k_2 is the rate constant for reaction of water with the oxocarbonium ion intermediate.

A similar argument can be advanced for incursion of attack by solvent on the protonated acetal with the

(14) F. A. Long, J. G. Pritchard, and F. A. Stafford, *J. Amer. Chem. Soc.*, **79**, 2362 (1957).

(15) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

tetramethylethylene glycol acetals. Geminal methyl group substitution at the 4 and 5 positions of the 1,3-dioxolane ring would greatly favor reclosure of the ring, if unimolecular C–O bond breaking was occurring, by restricting unfavorable rotation of the alcohol group away from the carbonium ion center. Since the alcohol group is held in close proximity to the carbonium ion, reaction of the carbonium ion with water might not be able to compete with ring closure. If ring closure to form starting material from a carbonium ion intermediate is extremely facile, then the reaction might only proceed readily to products if bond making with a water molecule can occur before the leaving group is completely free, *i.e.*, without formation of a carbonium ion as a discrete intermediate in the ring-opening reaction (1). Thus an A2-type reaction would allow products to be formed but at a very slow rate which, of course, is observed.

The lack of large anion effects is in accord with this explanation. The anions studied differ greatly in their ability to act as nucleophiles,[16] but the α-halo ethers that would be formed by nucleophilic attack of a halide anion on the protonated acetal would ionize rapidly to carbonium ion[17] which then could undergo a fast ring closure to regenerate the starting material. Thus, anion effects should be small and might only be observable with very powerful nucleophiles such as iodide ion.

The lack of large anion effects in these reactions is also in accord with a mechanism involving partially rate-determining protonation of the acetal by hydronium ion. Such a mechanism very likely occurs with acetals in which there is strong electron withdrawal in the leaving group so that basicity is greatly reduced while C–O bond breaking is facilitated.[18] Thus it has recently been found that for hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran the D_2O solvent isotope effect is close to unity and a pronounced general acid catalysis by formic acid can be observed, while with 2-(*p*-methoxyphenoxy)tetrahydropyran the ratio k_D/k_H is 2.48 and general acid catalysis can not be detected.[18] In the case of the tetramethylethylene glycol acetals, however, where strong electron withdrawal in the leaving group is not present, there is no reason to suspect that basicity has been significantly reduced.[19] Also the magnitude of the D_2O solvent isotope effect[2] and the large rate retardation produced by methyl group substitution at the reaction center provide strong arguments against the occurrence of rate-determining protonation in these reactions. Therefore, while slow protonation cannot be conclusively ruled out at this time for the tetramethylethylene glycol acetals, the bulk of the evidence points to the A2 mechanism 1.

The evidence in accord with an A2 mechanism lends support to the possibility that the weak general acid catalysis by formate buffer observed with 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane involves nucleophilic attack by formate ion on the protonated acetal. Favorable pathways not involving a carbonium ion are, of course, available for decomposition of an acylal intermediate to aldehyde in acidic solution.[20]

Registry No.—Table I (b), 2403-50-1; Table I (c), 2403-58-9; Table I (e), 17414-56-1; Table I (f), 936-51-6; Table I (g), 774-48-1; Table II (a), 3658-95-5; Table II (b), 3390-13-4; Table II (c), 17396-24-6; Table II (d), 17396-25-7; Table II (e), 17396-26-8; Table II (f), 7451-02-7; 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane, 1831-57-8; 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane, 16837-06-2; 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane, 16825-51-7.

Acknowledgment.—This work was supported by the National Institutes of Health Research Grant GM 10613.

(16) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 141 (1953).

(17) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 333.

(18) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).

(19) Steric hindrance to solvation of the conjugate acids might result in some reduction in basicity, but if hindrance to solvation was an important factor in these reactions more positive ΔS^* values would result in comparison with those found for normal acetals rather than the much more negative values actually observed.

(20) P. Salomaa, *Acta Chem. Scand.*, **11**, 239 (1957).

Intermediates in Nucleophilic Aromatic Substitution. IV.[1] Structures and Stabilities of Spiro Meisenheimer Complexes of Dinitro-Substituted Arenes[2]

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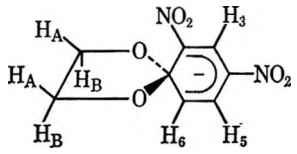
The rate constants for the formation and decomposition of the spiro Meisenheimer complex **7** formed by the reaction of methoxide ion with 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene (**9**) in methanolic solution have been determined at 6.65, 15.00, and 25.00°, allowing a determination of K, k_1, and k_2, and the energies and entropies of activation for the reactions. These data indicate **7** to be approximately 50% more stable than the analogous acyclic 1,1-dimethoxy-2,4-dinitronaphthalene complex (**10**) and further indicate that the driving force for the formation of **7** is much more entropy dependent than that for **10**. Complex **7** and the analogous spiro complexes of 2,4- (**2**) and 2,6-dinitrobenzene (**6**) systems have been isolated as stable crystalline materials. Studies of the ir and pmr spectra of these complexes substantiate the postulated stuctures. The anticipated A_2B_2-type spectra are observed for the dioxolane systems of complexes **2** and **7**.

The formation of a bright red coloration (λ_{max} 493 mμ) upon the addition of sodium hydroxide to an acetone solution of 1-(β-hydroxyethoxy)-2,4-dinitrobenzene (**1**) was first reported by Gitis and Kaminskii,[4] who mistakenly ascribed this observation to the formation of a Janovski complex.[5] In a reinvestigation of this work, Pollitt and Saunders[6] postulated, on the basis of visible and uv spectroscopic studies, that the color was due to the formation of a spiro Meisenheimer complex (**2**). Subsequently, the analogous trinitro



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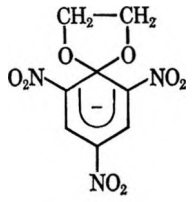
Meisenheimer complex was isolated from the reaction mixtures of 1-(β-hydroxyethoxy)-2,4,6-trinitrobenzene (**3**) and sodium[7] or potassium[8] glycolate; the ir and pmr spectra of this complex supported the postulated structure **4**.[7] Furthermore, the rate of decomposition



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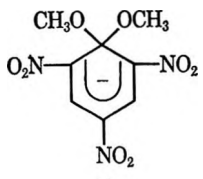
of **4** in aqueous sodium hydroxide solution was observed to be several orders of magnitude slower than that for noncyclic 1,1-dialkoxy Meisenheimer complexes (*e.g.*, **5**),[8] indicative of a greatly enhanced stability for the spiro complexes.



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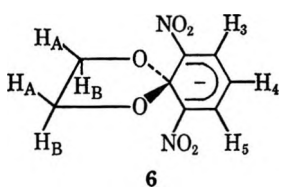
More recently, the pmr spectrum of the complex prepared by the *in situ* reaction of methoxide ion with **1** was examined.[9] The appearance of the low-field portion of the spectrum was consistent with the postulation of structure **2** for the product; the cyclohexadienylide proton chemical shifts and multiplicities were similar to those observed for 1,1-dialkoxy Meisenheimer complexes of 2,4-dinitrobenzene systems.[9,10] However, the methylene proton equivalence was reported for **2**;[9] this observation is inconsistent with the postulated structure.

The spiro Meisenheimer complexes possess a number of unique features which are relevant to the chemistry, particularly the structures and stabilities, of Meisenheimer complexes and to their role in nucleophilic aromatic substitution. The indicated[8] greater stabilities of the spiro complexes relative to the acyclic complexes should be reflected in the magnitudes of the appropriate kinetic and thermodynamic parameters; entropy effects might be expected to be particularly important for the spiro complexes. A convincing demonstration, lacking in previous studies,[7,9] of the structures of the spiro complexes should provide particularly compelling evidence for the sp^3 hybridization at C-1 of the cyclohexadienyl systems of Meisenheimer complexes. The existence of spiro complexes would require such a hybridization. Accordingly, in this paper we wish to report the synthesis, and isolation, and the determination of the chemical and physical properties of the crystalline complexes **2**, **6**, and **7** and present kinetic and



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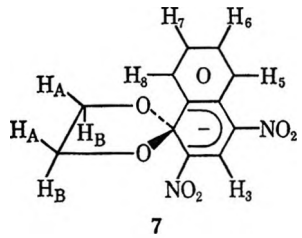

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(1) Part III: J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 977 (1968).

(2) Preliminary publication: C. E. Griffin, E. J. Fendler, W. E. Byrne, and J. H. Fendler, *Tetrahedron Lett.*, 4473 (1967).

(3) NASA Postdoctoral Fellow, 1966–1968.

(4) S. S. Gitis and A. Y. Kaminskii, *J. Gen. Chem. USSR*, **30**, 3771 (1960).

(5) For a recent review of the chemistry of Meisenheimer and Janovski complexes, see R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(6) F. J. Pollitt and B. C. Saunders, *J. Chem. Soc.*, 1132 (1964).

(7) R. Foster, C. A. Fyfe, and J. W. Morris, *Rec. Trav. Chim.*, **84**, 516 (1965).

(8) J. Murto, *Suomen Kemistilehti*, **B38**, 255 (1965).

(9) R. Foster, C. A. Fyfe, P. H. Emslie, and M. I. Foreman, *Tetrahedron*, **23**, 227 (1967).

(10) W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *J. Org. Chem.*, **32**, 2506 (1967).

thermodynamic data on the formation and decomposition of 7 in methanol.

Experimental Section

The solvents and reagents were prepared, purified, and standardized as previously described.[10] 1-(β-Hydroxyethoxy)-2,4-dinitrobenzene (1) was obtained from the Hummel Chemical Co.; after recrystallization from aqueous ethanol and drying, 1 melted at 110.5–111°.

1-(β-Hydroxyethoxy)-2,6-dinitrobenzene (8) was prepared by the addition of 10.95 ml (23 mmol) of freshly prepared 2.10 *M* potassium glycolate in ethylene glycol to a solution of 4.05 g (20 mmol) of 1-chloro-2,6-dinitrobenzene in 11 ml of ethylene glycol at 60°. The reaction mixture was heated at 100° for 2 hr and at 115–123° for 5 hr, cooled, and poured into 150 ml of ice water. After standing for 2 hr, the colorless crystals were removed by filtration and washed with cold water. After drying *in vacuo*, 8 melted at 53–54.5°.

Anal.[11] Calcd for $C_8H_8N_2O_6$: C, 42.2; H, 3.54; N, 12.3. Found: C, 42.09; H, 3.54; N, 12.40.

1-(β-Hydroxyethoxy)-2,4-dinitronaphthalene (9) was prepared by the addition of 11.9 ml (25 mmol) of 2.10 *M* potassium glycolate in ethylene glycol to a solution of 5.05 g (20 mmol) of 1-chloro-2,4-dinitronaphthalene in a mixture of 10 ml of ethylene glycol and 5 ml of dioxane at 70°. The reaction mixture was heated at 100–124° for 2.5 hr, poured into 150 ml of ice water, acidified to pH 4, and filtered to remove the product. This material was dissolved in benzene and extracted with aqueous sodium carbonate to remove the solvolysis product, 2,4-dinitro-1-naphthol. The benzene solution was reduced in volume to give light yellow crystals, which were recrystallized from aqueous ethanol: mp 94.5–95.5°.

Anal. Calcd for $C_{12}H_{10}N_2O_6$: C, 51.8; H, 3.63; N, 10.1. Found: C, 51.62; H, 3.70; N, 10.22.

The spiro complex (2) of 1-(β-hydroxyethoxy)-2,4-dinitrobenzene was prepared by the addition of 2.13 ml (12 mmol) of 5.84 *M* potassium methoxide in methanol to a solution of 2.85 g (12.5 mmol) of 1 in 3 ml of dry dioxane. The bright red solution was flushed with dry nitrogen, cooled to −78°, and then allowed to stand for several hours at 0°. The bright red crystals which were deposited were removed by filtration under dry nitrogen and were washed with benzene and with anhydrous ether. After drying *in vacuo* over phosphorus pentoxide, the product melted at 105° dec.

Anal. Calcd for $C_8H_7N_2O_6K$: C, 36.1; H, 2.65; N, 10.5; K, 14.7. Calcd for $C_8H_7N_2O_6K \cdot {}^1/_2C_4H_8O_2$: C, 38.7; H, 3.58; N, 9.03; K, 12.6. Found: C, 36.88; H, 3.55; N, 9.22; K, 12.86.

The same procedure was used to prepare complex 2 by the addition of 2.42 *M* potassium ethoxide in ethanol to a solution of 1 in dioxane and by the addition of 5.24 *M* potassium methoxide in methanol to a solution of 1 in a mixture of 3 ml of benzene and 1.3 ml of methanol. Complex 2 was also isolated by refluxing a solution of 1 in toluene with metallic sodium for 24 hr, followed by heating at 60–80° for 5 days. The dark red crystals were separated by centrifugation and washed twice with anhydrous ether.

The spiro complex (6) of 1-(β-hydroxyethoxy)-2,6-dinitrobenzene was prepared by the addition of 0.505 ml (3 mmol) of 5.95 *M* potassium methoxide in methanol to a solution of 0.7125 g (3.12 mmol) of 8 in 0.70 ml of dioxane. After evaporation of some of the solvent, purple crystals formed immediately on cooling. These crystals were removed by filtration, washed with benzene and with anhydrous ether, and kept in a vacuum desiccator over phosphorus pentoxide. The purified material melted at 220–230° dec. Complex 6 was also prepared by refluxing a solution of 8 in toluene with metallic sodium.

Anal. Calcd for $C_8H_7N_2O_6$: C, 36.1; H, 2.65; N, 10.5; K, 14.7. Calcd for $C_8H_7N_2O_6K \cdot {}^1/_2C_4H_8O_2$: C, 38.7; H, 3.58; N, 9.03; K, 12.6. Found: C, 37.19; H, 4.20; N, 7.70; K, 12.37.

The general procedure used for the preparation of 6 was also used to prepare the spiro complex (7) of 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene. Addition of 0.24 ml (1.41 mmol) of 5.95 *M* potassium methoxide in methanol to a solution of 0.40 g (1.44 mmol) of 9 in 0.55 ml of dioxane gave 7, which, after washing and drying, melted at 235° dec.

Anal. Calcd for $C_{12}H_9N_2O_6K$: C, 45.6; H, 2.87; N, 8.86; K, 12.4. Found: C, 45.20; H, 2.89; N, 12.14.

The attainment of the equilibrium for the formation of 7 from 9 in dilute methanolic sodium methoxide solutions was followed at 500 mμ in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. A pair of matched 10.0-mm cells with Teflon stoppers was used. The cell compartment was equipped with a set of Beckman dual thermospecers; the temperature was measured inside the cells and was maintained within ±0.02°. For the faster runs, an energy recording adapter (ERA) was used in conjunction with a Hewlett–Packard recorder. For these runs, rapid mixing was achieved by injecting an appropriate methanolic solution of 9 directly into the cell which contained the sodium methoxide solution. A thermostated Hamilton syringe was used, and the solution was injected through a small bore in the Teflon stopper.

All ir spectra were recorded as Nujol mulls on a Perkin-Elmer Model 221 spectrophotometer.

Pmr spectra (60 MHz) were obtained with a Varian Associates A-60 spectrometer at 25° (probe temperature maintained with a V6040 variable temperature controller). Unless otherwise noted, all spectra were determined on solutions in DMSO-d_6 using tetramethylsilane (TMS) as an internal reference; chemical shifts are given on the τ scale in parts per million relative to TMS (τ 10.00 ppm) and are accurate to ± 0.03 ppm. Chemical-shift data were taken from spectra determined at a sweep width of 500 Hz. The reported coupling constants are the average of at least three determinations at 50-Hz sweep widths and are accurate to ±0.2 Hz. Frequency swept double-resonance and 100-MHz experiments were carried out with a Varian Associates HA-100 spectrometer.

Results

The absorbances of 3.34×10^{-5} *M* 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene (9) in methanol and in methanolic sodium methoxide at 360 and 500 mμ are given in Table I. The 500-mμ band, which is absent in the spectrum of 9 in neutral methanol, increases in intensity with increasing methoxide ion concentration; maximum intensity is reached at a sodium methoxide concentration of 5.30×10^{-2} *M* and the intensity re-

TABLE I

INTERACTION OF 1-(β-HYDROXYETHOXY)-2,4-DINITRONAPHTHALENE (3.34×10^{-5} *M*) WITH METHANOLIC SODIUM METHOXIDE

Temp, °C	$[NaOCH_3]$, *M*	Optical density at 360 mμ[a]	Optical density at 500 mμ[a]	$k_{obsd} \times 10^3$, sec^{-1}	k_1, $l.\ mol^{-1}\ sec^{-1}$	$k_2 \times 10^3$, sec^{-1}	*K*, $l.\ mol^{-1}$
6.65	0.00238			1.23			
	0.00594			2.35			
	0.0119			4.56	0.358	0.390	918
	0.0178			6.90			
	0.0238			8.97			
15.00	0.00238			2.58			
	0.00594			4.75			
	0.0119			8.51	0.630	1.02	630
	0.0178			11.8			
	0.0238			16.4			
25.00	0.000	0.111	0.005				
	0.00238	0.182	0.201	6.48			
	0.00594	0.335	0.394	11.3			
	0.0119	0.374	0.660	18.7	1.28	3.60	356
	0.0178	0.398	0.712	26.7			
	0.0238	0.413	0.775	34.0			
	0.0534	0.425	0.900				
	2.11	0.450	0.900				

[a] Using a 1.00-cm cell.

(11) All analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

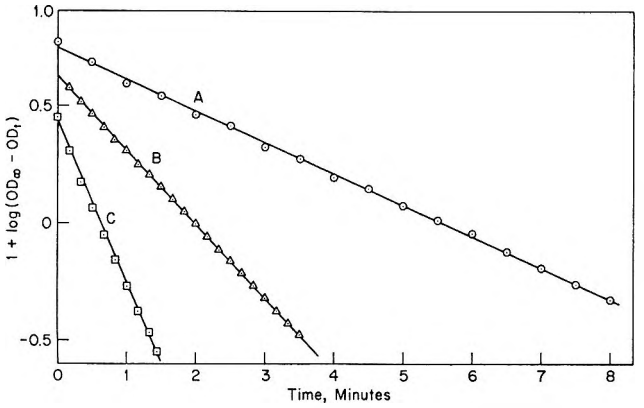


Figure 1.—Plot of $1 + \log (OD_\infty - OD_t)$ *vs.* time for the attainment of equilibrium in the cyclization of 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene (9): [9] = 3.34×10^{-4} *M*; (A) [$NaOCH_3$] = 5.94×10^{-3} *M*, 15.00°; (B) [$NaOHC_3$] = 5.94×10^{-3} *M*, 25.00°; (C) [$NaOCH_3$] = 17.8×10^{-3} *M*, 25.00°.

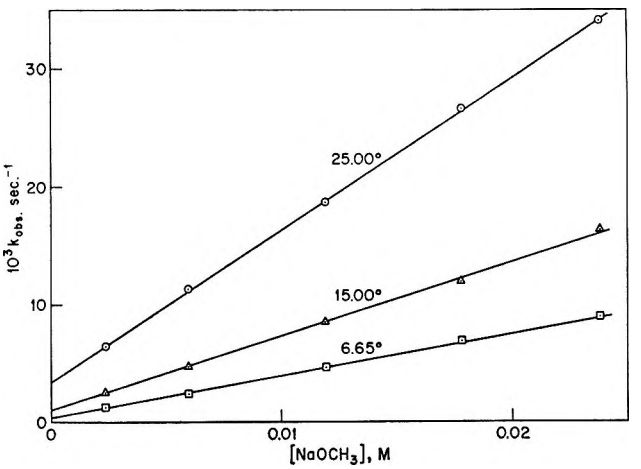


Figure 2.—Plot of $10^3 k_{obsd}$ for the attainment of equilibrium in the cyclization of 1-(β-hydroxyethoxy)-2,4-dinitronaphthalene (9) *vs.* $NaOCH_3$ concentration at 25.00, 15.00, and 6.65°.

mains constant up to 2.11 *M*. The constancy of the absorbance over a 40-fold increase in methoxide ion concentration indicates that the equilibrium

$$9 + OCH_3^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 7$$

is complete at a 5.30×10^{-2} *M* methoxide ion concentration. A linear Benesi–Hildebrand[12] plot was obtained at 25.00°, from which the extinction coefficient, ε, and the equilibrium constant, *K*, were calculated to be, respectively, 34,500 and 420. The equilibrium constant obtained by this method is in reasonable agreement with that calculated from the rate constants k_1 and k_2 (see Table I). However, owing to the inherent inaccuracies in the Benesi–Hildebrand calculation, the equilibrium constants given in Table I are considered to be appreciably more accurate.

At the lower methoxide ion concentrations, it was possible to follow the rate of attainment of equilibrium by measuring the increase in absorbance at 500 mμ. A first-order relationship was observed since the concentration of **9** was a 100-fold smaller than that of the methoxide ion. Such first-order plots for typical runs are given in Figure 1. Under the experimental conditions, the observed first-order equilibrium attainment, k_{obsd}, is expressed by

$$k_{obsd} = k_1[NaOCH_3] + k_2$$

Using the above equation, plots of k_{obsd} *vs.* sodium methoxide concentration at 6.65, 15.00, and 25.00° gave good straight lines (Figure 2) whose slopes are k_1 and intercepts are k_2. The experimental values of k_{obsd} at the three temperatures are given together with values for k_1, k_2, and *K* in Table I. Using the values for k_1 and k_2 at the three different temperatures, linear Arrhenius plots were obtained from which the energies and entropies of activation have been calculated (Table II). Allowing an over-all 5% error in the individual rate constants, at the temperature interval used (18.35°), the statistical error in the activation energy is ±0.8 kcal/mol and in the activation entropy is ±2.0 eu.[13]

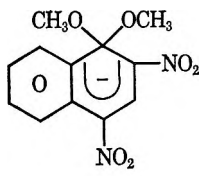
(12) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).

(13) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

Discussion

The order of stability and the ease of formation of spiro Meisenheimer complexes are 2,4-dinitrophenyl ≪ 2,4-dinitronaphthyl < 2,4,6-trinitrophenyl. This trend parallels, of course, the electron deficiency of the C-1 carbon atom and the stability of the corresponding noncyclic Meisenheimer complexes.[14] The absorption maximum at the higher wavelength is attributed to the formation of **7** since the isolated solid in DMSO and DMF has an absorption maximum at the same wavelength. The absorption maxima at the lower wavelength for **2**, **7**, and **4** are 290, 360 and 414 mμ. Similar bathochromatic shifts were observed for the 2,4-dinitrophenyl and 2,4-dinitronaphthyl Meisenheimer complexes[1] and for the 2,4-dinitro-6-X complexes as the electron-withdrawing power of X increased.[6]

The equilibrium constant for the formation of the 1,1-dimethoxy-2,4-dinitronaphthalene Meisenheimer complex (**10**) was such that it conveniently allowed the kinetic observation of its equilibrium attainment.[1]



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By analogy, it was expected that **7** would serve as a suitable model compound for a comparison of the rates of formation and decomposition of cyclic and noncyclic Meisenheimer complexes (Table II). The rate constant for the formation of **7** at 25.00° is some 40% higher than the corresponding value for **10**, but, more significantly, the greater stability of **7** over **10** is manifested by the values for its equilibrium constant, *K*, and its energies of activation, E_1 and E_2. The equilibrium constant for the formation of **7** at 25.00° is 356 l./mol, a value 50% higher than that for the formation of **10**.[1] The formation of **7** requires 2 kcal mol^{-1} less; its decomposition requires 4 kcal mol^{-1} more energy of activation than the formation and decomposition of **10**. All of these results suggest that the rigidly held

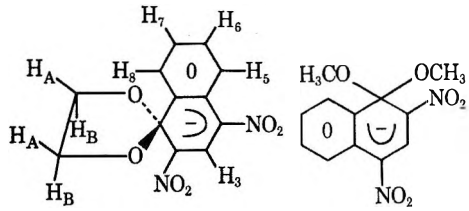
(14) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **90**, 4982 (1968).

cyclic structures **2**, **4**, **6**, and **7** are, not unexpectedly, considerably more stable than their noncyclic analogs.

The formation of noncyclic Meisenheimer complexes is accompanied by an increase in the order of these systems, as reflected in their negative entropies of activation. It is to be expected that the rigidity and orderliness of the complexes would be enhanced in the cyclic structures. These effects should be manifested by a decrease in $\Delta S_1^{\pm}$ and by an increase in $\Delta S_2^{\pm}$ for **7** in comparison to **10**. The experimental results amply bear out this expectation (Table II). From our previous work, it has been concluded that the stabilities of **10**[1] and the 1,1-dimethoxy-2,4,6-trinitrobenzene complex (**5**)[15] are dependent to a larger extent on the respective enthalpies than on the entropies of activation. These observations are in good agreement with the results of Miller's calculations.[16] It appears that for the formation of **7** the driving force is much more entropy dependent than that for **10**. Furthermore, the values of $\Delta S_2^{\pm}$ for **7** (-5 ± 2 eu) and **10**[1] (-18 ± 2 eu) indicate a greater solvent dependence for the decomposition of the cyclic complex **7** than for **10**. The importance of solvent participation has been emphasized previously for the decomposition of **4**.[8]

TABLE II

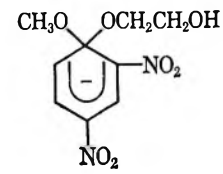
KINETIC AND THERMODYNAMIC PARAMETERS FOR THE FORMATION AND DECOMPOSITION OF MEISENHEIMER COMPLEXES **7** AND **10** IN METHANOL AT 25.00°



	7	**10**[a]
k_1, l. mol^{-1} sec^{-1}	1.28	0.92
$k_2 \times 10^3$, sec^{-1}	3.60	4.0
K, l. mol^{-1}	356	230
E_1, kcal mol^{-1}	11.8 ± 0.8	$13.8 \pm 0\ 8$
$\Delta S_1^{\pm}$, eu	-20 ± 2[b,c]	-17 ± 2[b,c]
E_2, kcal mol^{-1}	20.0 ± 0.8	$16.5 \pm 0\ 8$
$\Delta S_2^{\pm}$, eu	-5 ± 2[b,d]	-18 ± 2[b,d]

[a] Reference 2. [b] Calculated at 25.00°. [c] Calculated by using the second-order rate constants, k_1. [d] Calculated by using the first-order rate constants, k_2.

The mechanism of formation of complexes **2**, **6**, and **7** can best be described in terms of an initial rapid proton removal from the glycol ethers (**1**, **8**, and **9**) by the attack of methoxide ion, followed by the rate-determining internal cyclization of the resultant glycolate ions. The formation of **2** from **1** (and also **6** from **8**) by the action of metallic sodium in toluene, as well as by the action of potassium ethoxide in dioxane, is not only consistent with this mechanism, but eliminates the possibility of mixed noncyclic Meisenheimer complex formation, *e.g.*, the formation of **11** by the attack of methoxide ion on **1**. The possibility of the formation



11

of such mixed noncyclic complexes has not been eliminated by previous studies.

The postulated structures of complexes **2**, **6**, and **7** are fully supported by their pmr spectra; in each case, the expected peak multiplicities and relative intensities were observed. The pmr parameters of the cyclohexadienylide protons (H-3, H-5, and H-6) observed for a solution of the crystalline complex **2** in DMSO-d_6 were quite similar to those previously observed for noncyclic Meisenheimer complexes of 2,4-dinitrophenyl ethers.[9,10] The expected AMX pattern was observed with τ_3 1.45, τ_5 3.17, and τ_6 5.70 ppm[17] and $J_{3,5} = 2.7$ and $J_{5,6} = 10.7$ Hz. These parameters are in excellent agreement with those reported previously by Foster, *et. al*,[9] for the *in situ* reaction product of **1** and methoxide ion. However, contrary to this earlier report,[9] methylene proton equivalence was not observed in the spectrum of **2**. The methylene resonances were observed as a complex multiplet centered at τ 5.92 ppm (total width 30 Hz), clearly indicative of geminal proton nonequivalence. It would be anticipated that the methylene protons (H_A) *cis* to the nitro group in **2** would be at low field compared with those protons (H_B) *trans* to the nitro group. Eighteen of the 24 transitions expected for an A_2B_2 spectrum were obvious in this multiplet; analysis by the procedure of Abraham[18] gave $J_{cis} = 7.2$, $J_{trans} = 6.1$, and $J_{gem} = 7.6$ Hz and τ_A 5.87 and τ_B 5.97 ppm. Computer generated and experimental spectra were in good agreement; the assignments were verified by recording the spectrum at 100 MHz. The methylene groups of **2** are part of a 1,3-dioxolane ring, and the methylene parameters observed for **2** are quite similar to those observed for the model system, 2-methyl-1,3-dioxolane[18] ($J_{cis} = 7.1$, $J_{trans} = 6.0$, and $J_{gem} = 7.5$ Hz). These observations fully substantiate the postulated structure of **2**.

The spectra of samples of **2** prepared by different methods (reaction of **1** with potassium methoxide or ethoxide in dioxane, potassium methoxide in benzene, and metallic sodium in toluene) were all identical with the exception of resonances due to solvent (dioxane and benzene) of crystallization.

The postulated structure of the spiro complex **7** formed by the attack of methoxide ion on **9** was similarly supported by its pmr spectrum in DMSO-d_6. For **7**, H-3 appeared as a singlet at τ 0.94, H-8 as a multiplet centered at τ 1.19, and H-5–H-7 as a broad multiplet centered at τ 2.60 ppm. As anticipated, the nonequivalent methylene protons gave rise to a multiplet (centered at 5.65 ppm), but the resolution of this multiplet was not sufficient to allow an A_2B_2 analysis. Apparently, the difference between the chemical shifts

(15) The stability of **5** was estimated by the rates of symmetrical methoxyl exchange: J. H. Fendler, *J. Amer. Chem. Soc.*, **88**, 1237 (1966).

(16) D. L. Hill, K. C. Ho, and J. Miller, *J. Chem. Soc. B*, 299 (1966); J. Miller, *J. Amer. Chem. Soc.*, **85**, 1625 (1963); J. Miller, private communication to J. H. Fendler, 1967.

(17) As has been observed in previous studies,[5,9,10] the chemical shifts of the cyclohexadienylide protons of Meisenheimer complexes are upfield from those of the corresponding aromatic protons of the starting aromatic substrates. This effect is also observed in a comparison of the spectra of **2** and the glycol ether **1** (τ_2 1.39, τ_5 1.62, τ_6 2.49, and τ_{CH_2} 6.23, 5.67 ppm; $J_{56} = 3.1$ and $J_{56} = 9.9$ Hz; spectrum recorded in DMSO-d_6).

(18) R. J. Abraham, *J. Chem. Soc.*, 256 (1965).

of H_A and H_B is significantly less than in the case of **2** as a result of the more nearly comparable anisotropic effects of the 2-nitro and 5,6-benzo groups in **7**.[19,20] For the starting ether **9**, the following parameters were observed: τ_3 1.19, $\tau_{6,7}$ 2.00, $\tau_{5,8}$ 1.35, τ_{CH_2} 6.12, and τ_{OH} 5.20 ppm. The absolute magnitudes of the parameters observed for **7** and **9** and the chemical-shift differences for H-3 and H-5–H-8 between **7** and **9** are quite similar to those previously observed for 1,1-dialkoxy complexes of the 2,4-dinitronaphthalenes and the parent ethers.[1] The assignments for **7** and **9** were made on the basis of the spectra of these noncyclic reference complexes.[1]

The pmr spectrum of complex **6** in DMSO-d_6 was also in full accord with the postulated structure. The expected A_2B pattern was observed for the cyclohexadienylide protons with τ_3 and τ_5 2.73 and τ_4 5.22 ppm and $J_{3,4}$ and $J_{4,5}$ = 8.2 Hz. These parameters are quite similar to those reported by Foster and Fyfe[5] for an *in situ* generated sample of **6**. The dioxolane methylene protons of **6** were equivalent as required by the symmetry of the complex; these protons gave rise to a sharp singlet at τ 6.12 ppm. The parent ether **8** showed an A_2M aromatic spectrum (τ_3 and τ_5 1.72 and τ_4 2.48 ppm; $J_{3,4}$ and $J_{4,5}$ = 8.9 Hz); as in the cases of **1** and **9**, the methylene groups of **8** possessed different chemical shifts (A_2M_2 pattern; τ 6.35, 5.89 ppm). The upfield shifts ($\Delta\delta$) observed for the cyclohexadienylide protons of **6** relative to the corresponding aromatic protons of **8** ($\Delta\delta_4$ 2.74, $\Delta\delta_{3,5}$ 1.01 ppm) are similar in magnitude to those observed in previous studies,[10] indicating a comparable electron density distribution in the cyclohexadienylide system.

The salient ir absorption characteristics of complexes **2**, **6**, and **7** were quite similar to those observed for previously studied Meisenheimer complexes.[1,10] In particular, the covalent nature of the bonding at C-1 of the complexes was supported by the observation of very strong and broad ketal bands centered at 1110 cm^{-1} for the benzenoid complexes **2** and **6** and at 1140 cm^{-1} for the naphthalenoid complex **7**. Previously studied complexes have been characterized by similar ketal bands at 1178–1176 cm^{-1} (2,4-dinitrophenyl systems[10]) and at 1126–1058 cm^{-1} (2,4-dinitronaphthyl systems[1]). The remaining features of the spectra are quite similar to those reported for the analogous 1,1-dialkoxy complexes.[1,10,21] Both assymmetric and symmetric nitro group stretching frequencies (1549–1542 and 1340–1330 $cm.^{-1}$)[22] and asymmetric and symmetric C–O–C stretching frequencies (1274–1230 and 1071–1050 cm^{-1})[23] are observable in the spectra of the complexes.

No evidence was obtained in the studies of the spectra of complexes **2**, **6**, and **7**, regardless of the reagents employed in their preparation, for the formation of mixed noncyclic complexes, *e.g.*, **11**. The *in situ* formation of complex **2** by the gradual addition of an equivalent of potassium methoxide to a solution of **1** in DMSO-d_6 was followed by pmr spectroscopy; the appearance of resonances attributable to the mixed complex **11** were not observed during the formation of **2**. Throughout the reaction, the observed spectrum of the reaction mixture was a superposition of the spectra of **1** and **2**. On the addition of methoxide ion or other base to a nitroaryl glycol ether (*e.g.*, methoxide ion plus **1**), three basic equilibrium processes are possible: (1) proton removal from **1** to yield the glycolate ion ($\mathbf{1}^-$) and methanol, (2) internal cyclization of $\mathbf{1}^-$ to yield the spiro complex **2**, and (3) direct attack by methoxide ion at C-1 of **1** to yield the noncyclic mixed complex **11**.

$$\mathbf{1} + CH_3O^- \rightleftharpoons \mathbf{1}^- + CH_3OH \quad (1)$$

$$\mathbf{1}^- \rightleftharpoons \mathbf{2} \quad (2)$$

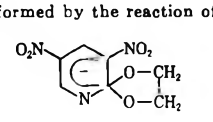
$$\mathbf{1} + CH_3O^- \rightleftharpoons \mathbf{11} \quad (3)$$

It is apparent from the preceding studies that reaction 2 is highly favored over reaction 3 on both thermodynamic and kinetic grounds; the enhanced stability of the spiro complexes results in their essentially exclusive formation at the expense of the noncyclic mixed complexes. The enhanced stability of the spiro complexes is also shown by their failure to undergo rearrangement or deuterium exchange with solvent; solutions of the complexes in DMSO-d_6 do not show detectable pmr changes over a period of months. It has been shown previously that 1,1-dialkoxy complexes of 2,4-dinitrobenzenes undergo both rearrangement to 1,2 complexes and exchange of cyclohexadienylide protons for solvent deuterium.[1,10,24] Also, in the presence of excess methoxide ion, 1,1-dialkoxy complexes of 2,4-dinitronaphthalene systems undergo rapid and complete exchange of ring protons with solvent (DMSO-d_6) deuterium;[1] no comparable reaction is observed with the more stable spiro complex **7**.

Registry No.—**2**, 12296-65-0; **6**, 12296-66-1; **7**, 12296-67-2; **8**, 17512-03-7; **9**, 17512-18-4.

Acknowledgment.—We are indebted to Drs. S. Castellano and M. P. Williamson for helpful discussions and to Dr. B. D. Martin for assistance in the determination of the pmr spectra. This work was supported, in part, by the U. S. Atomic Energy Commission and instrumentation provided by a grant (FR 00292) from the National Institutes of Health was used.

(19) A similar, but more exaggerated, effect has been observed in the spectrum of the complex (i) formed by the reaction of sodium methoxide with



i

2-(β-hydroxyethoxy)-3,5-dinitropyridine.[20] Although the lack of symmetry of i would require geminal proton nonequivalence for the dioxolane protons, a singlet was observed for these protons.

(20) C. A. Fyfe, *Tetrahedron Lett.*, 659 (1968).

(21) Copies of the ir spectra of complexes **2**, **6**, and **7** and the starting ethers **1**, **8**, and **9** are available on request.

(22) R. D. Kross and V. A. Fassel, *J. Amer. Chem. Soc.*, **78**, 4225 (1956)

(23) A. Katritzky and H. A. Coats, *J. Chem. Soc.*, 2062 (1959).

Kinetics of Iodine Exchange between Zinc Iodide and *n*-Propyl and *n*-Butyl Iodide in Acetonitrile

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The exchange of iodine between zinc iodide and *n*-propyl iodide and between zinc iodide and *n*-butyl iodide has been studied in the temperature range 40–59° and in the zinc iodide concentration range 5×10^{-4}–10^{-2} *M*. This exchange has been found to be first order with respect to *n*-propyl iodide or *n*-butyl iodide and zero order with respect to zinc iodide. The values of the Arrhenius parameters, E_a and log *A*, for *n*-propyl iodide are 22.6 ± 0.2 kcal/mol and 11.9 ± 0.3 (*A* in sec^{-1}), respectively, and for *n*-butyl iodide these values are 19.4 ± 0.8 and 9.6 ± 0.2.

The following research provides a test of the commonly accepted generalization that SN2 kinetics are to be expected for nucleophilic exchange reactions of primary alkyl halides whereas SN1 kinetics are more probable for tertiary or secondary alkyl halide exchange. Acetonitrile was chosen for the solvent, and in it was dissolved the poor nucleophile zinc iodide along with a normal alkyl halide. The zinc iodide was labeled with iodine-131 in order that the exchange rate could be followed.

Determination of the exchange rate of iodine atoms between *n*-butyl iodide and zinc iodide in acetonitrile was previously made by Hodgson, Evans, and Winkler[2] by labeling these compounds with radioactive iodine. These investigators found the exchange to be first order with respect to each reactant. The zinc iodide order determination was made at 100° and was based on rate measurements made on two solutions with the same *n*-butyl iodide concentration but different concentrations of zinc iodide.

Experimental Section

Labeling of zinc iodide was done with carrier-free sodium iodide obtained from Oak Ridge National Laboratories. A 30-mCi sample of NaI^{131} in 2.0 ml of solution containing 0.2% cysteine hydrochloride was diluted to 20 ml with 0.001% sodium thiosulfate solution and 10 μCi was taken from this and rinsed with deionized water into a 25-ml volumetric flask, and the resulting solution was evaporated to dryness. The residue was dissolved in 25 ml of acetonitrile and 1.0–2.0-ml portions were withdrawn from this solution and used to label the zinc iodide.

The zinc iodide used was national formulary quality. It was dried for 1 hr in an electric oven at a temperature of 127°. The dried salt was stored in a desiccator until used.

The *n*-propyl iodide was Eastman Organic Chemical, white-label grade. If this material showed any yellow discoloration, it was shaken with mercury until the yellow color disappeared, and the clear, colorless liquid was used. A portion of this liquid was run through a gas chromatograph, and the results showed the presence of approximately 2% impurity with a boiling point, estimated from the chromatogram, to be 117–125°. The *n*-butyl iodide and isopropyl iodide were also Eastman Organic Chemical, White Label grade but were not chromatographed.

The acetonitrile was industrial grade and was supplied by Matheson Coleman and Bell Co. It was dried by shaking with anhydrous potassium carbonate, then filtered, and distilled. The fraction boiling at 81.4–81.6° (760 mm) was collected and used as solvent.

Stock solutions to be used to prepare exchange solutions were made by weighing the solute in a weighing bottle to the nearest tenth of a milligram. The solute was rinsed into a volumetric flask and diluted to the appropriate volume with acetonitrile. Exchange solutions were prepared by pipeting the required amount from the stock solutions and adding acetonitrile.

The zinc iodide stock solution so prepared was found to be turbid probably owing to the presence of small amounts of zinc oxide which failed to dissolve in acetonitrile. The solution was therefore filtered and standardized by titration with freshly prepared standard silver nitrate solution using eosin indicator. The silver nitrate in turn had been standardized by titration with a solution made from dried, weighed, reagent grade potassium chloride using potassium dichromate indicator.

Stock solutions to be used at 59.1° were swirled and swept for 5 min with nitrogen gas which was dried by passing it through concentrated sulfuric acid. After all reactants were mixed, the solution was swept for 3 min with nitrogen if it was to be used at 59.1°.

Exchange reactions were carried out in 25- or 50-ml volumetric flasks fitted with ground-glass stoppers which were lubricated with Fisher Cello-Seal. The flasks were placed in racks in a thermostat equipped with a stirrer, heating element, and a thermoregulator. The temperature of the water which filled the thermostat was constant within ±0.05°.

Samples were counted in a Picker Model 2804 Well-Type scintillation detector in conjunction with a Picker Model Number 5832 Spectroscaler II. The 364-keV γ radiation from I^{131} was counted.

Samples which were to undergo exchange were prepared by adding the required amounts of zinc iodide solution, tracer, and acetonitrile to a 25- or 50-ml volumetric flask. These reactants were allowed to equilibrate overnight. At the time the exchange reaction was begun, organic iodide solution was added to the volumetric flask. Time of mixing was taken as the time at which half the organic iodide had been added. The mixture was shaken 100 times if the exchange rate was to be measured below 50° or swirled with nitrogen if the exchange rate was to be measured above 50°. Comparison of the exchange rates of solutions run at 47.5° swept with nitrogen with those not swept with nitrogen showed that sweeping with nitrogen did not change the exchange rate at this temperature.

After the reactants were mixed, the volumetric flasks containing the individual samples were placed in the thermostat and 1.0-ml portions were withdrawn from each flask at appropriate time intervals. The milliliter portion was run into 1.0 ml of benzene which had been chilled in ice, and the resulting mixture was shaken vigorously 75 times and then centrifuged for 5 min. Most of the organic iodide dissolved in the benzene layer, and most of the zinc iodide dissolved in the water layer. Completeness of separation was measured by dissolving labeled zinc iodide in acetonitrile and shaking this solution with milliliter portions of benzene and water. In the water layer was found 95.3% of the activity. Comparison of the observed distributions of activities in solutions which had come close to equilibrium with those calculated from concentrations indicate that less than 1% of the *n*-alkyl iodide activity appears in the water layer.

(1) This report is based on a portion of a thesis submitted by B. F. Howell in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Missouri, Aug 1964. It has been presented at the 16th Annual Midwest Chemistry Conference, Kansas City, Mo., Nov 1964.

(2) G. W. Hodgson, H. G. V. Evans, and C. A. Winkler, *Can. J. Chem.*, **29**, 60 (1951).

After centrifuging, the two layers were separated by withdrawing the water layer from under the benzene layer with a pipet and allowing the water layer to flow into another test tube of the same size. Water was added to the test tube containing the water layer until the volumes of the two solutions were equal. The samples were then counted. The minimum number of counts was 4000, and the minimum time of counting was 3 min.

The number of counts and the counting time were recorded for each water and benzene sample. Solutions from the same sample in the thermostat were always counted consecutively so that the error due to I^{131} decay was inappreciable.

Correction factors for the expansion of solvent with temperature were made for all concentrations reported.

Calculation of Results.—Counting rates for the water layer containing zinc iodide and the benzene layer containing propyl iodide were used to calculate the exchange rate, R, using eq 1[3]

$$R = \frac{ab(0.693)}{(a + b)t_{1/2}} \quad (1)$$

in which a is the molar concentration of organic iodide in the sample, b is the concentration of zinc iodide in gram equivalent per liter, and $t_{1/2}$ is the time of half-exchange which is evaluated by plotting the logarithm of $(1 - f)$ as a function of time where f is the fraction of exchange which has occurred at a particular time.

Values of log R at constant values of b were plotted against log a to determine the reaction order with respect to n-propyl iodide and the value of the rate constant, k. The order with respect to zinc iodide was determined by plotting log R at constant values of a against log b.

Results

Representative results for order determinations using n-propyl iodide and zinc iodide appear in Table I,

TABLE I

ORDER DETERMINATIONS FOR IODIDE EXCHANGE BETWEEN n-PROPYL IODIDE AND LABELED ZINC IODIDE IN ACETONITRILE AT 40.0°

n-PrI (mol l.$^{-1}$)	ZnI_2 (equiv l.$^{-1}$)	$t_{1/2}$ (hr)	$R \times 10^4$ (mol l.$^{-1}$ hr^{-1})	$k \times 10^4$ [a] (hr^{-1})
0.981	0.00205	6.71	2.12	1.94
0.686	0.00513	28.9	1.22	1.66
0.490	0.00513	44.9	0.784	1.60
0.294	0.00513	70.4	0.496	1.68
0.981	0.0200	91.0	1.48	1.51
0.981	0.0159	86.3	1.26	1.28
0.981	0.0120	65.4	1.26	1.28
0.981	0.00991	65.9	1.03	1.05
0.981	0.00794	43.4	1.28	1.31
0.981	0.00598	28.1	1.46	1.49
0.981	0.00397	15.4	1.78	1.82

[a] Order for ZnI_2, 0.0; order for n-PrI, 1.09.

and a summary of the exchange results at various temperatures appears in Table II. Tables III and IV contain similar representative data obtained using n-butyl iodide.

From these data it appears that the reaction is first order with respect to n-propyl iodide and that the order with respect to zinc iodide is zero or slightly negative. The rate constant, k, shown in Table I is calculated for an over-all first-order reaction. The activation energy for the n-propyl iodide–zinc iodide exchange, calculated by the method of least squares, has the value 22.6 kcal/mol with a standard deviation of 0.2, and the

(3) A. C. Wahl and N. A. Bonner, "Radioactivity Applied to Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1951.

TABLE II

SUMMARY OF EXCHANGE DATA FOR n-PROPYL IODIDE AND ZINC IODIDE

Temp (°C)	n-PrI (mol l.$^{-1}$)	ZnI_2 (equiv l.$^{-1}$)	No. of trials	$k \times 10^4$ (hr^{-1})	σ_k
40.0	0.981–0.0490	0.0200–0.00115	14	1.5	0.2
47.5	0.968–0.387	0.0200–0.00489	14	3.0	0.1
50.0	0.725–0.0967	0.0928–0.00769	14	5.2	0.1
59.1	0.954–0.191	0.0385–0.00100	7	13.0	0.6

TABLE III

ORDER DETERMINATIONS FOR IODIDE EXCHANGE BETWEEN n-BUTYL IODIDE AND LABELED ZINC IODIDE IN ACETONITRILE AT 40.0°

n-BuI (mol l.$^{-1}$)	ZnI_2 (equiv l.$^{-1}$)	$t_{1/2}$ (hr)	$R \times 10^4$ (mol l.$^{-1}$)	$k \times 10^4$ [a] (hr^{-1})
0.964	0.00811	63.6	0.876	0.909
0.771	0.00811	58.7	0.977	1.27
0.578	0.00811	77.5	0.715	1.24
0.385	0.00811	153	0.359	0.931
0.964	0.00609	50.2	0.836	0.867
0.964	0.00406	28.3	0.989	1.03
0.964	0.00304	19.4	1.08	1.12

[a] Order for ZnI_2, 0.0; order for n-BuI, 0.9. Average $k = (1.1 \pm 0.2) \times 10^{-4}$.

TABLE IV

SUMMARY OF EXCHANGE DATA FOR n-BUTYL IODIDE AND ZINC IODIDE

Temp (°C)	n-BuI (mol l.$^{-1}$)	ZnI_2 (equiv l.$^{-1}$)	No. of trials	$k \times 10^4$ (hr^{-1})	σ_k
40.0	0.964–0.385	0.00811–0.00304	7	1.1	0.2
47.5	0.467–0.0953	0.0930–0.0281	8	2.9	0.2
60.0	0.902–0.181	0.00497–0.00199	12	7.3	1.2

value of log A, the frequency factor in the logarithmic form of the Arrhenius equation is 11.9 (A is measured in sec^{-1}) with a standard deviation of 0.3.

It may be seen from Tables III and IV that results for n-butyl iodide and n-propyl iodide are similar; the order for n-butyl iodide is also one, and that for zinc iodide is once again zero within the limits of experimental error. Rate constants are smaller for n-butyl iodide as would be predicted from a consideration of ponderal effects. The activation energy is 19.4 ± 0.8 kcal/mol and log A is 9.6 ± 0.2 where A is expressed in reciprocal seconds.

Exchange experiments with zinc iodide were also performed with isopropyl iodide. It was not possible to obtain precise results with this substance since log $(1 - f)$ against time plots were found to be curved, possibly because of gradual dehydrohalogenation of the isopropyl iodide. This process is indicated by the appearance of a yellow color in the solutions with the passage of time. The yellow color was found spectrophotometrically to be due to the presence of iodine which could form readily from hydrogen iodide under the existing reaction conditions. The experimental results did, however, show that exchange is much slower with isopropyl iodide than with comparable solutions of n-propyl iodide at the same temperature. Time of half-exchange in n-propyl iodide is 51.2 hr, whereas in isopropyl iodide it is 226 hr. This sort of result was observed in approximately 50 trials made with isopropyl iodide. Secondly, exchange with isopropyl iodide appears also to be zero order with respect to zinc iodide. This fact is indicated by comparing the

result obtained in six trials involving exchange between zinc iodide having concentrations ranging from 1.11 to 8.89×10^{-4} N and 1 M isopropyl iodide with those employing $0.7–3.5 \times 10^{-2}$ N zinc iodide and 1 M isopropyl iodide. The time of half-exchange using the more dilute zinc iodide is much less than that using the more concentrated zinc iodide, characteristic behavior for a zero-order reactant.

Attempts were made to evaluate the effects of various impurities on the reaction order for zinc iodide. When 80 λ's of water was added to various concentrations of zinc iodide solutions, while the propyl iodide concentration was held constant, it was observed that water accelerated the reaction at small concentrations of zinc iodide but that the effect was not significant above concentrations of 10^{-2} N. Results of this study appear in Table V. Additional experiments showed that

TABLE V
THE EFFECT OF ADDED WATER ON THE EXCHANGE RATE

Run no.	Temp (°C)	n-PrI (mol l.$^{-1}$)	ZnI_2 (equiv l.$^{-1}$)	H_2O (mol l.$^{-1}$)	$R \times 10^4$ (mol l.$^{-1}$ hr^{-1})
49-3	59.1	0.954	0.0118	0.424	19.6
49-4	59.1	0.954	0.00884	0.424	19.8
49-5	59.1	0.954	0.00600	0.424	22.0
49-6	59.1	0.954	0.00295	0.424	28.5
49-7	59.1	0.954	0.00997	0.424	76.4

addition of much larger amounts of water does not result in a further rate increase.

The exchange rate of n-propyl iodide with a solution containing only the carrier-free sodium iodide was measured. The amount of tracer customarily used to label the zinc iodide solution produced a solution which was approximately 3×10^{-16} M sodium iodide. When exchange was allowed to occur between the tracer and 2 M n-propyl iodide it was 95% complete in 20 min which indicates that the iodide ion as such was not present during zinc iodide exchange because zinc iodide exchange takes place much more slowly.

Free iodine was added to acetonitrile solutions of labeled zinc iodide and unlabeled n-propyl iodide, and the exchange rate was measured in an attempt to evaluate the effect of iodine. The rate of this exchange was measured by separating the iodine and the zinc iodide from n-propyl iodide with an 0.1 M water solution of sodium thiosulfate. The rate of this exchange was nearly the same as the rate of exchange of n-propyl iodide and iodine alone and only about one-fourth as fast as the exchange between zinc iodide and propyl iodide alone. Results appear in Table VI.

TABLE VI
EXCHANGE RATES IN THE PRESENCE OF IODINE

Temp (°C)	n-PrI (mol l.$^{-1}$)	ZnI_2 (equiv l.$^{-1}$)	I_2 (mol l.$^{-1}$)	$t_{1/2}$ (hr)	$R \times 10^4$ (mol l.$^{-1}$ hr^{-1})
59.1	0.954	0.00590	0.00110	18.4	3.01
59.1	0.954	0	0.00110	4.29	3.58
59.1	0.954	0.00199	0	0.995	13.8

Exchange rates were also measured for zinc iodide and n-propyl iodide in the presence of added iodide ion. Enough iodide ion was added, in the form of potassium iodide, on a mole to mole basis to react with the zinc iodide to produce what was presumed to be ZnI_3^-, a complex which is known to exist in water solution[4] and in N,N-dimethylformamide.[5] The reaction order was determined by using equimolar amounts of ZnI_2 and I^- in varying concentrations while holding the n-propyl iodide concentration constant. The rate was found to be slower than that of iodide ion alone, but faster than that of zinc iodide. The order with respect to ZnI_3^- was found to be approximately one-third, and exchange in this system is probably by means of iodide ion. Data appear in Table VII. These results suggest that ZnI_3^- is not involved in the rate-determining step of the zinc iodide–n-propyl iodide exchange even when equimolar quantities of zinc iodide and potassium iodide are used.

TABLE VII
THE EFFECT OF ADDED IODIDE ON THE EXCHANGE RATE

Temp (°C)	n-PrI (mol l.$^{-1}$)	ZnI_2 (equiv l.$^{-1}$)	Added I^- (mol l.$^{-1}$)	$t_{1/2}$ (hr)	$R \times 10^4$ (mol l.$^{-1}$ hr^{-1})
42.5	0.763	0.0119	0.00537	0.818	1.43
42.5	0.763	0.00848	0.00384	0.630	1.34
42.5	0.763	0.00678	0.00307	0.546	1.24
42.5	0.763	0.00509	0.00230	0.437	1.13
42.5	0.763	0.00339	0.00153	0.323	1.05
42.5	0.763	0.00170	0.000767	0.202	0.843

Discussion

Comparison of preliminary exchange results between sodium iodide and n-propyl iodide with results obtained by Thuillier and Daudel[6] gave reasonably good agreement. Both sets of results showed the exchange to be first order in each reactant.

As mentioned previously Hodgson, *et al.*, have measured exchange rates between zinc iodide and n-butyl iodide in acetonitrile and have found first-order dependence on both reactants at 100°.[2] The rate constant reported by these investigators at 47.5° is 6.0×10^{-3} l. mol^{-1} hr^{-1} which, if calculated assuming zero-order dependence upon zinc iodide, becomes 2.88×10^{-4} hr^{-1} and is seen to agree well with the value 2.9×10^{-4} hr^{-1} obtained by the authors. On the basis of their observation that the apparent degree of ionization of zinc iodide does not change with changing zinc iodide concentrations, the Canadians conclude that simple iodide ion is not the main reacting species. The authors agree with this conclusion since exchange by simple iodide ion produces one-third-order dependence upon zinc iodide concentration for complete ionization

$$ZnI_2 \longrightarrow Zn^{2+} + 2I^- \quad (2)$$

and one-half-order dependence for incomplete ionization of zinc iodide.[7] The Canadian chemists conclude

$$ZnI_2 \longrightarrow ZnI^+ + I^- \quad (3)$$

that either undissociated molecules (ion pairs) of zinc iodide are involved in the exchange or else exchange is

(4) F. Albert Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, New York, N. Y., 1962, p 477.
(5) R. L. Beyer, Ed.S. Thesis, Kansas State Teachers College, Aug 1967.
(6) G. Thuillier and P. Daudel, *Compt. Rend.*, **243**, 147 (1956).
(7) J. Minor, M.S. Thesis, Kansas State Teachers College, Aug 1967.

by means of a complex ion such as ZnI_3^- produced by the following reaction. Therefore, if the reaction order

$$2ZnI_2 \longrightarrow ZnI_3^- + ZnI^+ \quad (4)$$

for zinc iodide at 100° is indeed one, the reaction proceeds by different mechanisms at 100° and 40–60°.

In calculating results for exchange rates, corrections for the 4.7% zinc iodide activity in the organic layer and the <1% *n*-alkyl iodide activity in the inorganic layer were not made by the authors because the measured exchange proceeded to within 99% of the theoretical value in cases where it was followed this long. If the amounts of zinc iodide and alkyl iodide going into the benzene and water layers, respectively, were seriously biasing the results, the theoretical and observed values for the amount of exchange at equilibrium would not be within 1% of each other.[8]

It was found that exchange reactions performed with zinc iodide and *n*-propyl iodide at 59.1° gave erratic results and showed a pronounced rate increase with the passage of time when run in the presence of atmospheric oxygen. Therefore studies made at this temperature were done using solutions swept with nitrogen.

A mechanism which is consistent with the first-order rate dependence observed for *n*-propyl iodide and zero-order dependence observed for zinc iodide is one in which a solvent molecule approaches the iodine-containing carbon atom from the side opposite the iodine and produces an ion pair. The formation of these complexes is proposed as the rate-determining step. A weakening of the carbon–iodine bond is indicated since the activation energy is only 22.9 kcal/mol for *n*-propyl iodide whereas the bond strength is 46 kcal/mol.[9] Solvent assistance in the bond-breaking step is assumed to occur since *n*-propyl iodide undergoes exchange with zinc iodide many times faster than does isopropyl iodide, contrary to what would be expected for unimolecular decomposition of alkyl iodides. This result would be expected if solvent assistance is involved since the carbon-containing iodine in isopropyl iodide is more sterically hindered.

Zinc iodide probably exists primarily as undissociated molecules in acetonitrile.[2] Since zinc iodide is a Lewis acid it can easily attach itself to the iodide ion in the ion pair and either give an iodide ion to the propyl group at the same time or shortly thereafter.

$$CH_3C{\equiv}N: + R{-}I \underset{k}{\rightleftharpoons} [CH_3\overset{+}{C}{=}N{:}R \longleftrightarrow CH_3C{\equiv}\overset{+}{N}{:}R]I^- \quad (5, \text{rate determining})$$

$$[CH_3C{\equiv}N{:}R]^+I^- + I^*ZnI \longrightarrow CH_3C{\equiv}N + RI^* + ZnI_2 \quad (6)$$

Although this mechanism is consistent with experimental observations reported in this paper, the possibility of other mechanistic explanation is, of course, not precluded.

The proposed mechanism assumes that the reaction is in reality bimolecular: first order in alkyl iodide and first order in acetonitrile. A further indication of bimolecularity in the rate-determining step is the value of the Arrhenius frequency factor, $10^{11.9}$ l. mol^{-1} sec^{-1}. This is very close to the value, 10^{11}–10^{12} l. mol^{-1} sec^{-1},[10] calculated from collision theory for a bimolecular reaction, whereas the value for a unimolecular reaction is 10^{13}–10^{14} sec^{-1}.

At first glance, the results of this study appear to violate the usual rules governing SN1 and SN2 reactivity of alkyl halides. However, if a solvent molecule is regarded as making a nucleophilic attack on the alkyl halide molecule in the rate-determining step, then the observed results agree with results of other investigators who have studied SN1 and SN2 reactivities.

Registery No.—Iodine, 7553-56-2; zinc iodide, 10139-47-6; *n*-propyl iodide, 107-08-4; *n*-butyl iodide, 542-69-8; acetonitrile, 75-05-8.

(8) This point has been adequately verified in the author's laboratory in working with systems involving labeled zinc iodide, *n*-butyl iodide, and N,N-dimethylformamide. Incomplete separation of the organic and inorganic iodides has lead to experimental equilibrium values which were off as much as 70% from the theoretical equilibrium values.

(9) S. Glasstone and D. Lewis, "Elements of Physical Chemistry," D. Van Nostrand Co., Inc., Princeton, N. J., 1960, p 92, taken from Szwarc, *Quart. Rev.* (London), **5**, 22 (1951).

(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1961, p 75.

The Scope of the Pummerer Reaction[1]

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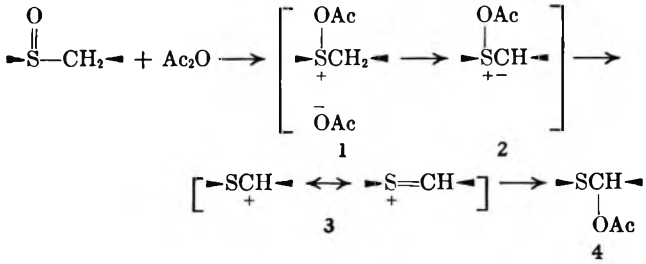
Received May 2, 1968

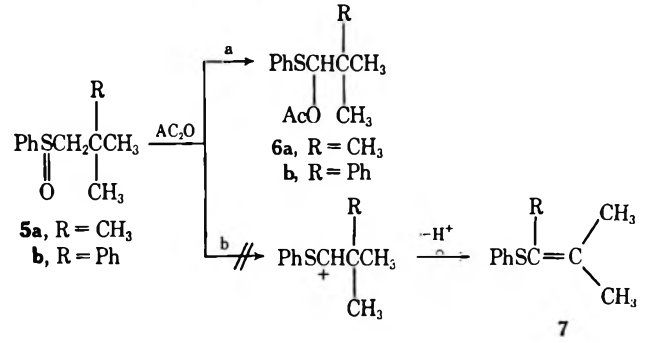
The reactions of acetic anhydride with certain hindered sulfoxides, β-oxy sulfoxides, vinyl sulfoxides, and unsymmetrical sulfoxides are described.

The decomposition of sulfoxides in hot acetic anhydride,[3] a reaction analogous to that reported by Pummerer,[4] has been shown to be an attractive preparative route to α-acetoxy sulfides[3] and certain α,β-unsaturated sulfides.[5,6] The acyloxysulfonium salt **1**, the ylide **2**, and the carbonium ion[7] **3** have been suggested as intermediates; however, the mechanism of the reaction has not been vigorously defined and has been the subject of much speculation.[8]



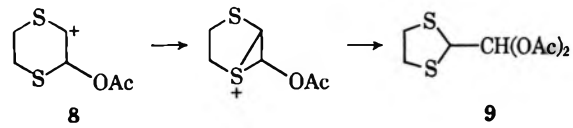
We would like to report at this time additional examples which relate to the scope of this reaction.

Hindered Sulfoxide.—The reaction of acetic anhydride with the hindered sulfoxides **5a** and **5b** were examined at 100° in an atmosphere of nitrogen. In both cases very selective reactions occurred to give the α-acetoxy sulfides **6**. In neither case were there any



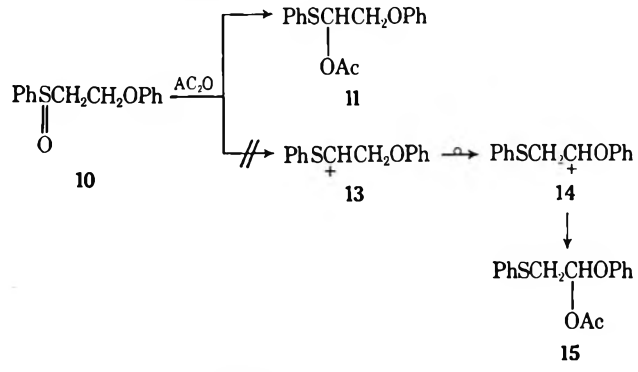
products found of type **7**, which could logically result by reaction as shown in path b. The acetates **6a** and **6b** were isolated pure, and their structures were established by their conversion into the 2,4-dinitrophenylhydrazones of the corresponding aldehydes. The reactions of **5a** and **5b** were slow in comparison with similar reactions with unhindered sulfoxides. The conversion of **5a** into **6a** at 100° was 55% after 21 hr and 87% after 42 hr; after 66 hr no starting sulfoxides could be detected (vpc). *n*-Butyl methyl sulfoxide, by comparison, was found to be reacted completely in 4.5 hr at 100°.

β-Oxy Sulfoxides.—The formation of the rearranged acetate **9** from **8** (formed *in situ*) has been cited[7b] as evidence for the carbonium-ion intermediate of type **3** in the Pummerer reaction. We have examined the



reaction of acetic anhydride with **10** and **16**, both of which could give more stable rearranged carbonium ion as intermediates, to determine whether rearrangement products might be generally formed from reaction of acetic anhydride with β-oxy sulfoxides.

The reaction of β-(phenylsulfinyl)phenetole (**10**) with acetic anhydride was carried out for 23.5 hr at 100°. The products were recovered **10** (~19.6%), β-(phenylsulfonyl)phenetole (~5.4%), and β-acetoxy-β-(phenylthio)phenetole (**11**, mp 70–71°, 76%). The



acetate **11** was obtained pure, and its structure was confirmed by its conversion into β-phenoxyacetaldehyde semicarbazone. There was no evidence for the formation of **15**, which could result by rearrangement of the carbonium ion **13** to the more stable carbonium ion **14**.[9]

Simarily, reaction of the sulfoxide **16**[10] with acetic anhydride for 24 hr at 100° gave recovered sulfoxide **16** (23%) and the acetate **17** (55%). Desulfurization of the product with Raney nickel gave only tetrahydrofurfuryl acetate, derived from **17**. There was no

(1) Supported by a Grant from the U. S. Army Research Office, Durham, N. C. (DA-ARO-D-31-124-G848).

(2) From the Ph.D. Thesis of L. D. Edwards, The University of Minnesota, 1967.

(3) L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959).

(4) R. Pummerer, *Ber.*, **42**, 2282 (1909); **43**, 1401 (1910).

(5) W. E. Parham and R. Koncos, *J. Amer. Chem. Soc.*, **83**, 4034 (1961).

(6) W. E. Parham, L. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, **29**, 2211 (1964).

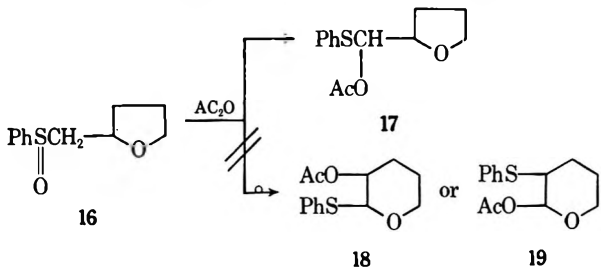
(7) (a) F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955); (b) W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, **28**, 2686 (1963); (c) C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Lett.* 5299 (1967); (d) W. E. Parham and S. H. Goren, *J. Org. Chem.*, **30**, 728 (1965).

(8) For discussion and leading references, see T. L. Moore, *ibid.*, **32**, 2786 (1967), and ref 7.

(9) For leading references, see ref 7b.

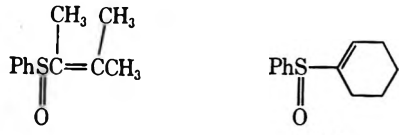
(10) This sulfoxide was chosen since it is known that tetrahydrofurfuryl tosylate undergoes rearrangement upon solvolysis to 3-acetoxytetrahydrofuran, and the rearranged carbonium ion would be more stable since the vacant p orbital would be adjacent to oxygen rather than sulfur. *Cf.* D. Gagnaire and A. Butt, *Bull. Soc. Chim. Fr.*, 309 (1961), and S. Moon and J. M. Lodge, *J. Org. Chem.*, **29**, 3453 (1964).

evidence (vpc) for 3-acetoxytetrahydropyran or 2-acetoxytetrahydropyran, which would have been formed had the product contained the rearrangement products **18** or **19**. Authentic 3-acetoxytetrahydropyran and 2-acetoxytetrahydropyran were prepared for the analysis.

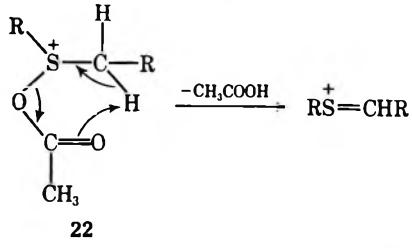


Since no rearrangement products accompanied the reaction of sulfoxides **5**, **10**, and **16**, in their reaction with acetic anhydride, it was concluded that carbonium ions, if formed as intermediates, undergo solvolysis quite rapidly; rearrangement products are to be expected only in cases, such as **8**, where structural features for rearrangement are exceptionally favorable.

We have observed that vinyl sulfoxides, such as 2-methyl-3-phenylsulfinyl-2-butene (**20**) and cyclohexenyl phenyl sulfoxide (**21**), are stable to hot acetic



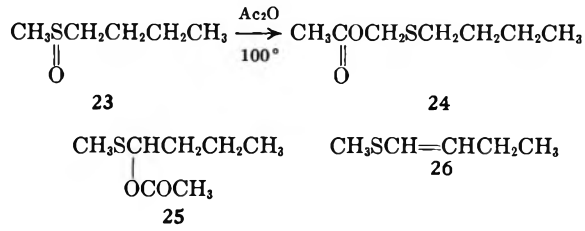
anhydride (100° for 24 hr). Similarily, phenyl *p*-tolyl sulfoxide and phenyl *o*-tolyl sulfoxide were recovered, essentially quantitatively, even when benzoic anhydride at 187° was used in place of hot acetic anhydride. Failure of vinyl sulfoxides to undergo the Pummerer reaction with acetic anhydride is consistent with the conclusion that elimination of acetic acid from **1** occurs by a cyclic elimination mechanism[7a] as shown in **22**. The possibility cannot, however, be excluded



that the ylide **2** is an intermediate and that hydrogen atoms in vinyl sulfoxides are not acidic enough to undergo E1 or E2 elimination reactions under the conditions of reaction.

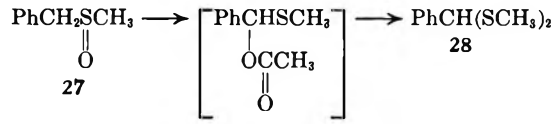
In a recent study of the selectivity of the Pummerer reaction, Johnson, Sharp, and Phillips[7c] concluded that removal of the proton from **1** is the product-determining (and possibly rate-determining) step of the reaction and that carbonium ions of type **3** are formed as intermediates. These workers observed that the only products formed from a series of unsymmetrical methyl alkyl sulfoxides were those derived by migration of acetate to the least substituted α carbon. Our results with two unsymmetric sulfoxides were less definitive than those reported, but were in agreement and consistent with the conclusion that the most acidic hydrogen of the sulfoxide is preferentially lost.

The reaction of **23** with acetic anhydride was carried out at 100° for 4.5 hr. Analysis of the crude product



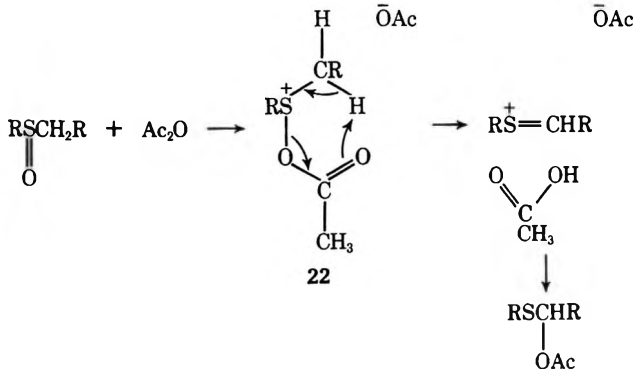
(vpc) showed the absence of sulfoxide and the presence of **24** (~50.3%) and **26** (~4%, identical retention time to authentic material). The acetate **24** was obtained pure by vpc. No other products were detected in large amounts, and the poor material balance was not explained or improved in a subsequent experiment. These results compare with a 64% yield of **24** obtained by reaction of **23** with acetic anhydride in boiling benzene.[7c]

The reaction of benzyl methyl sulfoxide (**27**) with acetic anhydride (100°, 20 hr) gave, subsequent to extraction, water wash, and chromatography, a 57%



yield of the dimethyl mercaptal of benzaldehyde (**28**). The product **28** can be rationalized by assuming that the original Pummerer reaction occurred (preferentially) on the more acidic benzyl carbon atom.

While it is recognized that the mechanism of the Pummerer reaction may vary markedly with subtle changes in structure of starting sulfoxide and with changes in reaction conditions, as is characteristic of other elimination and substitution processes, we currently favor the reaction sequence shown in the accompanying equation as the most general one for those reactions involving anhydrides.



This reaction sequence is consistent with (a) the observation that the most acidic hydrogen atom of the sulfoxide is preferentially eliminated; (b) the observation that sulfoxides such as **20** and **21**, which are geometrically unsuited for formation of transition states similar to **22**, are stable to the usual reaction conditions; and (c) the observed rearrangement, characteristic of carbonium-ion intermediates, that has been observed with a sulfoxide where structural features for rearrange-

ment are exceptionally favorable. Alternative mechanisms cannot, however, be eliminated and details of mechansims of this modified Pummerer reaction cannot be considered as settled.

Experimental Section

2,2-Dimethylpropyl Phenyl Sulfide.—Thiophenol (132 g, 1.2 mol) and neopentyl *p*-toluenesulfonate (145 g, 0.6 mol, mp 45–47.5°, 82% yield from *p*-toluenesulfonyl chloride and neopentyl alcohol[11]) were added successively to a solution prepared from sodium (27.7 g, 1.2 g-atom) and 2-ethoxyethanol. The mixture was heated at the reflux temperature under nitrogen for 20 hr and was then cooled and filtered. The precipitate was washed with ether, and water (2000 ml) was added to the combined filtrate and ether wash. The resulting mixture was extracted with four 200-ml portions of ether, and the ether extract was washed with water, dried ($MgSO_4$), and distilled to give 100 g (92.6% yield) of 2,2-dimethylpropyl phenyl sulfide: bp 75–76° (0.85 mm); $n^{26.5}D$ 1.5339. The nmr spectrum of the sulfide (neat) showed τ 2.50–2.98 (m, aromatic H, wt 5), 7.20 (s, SCH_2, wt 2), 9.02 (s, CH_3, wt 9).

Anal. Calcd for $C_{11}H_{16}S$: C, 73.27; H, 8.95; S, 17.78. Found: C, 72.99; H, 9.17; S, 17.68.

2,2-Dimethylpropyl Phenyl Sulfoxide (5a).—Hydrogen peroxide (30%, 11.4 g, 0.10 mol) was added dropwise to a solution of 2,2-dimethylpropyl phenyl sulfide (18.03 g, 0.10 mol), methanol (400 ml), and formic acid (97%, 10 ml), and the mixture was refluxed for 17 hr. Methanol (325 ml) was removed from the mixture by distillation, and the residual liquid was diluted with water (500 ml) and extracted with ether (~300 ml). The dried ($MgSO_4$) extract was distilled to give 14.8 g (75.5% yield) of 2,2-dimethylpropyl phenyl sulfoxide: bp 83–86° (0.1 mm); $n^{23.5}D$ 1.5358. The nmr spectrum of **5a** (32% CCl_4) showed τ 2.33–2.75 (m, aromatic H, wt 5), τ_A 7.38, τ_B 7.52 (AB pattern, $-SOCH_2-$, wt 2, J_{AB} = 13.5 Hz), τ 8.85 (s, CH_3, wt 9).

Anal. Calcd for $C_{11}H_{16}OS$: C, 67.30; H, 8.22; S, 16.33. Found: C, 67.58; H, 8.31; S, 16.26.

2,2-Dimethylpropyl phenyl sulfone was prepared [55% yield, mp 38–39° from petroleum ether (bp 60–68°)–benzene] by oxidation of **5a** with hydrogen peroxide in acetic acid (2.5 hr at the reflux temperature).

Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60; S, 15.10. Found: C, 62.15; H, 7.40; S, 15.00.

Reaction of 2,2-Dimethylpropyl Phenyl Sulfoxide with Acetic Anhydride. A.—A mixture of **5a** (3.0 g, 0.015 mol) and acetic anhydride (4.6 ml) was heated under an atmosphere of nitrogen for 21 hr at 95°. The mixture was distilled to give 2.9 g of crude 1-acetoxy-2,2-dimethylpropyl phenyl sulfide (**6a**): bp 67–77° (0.8 mm); $n^{20}D$ 1.520. The product (1.83 g) was chromatographed on alumina (50 g), and the acetate (1.16 g) was eluted with petroleum ether (bp 60–68°)–benzene (4:1, 600 ml). The nearly pure acetate was rechromatographed as described above (on 30 g of alumina) to give pure **6a**: 0.88 g, 30.8% yield; $n^{26}D$ 1.5221; nmr (~10% CCl_4), τ 2.4–3.0 (m, aromatic H, wt 5), 4.05 (s, $-SCH-$, wt 1), 8.1 (s, CH_3CO, wt 1), 8.95 [s, $(CH_3)_3C$, wt 9].

Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.80; H, 7.62; S, 13.51.

B.—The reaction was repeated as described in A for 24 hr at 100°, and the mixture was analyzed by gas chromatography (liquid phase 20% SE-30, 125°); hexamethylbenzene was used as an internal standard. The mixture contained 1-acetoxy-2,2-dimethylpropyl phenyl sulfide (46.9 ± 0.5%) and 2,2-dimethylpropyl phenyl sulfoxide (53.1 ± 0.5%).

C.—The reaction was repeated, and the mixture was analyzed by vpc (liquid phase 20% Apiezon L, 200°). The per cent conversion of starting sulfoxide was 55, 87, and 100% after 21, 42, and 66 hr, respectively. These analyses showed the presence of only **5a** and **6a**; no 2-methyl-3-phenylthio-2-butene (**7a**) was detected.

Reaction of 1-acetoxy-2,2-dimethylpropyl phenyl sulfide (0.50 g, 0.0021 mol) with 2,4-dinitrophenylhydrazine reagent[12a] gave the **2,4-dinitrophenylhydrazone of trimethylacetaldehyde** (0.32 g, 57% yield, mp 209.5–212°) which was identical with the derivative (mp 210–211°, mmp 209–212°) prepared[13] from trimethylacetaldehyde.

2-Methyl-3-phenylthio-2-butene (**7a**).—A mixture of methyl isopropyl ketone (43.07 g, 0.5 mol) and thiophenol (40.0 g, 0.36 mol) was stirred at 0°, and dry hydrogen chloride was passed through the stirred mixture while thiophenol (70.17 g, 0.64 mol) was added dropwise; the reaction temperature was maintained below 10°. Hydrogen chloride was passed through the mixture for an additional 40 min. The mixture was then allowed to warm to 30° and was distilled to give 75.8 g of product: bp 113–117° (10 mm); $n^{26}D$ 1.5725. The distillate was dissolved in ether, and the ether solution was extracted with 2 *M* sodium hydroxide to remove thiophenol. The dried (Na_2SO_4) extract was distilled through a 20-cm spiral wire column. The product (46.5 g) was shown to contain two products by vpc (liquid phase 20% SE-30, 105°) and was purified by fractionation through a Nester-Faust spinning-band column to give 41.26 g (46.3% yield) of pure **7a**: bp 49.5–50.5° (0.03 mm); $n^{26}D$ 1.5698 [lit.[14] bp 64° (0.7 mm); $n^{25}D$ 1.5696]; nmr (~10% CCl_4), τ 2.8–3.1 (m, aromatic H, wt 5) and 7.9–8.3 (m, CH_3, wt 9).

2-Methyl-3-phenylsulfinyl-2-butene (**20**).—The oxidation of **7a** (5.35 g, 0.03 mol) with hydrogen peroxide was carried out as described for 2,2-dimethylpropyl phenyl sulfide. The crude product was chromatographed on silica gel, and the column was developed with petroleum ether (bp 60–68°), petroleum ether–benzene (9:1, 150 ml; 7:3, 150 ml; 2:3, 150 ml), benzene (450 ml), benzene–chloroform (9:1, 150 ml, 7:3, 150 ml, 2:3, 150 ml), chloroform (450 ml), and chloroform–ether (9:1, 450 ml). The last fraction gave 4.02 g (71% yield) of pure **20**: mp 75–76.5°; nmr (10% CCl_4), τ 2.50–2.80 (aromatic H, wt 5) and 7.8, 8.2, and 8.4 (three singlets, CH_3, wt 9).

Anal. Calcd for $C_{11}H_{14}OS$: C, 68.02; H, 7.27; S, 16.48. Found: C, 67.89; H, 7.18; S, 16.35.

2-Methyl-2-phenylpropyl phenyl sulfide was prepared from neophyl chloride[15] (84.3 g, 0.50 mol), thiophenol (63.5 g, 0.575 mol), and potassium hydroxide (32.3 g, 0.575 mol) in dimethylacetamide (425 ml) essentially as described[16] for other sulfides (20 hr at reflux). There was obtained 119 g (98.6% yield) of sulfide: bp 100–104° (0.01 mm); $n^{25.5}D$ 1.5950. A redistilled sample, bp 117.5–118.5° (0.02 mm), $n^{25.5}D$ 1.5969, of product showed an nmr spectrum in 10% CCl_4 of τ 2.5–3.1 (m, aromatic H, wt 10), 6.9 (s, $-SCH_2-$, wt 2), and 8.7 (s, CH_3-, wt 6).

Anal. Calcd for $C_{16}H_{18}S$: C, 79.31; H, 7.49; S, 13.21. Found: C, 79.60; H, 7.25; S, 13.11.

2-Methyl-2-phenylpropyl phenyl sulfoxide (**5b**) [39.5 g, 77.2% yield, mp 34–37°, bp 149–152° (0.007 mm), $n^{25}D$ 1.5927] was prepared by oxidation of 2-methyl-2-phenylpropyl phenyl sulfide (48.5 g, 0.2 mol) as described for the oxidation of **5a**. The nmr spectrum of **5b** (10% CCl_4) showed τ 2.5–3.0 (m, aromatic H, wt 10), 7.15 (s, $-SOCH_2-$, wt 2), and 8.35 and 8.55 (two singlets, CH_3, wt 6).

Anal. Calcd for $C_{16}H_{18}OS$: C, 74.39; H, 7.02; S, 12.39. Found: C, 74.62; H, 7.01; S, 12.22.

Reaction of 2-Methyl-2-phenylpropyl Phenyl Sulfoxide with Acetic Anhydride.—The reaction of **5b** (12.95 g, 0.05 mol) with acetic anhydride (15 ml) was carried out as described for **5a**. The crude product (14.4 g, $n^{25}D$ 1.5650) was chromatographed on silica gel (300 g). Elution of the column with petroleum ether (bp 60–68°)–chloroform (9:1, 1200 ml; 7:3, 1200 ml; 3:2, 1200 ml; 1:1, 1200 ml; 2:3, 600 ml) gave only a trace of material which was discarded. Elution of the column with petroleum ether–chloroform (2:3, 3000 ml) gave 8.2 g (53.9% yield) of 1-acetoxy-2-methyl-2-phenylpropyl phenyl sulfide (**6b**, $n^{25}D$ 1.5594); elution of the column with additional petroleum ether–chloroform (2:3, 1500 ml) gave 4.35 g (33.6%) of recovered 2-methyl-2-phenylpropyl phenyl sulfoxide, which had $n^{25}D$ 1.5608. The nmr spectrum of **6b** (10% CCl_4) showed τ 2.5–3.1 (m, aromatic H, wt 10), 3.7 (s, SCH, wt 1), 8.3 (s, CH_3CO, wt 3), and *ca.* 8.5 (two singlets, CH_3C, total wt 6).

Anal. Calcd for $C_{18}H_{20}O_2S$: C, 71.98; H, 6.71; S, 10.65. Found: C, 71.77; H, 6.89; S, 11.00.

(11) F. M. Beringer and H. S. Schultz, *J. Amer. Chem. Soc.*, **77**, 5533 (1955).

(12) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1956: (a) p 219; (b) p 218.

(13) W. Reeve and H. Adkin, *J. Amer. Chem. Soc.*, **62**, 2876 (1940).

(14) T. L. Jacobs and G. E. Illingworth, Jr., *J. Org. Chem.*, **28**, 2692 (1963).

(15) W. T. Smith and J. T. Sellas, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 702.

(16) J. R. Campbell, *J. Org. Chem.*, **29**, 1830 (1964).

The acetate **6b** (0.25 g, 0.00083 mol) was treated with 2,4-dinitrophenylhydrazine reagent. The solid, collected after 24 hr, was recrystallized from ethanol to give 0.20 g (74% yield) of the **2,4-dinitrophenylhydrazone of 2-methyl-2-phenylpropanal** [melting point and mixture melting point of a sample (mp 143–144°) prepared from authentic 2-methyl-2-phenylpropanal was 143–144°].

Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.58; H, 5.14; N, 16.79.

β-(Phenylthio)phenetole was prepared from thiophenol (23.2 g, 0.21 mol), β-chlorophenetole[17] (31.4 g, 0.20 mol), and sodium hydroxide (8.4 g, 0.21 mol) in ethanol (100 ml). After 1 hr at the reflux temperature, the mixture was processed to give 42.4 g (92% yield) of product, mp 66–67.5° (from ethanol).

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.00; H, 6.13; S, 13.92. Found: C, 73.26; H, 6.14; S, 14.00.

β-(Phenylsulfinyl)phenetole (10), mp 66–68° (from petroleum ether–benzene), was prepared in 85% yield by oxidation of β-(phenylthio)phenetole in acetic acid with hydrogen peroxide at 10°. The nmr spectrum of **10** (~10% $CDCl_3$) showed τ 2.3–3.3 (m, aromatic **H**, wt 10), $SOCH_2$ centered at 6.85 (t, wt 2), 5.3–6.1 (O-CH_2, AB pattern, further split by two other protons with J_{AB} = 10.6 Hz, calculated chemical shifts τ_A 5.58 and τ_B 5.84, wt 2).

Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; S, 13.02 Found: C, 68.26; H, 5.75; S, 13.28.

Oxidation of **10** (2.3 g, 0.01 mol) with 30% hydrogen peroxide [20.5 mol, 0.2 mol in formic acid (30 ml)], and carbon tetrachloride (50 ml) at the reflux temperature gave crude β-(phenylsulfonyl)phenetole which was purified by liquid chromatography on silica gel. The column was eluted with petroleum ether (bp 60–68°) and combinations of petroleum ether and chloroform. Nearly pure **β-(phenylsulfonyl)phenetole** [mp 125–126.5, 127–128° from hexane–benzene (lit.[18] mp 120°)] was obtained by use of petroleum ether–chloroform (7:3); the nmr spectrum of the sulfone (11% $CDCl_3$) showed τ 2.0–3.5 (m, aromatic **H**, wt 10), O-CH_2 centered at 5.65 (t, wt 2), SO_2CH_2 centered at 6.4 (t, wt 2).

Anal. Calcd for $C_{14}H_{14}O_3S$: C, 64.10; H, 5.38; S, 12.23. Found: C, 64.37; H, 5.32; S, 12.26.

Reaction of 10 with Acetic Anhydride.—Acetic anhydride (9 ml, 0.097 mol) and **10** (7.39 g, 0.03 mol) were mixed and heated at 100° under nitrogen. At the end of 23.5 hr the mixture was cooled and diluted with water (1500 ml) and extracted with ether (five 100-ml portions). The ether extract was washed with saturated sodium bicarbonate [three 100-ml portions and water (100 ml)], dried ($MgSO_4$), and concentrated. The semisolid (10.3 g) was chromatographed on silica gel (100 g). Elution of the column with petroleum ether (bp 60–68°) and with petroleum ether–chloroform (9:1, 600 ml) gave 0.129 g of tar which was discarded; elution with petroleum ether–chloroform (4:1, 3900 ml) gave 5.29 g (76% yield based on recovered starting material) of β-(acetoxy)-β-(phenylthio)phenetole (**11**). Elution of the column with petroleum ether–chloroform (4:1, 900 ml) gave, after recrystallization of the product from hexane–benzene, 0.35 g (5.4% yield) of β-(phenylsulfonyl)phenetole (mp and mmp 126.5–128.5). Elution of the column with petroleum ether–chloroform (1:1, 1200 ml) gave 1.47 g (19.6% recovery of **10**, mp 67–68.5° from hexane–benzene).

Acetate **11**, mp 70–71.5°, showed an nmr spectrum (~10% $CDCl_3$) of τ 2.4–3.3 (m, aromatic **H**, wt 10) and 8.0 (s, CH_3CO, wt 3). The three remaining protons formed a typical ABX pattern, with the X proton, SCH, centered at τ 3.65, wt 1, and J_{AX} = 6.6 Hz and J_{BX} = 5.2 Hz; the AB protons, CH_2O, gave a pattern such that the outside lines were unobservable, and three observable bands appeared at τ 5.81, 5.89, and 5.92, wt 2.

Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.66; H, 5.59; S, 11.10. Found: C, 66.66; H, 5.54; S, 11.10.

In another run (20.5 hr at 100°) the acid was not neutralized. The entire product was distilled. There was obtained 1.71 g (31% yield) of **phenyl-2(phenylthio)vinyl ether**: bp 132–140° (0.02 mm); $n^{26}D$ 1.6289 [lit.[19] bp 110–113° (0.05 mm); $n^{20}D$ 1.6350].

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30; S, 14.04. Found: C, 73.70; H, 5.58; S, 14.19.

The **hydrolysis of 11** (0.58 g, 0.002 mol) was achieved using mercuric chloride (1.09 g, 0.004 mol) and sulfuric acid (0.5 ml) in water (20 ml) and methanol (20 ml). The mixture was heated for 0.5 hr at the reflux temperature and was then filtered. The filtrate and wash (methanol) of the precipitate were combined, diluted with water, and extracted with ether. The extract was washed (saturated sodium bicarbonate), dried ($MgSO_4$), and concentrated. The semicarbazone of the residue was prepared in the usual way[12b] and melted at 148.5–150° (from ethanol) (lit.[20] mp 145°). The product was identical (mmp 148.5–150°) with the semicarbazone prepared[12b] from authentic phenoxyacetaldehyde (mp 150–151°).

Anal. Calcd for $C_9H_{11}N_3O_3$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.79; H, 5.79; N, 21.36.

Phenyl tetrahydrofurfuryl sulfide [84.5% yield, bp 93–95° (0.15 mm), $n^{22}D$ 1.5702] was prepared from thiophenol and tetrahydrofurfuryl tosylate[21] by a procedure similar to that described for 2,2-dimethylpropyl phenyl sulfide. The nmr spectrum of the sulfide (10% CCl_4) showed τ 2.6–3.1 (m, aromatic **H**, wt 5), 5.85–6.6 (m, $CHOCH_2$, wt 3), and 6.7–7.4 (ABX, SCH_2, and 7.9–8.65 (m, CCH_2CH_2C, wt 4).

Anal. Calcd for $C_{11}H_{14}OS$: C, 68.02; H, 7.27; S, 16.47. Found: C, 68.30; H, 7.54; S, 16.18.

Phenyl tetrahydrofurfuryl sulfoxide (16) was prepared by oxidation of phenyl tetrahydrofurfuryl sulfide (19.43 g, 0.10 mol) with hydrogen peroxide in acetic acid at 10°. The crude sulfoxide (19.0 g) was chromatographed on silica gel (150 g). Most of the sulfoxide was eluted with benzene, benzene–chloroform, and chloroform, and slightly impure **16** containing trace amounts of sulfide and diphenyl disulfide (vpc, liquid phase 20% SE-30, 150°) was obtained in 80% yield (16.8 g). This product was distilled to give pure **16**: bp 135–137° (0.02 mm); $n^{27}D$ 1.5652; nmr (10% CCl_4), τ 2.2–2.8 (m, aromatic **H**, wt 5), 5.6–6.6 (m, $-CHOCH_2-$, wt 3), 7.0–7.3 (two doublets, $-SOCH_2C$, wt 2), and 7.8–8.6 (m, $-CCH_2CH_2C$, wt 4).

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.57; H, 6.98; S, 15.33.

Phenyl tetrahydrofurfuryl sulfone was obtained as an oil ($n^{23.5}D$ 1.5440) which was distilled in a Babcock distillation apparatus.

Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.40; H, 6.24; S, 14.14. Found: C, 58.21; H, 6.21; S, 14.34.

The reaction of phenyl tetrahydrofurfuryl sulfoxide with acetic anhydride was carried out as described for **5a**. The crude product (3.9 g) was chromatographed on silica gel (80 g), and the column was developed with petroleum ether, benzene, and chloroform, using various logical mixtures of these solvents. There was obtained 2.7 g ($n^{25}D$ 1.5404, 55% yield) of acetoxytetrahydrofurfural phenyl sulfide (**17**, with benzene–chloroform, 3:2, 600 ml) and 0.944 g ($n^{25}D$ 1.5640, 23% recovery) of phenyl tetrahydrofurfuryl sulfoxide.

The nmr spectrum (10% CCl_4) of **17** showed τ 2.4–3.0 (m, aromatic, **H**, wt 5), centered at 3.9 and 4.1 (two doublets, SCH, wt 1), 5.8–6.5 (m, $-CHOCH_2$, wt 3), and 7.9–8.4 (CH_3CO and $-CCH_2CH_2C-$, wt 7).

Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.89; H, 6.39; S, 12.68. Found: C, 61.60; H, 6.51; S, 12.48.

Proof of Structure of Acetoxytetrahydrofurfural Phenyl Sulfide.—A mixture of **17** (2.434 g, 0.00965 mol), Raney nickel (*ca.* 45 g), and absolute ethanol (125 ml) was heated at the reflux temperature for 7.5 hr. The mixture was filtered, the nickel was washed with ethanol, and the combined filtrate was dried ($MgSO_4$) and concentrated under a 30-cm spiral wire column. The residue was transferred with ether, and the ether was dried ($MgSO_4$) and concentrated to give 1.1 g (80% yield) of pure (vpc, liquid phase 20% Carbowax 20M, 110°) tetrahydrofurfural acetate ($n^{25}D$ 1.4360). Tetrahydrofurfuryl alcohol (retention time 20.5 min), 2-acetoxytetrahydropyran[22] (retention time 18 min), and 3-acetoxytetrahydropyran (retention time 25.5 min) were shown to be absent (vpc).

3-Acetoxytetrahydropyran.—The procedure of Moon and Lodge[10] gave a mixture of isomeric acetates (20% yield) composed (vpc, liquid phase 20% Carbowax 20M, 100°) of about 87% tetrahydrofurfuryl acetate.

(17) W. H. Bentley, E. Haworth, and W. H. Perkin, *J. Chem. Soc.*, **69**, 161 (1896).

(18) T. Nambara, *J. Pharm. Soc. Jap.*, **74**, 17 (1954); *Chem. Abstr.*, **49**, 1640*d* (1955).

(19) A. V. Kalabina, E. F. Kolmakova, T. I. Bychkova, Yu. K. Maksyatin, E. A. Denisevich, and G. I. Smolina, *Zh. Obshch. Khim.*, **35**, 979 (1965).

(20) A. Halasz, *Bull. Soc. Chim. Fr.*, **8**, 170 (1941).

(21) G. Barger, R. Robinson, and L. H. Smith, *J. Chem. Soc.*, 719 (1937).

(22) D. M. DeLaitsch, Ph.D. Thesis, University of Minnesota, 1950, p 70.

3-Acetoxytetrahydropyran, bp 70–71° (6 mm), n^{26}D 1.4383 was prepared by a modification of the procedure of Barker[23] and coworkers who prepared 3-hydroxytetrahydropyran. The crude 3-hydroxypyran (16.8% over-all yield from dihydropyran) was acetylated in pyridine with acetic anhydride to give 3-acetoxytetrahydropyran.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 57.97; H, 8.09.

Cyclohexenyl phenyl sulfoxide was prepared by oxidation of cyclohexenyl phenyl sulfide[24] essentially as described for the preparation of 5a. The crude sulfoxide (19.9 g) was purified by chromatography on silica gel (200 g) and **21** (11.5 g, 56% yield) was eluted with benzene–chloroform (1:1, 1000 ml; 3:7, 450 ml) and with chloroform (450 ml). The product showed only one peak in vpc (the liquid phase 20% SE-30, 150°) and was distilled, bp 121–122° (0.05 mm), n^{25}D 1.5881.

Anal. Calcd for $C_{12}H_{14}OS$: C, 69.88; H, 6.84; S, 15.52. Found: C, 69.59; H, 6.89; S, 15.70.

Reaction of *n*-Butyl Phenyl Sulfoxide with Acetic Anhydride.—The reaction of *n*-butyl phenyl sulfoxide[25] (6.0 g, 0.033 mol) with acetic anhydride (9 ml, 0.095 mol) was carried out under nitrogen for 19 hr at 104°. Distillation of the residue gave 4.41 g (82% yield) of 1-butenyl phenyl sulfide: bp 98–102° (0.15 mm); n^{25}D 1.5675 [lit.[26] bp 62° (0.22 mm); n^{20}D 1.5700].

Anal. Calcd for $C_{10}H_{12}S$: C, 73.14; H, 7.37; S, 19.49. Found: C, 72.93; H, 7.51; S, 19.46.

Reaction of *n*-Butyl Methyl Sulfoxide with Acetic Anhydride.—The product obtained (100°, 20 hr, under nitrogen) from **23**[27] (4.0 g, 0.034 mol) and acetic anhydride (10 ml) was treated with water (150 ml) and then extracted with ether. The extract was washed with aqueous bicarbonate and with water and was then dried and concentrated. The residue (3.91 g) was chromatographed on silica gel (100 g). 1-Acetoxymethyl *n*-butyl sulfide, n^{25}D 1.4554, bp 86–87° (9 mm) [lit.[28] n^{25}D 1.4538, bp 53–60° (15 mm)], which showed only one peak when analyzed by vpc (liquid phase 20% diisodecylphthalate, 150°; liquid phase 20% DC-710, 100°), was eluted mostly with petroleum ether (bp 60–68°) and benzene in the ratio of 2:3. The nmr spectrum of **24** (48% CCl_4) showed τ 4.9 (s, OCH_2S, wt 2), $SCHC_2$ centered at 7.37 (t, J = 7 Hz, wt 2), and 8.0 (s, CH_3CO, wt 3).

Anal. Calcd for $C_7H_{14}O_2S$: C, 51.84; H, 8.70; S, 19.75. Found: C, 52.11; H, 9.00; S, 19.58.

The reaction was repeated, and the crude products were analyzed by vpc (liquid phase 20% DC-710, programmed 40–100°). The yield of **24** was ~50.3%; the yield of 1-butenyl methyl sulfide was 3.9%, and butraldehyde and butyric acid by vpc (Porapak Q, column temperature 130 and 170°, respectively) were shown to be absent.

***cis,trans*-1-Butenyl Methyl Sulfide.**—Hydrogen chloride was bubbled through methyl mercaptan (62.2 g, 1.29 mol) cooled in a Dry Ice–acetone bath, and butraldehyde (46 g, 0.65 mol) was added over a 45-min period. The cold mixture was allowed to stand for 1 hr and was then allowed to warm to 30° and was washed with 2 *N* sodium hydroxide. Phosphoric acid (6 drops) was added, and the dried liquid was distilled rapidly, at atmospheric pressure, through a 12-cm Vigreux column (maximum head temperature 126°). The distillate was washed in ether with 2 *N* sodium hydroxide (two 50-ml portions) and water. The dried solution was distilled to give 20.9 g (31.7% yield) of 1-butenyl methyl sulfide: bp 123–126°; n^{25}D 1.4809. The nmr spectrum of **26** (75% CCl_4) showed τ 9 (two triplets separated by 1 Hz, CH_3–C, centered at a distance to the outside lines of 8 Hz, wt 3), CH_3S and =C—CH_2— (m, τ 7.6-8.2, wt 5), and 3.9–4.9 (AB pattern, SCH=CHC, J_{ABcis} = 9.2 and $J_{ABtrans}$ = 14.8 Hz, calculated chemical shift τ (CH=, *cis*) 4.32, τ (SCH=C, *trans*) 4.26, τ (SC=CH, *cis*) 4.46, and τ (SC=CH, *trans*) 4.48, total wt 2).

Anal. Calcd for $C_5H_{10}S$: C, 58.80; 9.87; S, 31.33. Found: C, 58.57; H, 9.80; S, 31.25.

Reaction of Benzyl Methyl Sulfoxide with Acetic Anhydride.—A solution of benzyl methyl sulfoxide[7a] (7.7 g, 0.05 mol) in acetic anhydride (15 ml) was heated at 100° under nitrogen for 20 hr. The cooled mixture was treated with water (200 ml) to hydrolyze the anhydride, and the mixture was extracted with ether. The ether was washed with aqueous bicarbonate and was dried ($MgSO_4$). The organic product (9.38 g) was chromatographed on silica gel (100 g), and the column was eluted with petroleum ether to give 2.63 g (57% yield) of the dimethyl mercaptal of benzaldehyde. The product showed only one peak on vpc (liquid phase 20% SE-30, 100°) and gave upon oxidation with hydrogen peroxide bis(methylsulfonyl)benzal: mp 168–169°; mmp 168–169° (lit.[29] mp 162–163°).

Registry No.—2,2-Dimethylpropyl phenyl sulfide, 7210-80-2; **5a**, 10335-98-5; 2,2-dimethylpropyl phenyl sulfone, 10269-15-5; **5b**, 17413-99-9; **6a**, 17414-00-5; **6b**, 17414-01-6; **7a**, 17414-02-7; 2-methyl-2-phenylpropyl phenyl sulfide, 17414-03-8; β-(phenylthio)phenetole, 17414-04-9; **10**, 17414-05-0; β-(phenylsulfonyl)-phenetole, 17414-06-1; **11**, 17414-07-2; phenyl tetrahydrofurfuryl sulfide, 17414-08-3; **16**, 17414-09-4; phenyl tetrahydrofurfuryl sulfone, 17414-10-7; **17**, 17414-11-8; **20**, 17414-14-1; **21**, 17414-12-9; **24**, 17414-13-0; **26** (*cis*), 17414-15-2; **26** (*trans*), 17414-27-6.

(23) S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen, and G. Zweifel, *Tetrahedron*, **7**, 10 (1959).

(24) N. W. Gill, M.S. Thesis, University of Minnesota, 1964, p 20.

(25) A. Cerniani, G. Modena, and P. E. Todesco, *Gazz. Chim. Ital.*, **90**, 3 (1960).

(26) E. Benzing (to Monsanto Chemical Co.), U. S. Patent 3,118,002 (Jan 14, 1964); *Chem. Abstr.*, **60**, 11899*d* (1964).

(27) L. Bateman, J. I. Cunneen, and J. Ford, *J. Chem. Soc.*, 3056 (1956).

(28) S. Oae, T. Kaito, and S. Kawamura, *Tetrahedron*, **19**, 1783 (1963).

(29) J. Bongartz, *Ber.*, **21**, 478 (1888).

The Mechanism of the Prins Reaction. VII. Kinetic Studies of the Prins Reaction of Styrenes[1]

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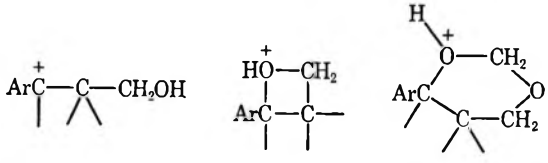
Pseudo-first-order rate constants of styrene disappearance for the Prins reaction and hydration of a number of *para*-substituted styrenes have been measured in water solution. By varying the concentration of formaldehyde it was found that the rate depends on the total concentration of formaldehyde hydrate and its oligomers. The Hammett ρ (using σ^+) for the Prins reaction of styrenes in water solution has been determined to be -1.61 at 75.5°.

Most of the previous studies of the acid-catalyzed condensation of formaldehyde with various styrenes have centered on the stereochemistry of the reaction.[4-7] These investigations reveal that *cis* addition accounts for a large fraction of the products, in contrast to the *trans* addition which is found to be a normal result with acyclic and aliphatic olefins.[8-12] As a result of such studies a number of possible intermediates (**1**–**3**) have been proposed for the condensation of formaldehyde with styrenes to form, ultimately, the major product of the reaction,[13,14] a 4-phenyl-1,3-dioxane.



1 **2** **3**

A study of the Prins reaction of styrene in acetic acid showed not only that the reaction is complex, but that, when a large excess of formaldehyde is used in 10% sulfuric acid solutions with acetic acid solvent, the major product is 4-phenyl-1,3-dioxane.[15] At low formaldehyde/styrene ratios, telomers are the major products. These results were interpreted in terms of an open carbonium-ion intermediate (**1**).[15] More recently, a kinetic study of the Prins reaction of α-methylstyrene in sulfuric acid solution has shown that the rate of the reaction is first order with respect to olefin and depends on the sum of the concentrations of formaldehyde hydrate and its oligomers. These results were interpreted to mean that all forms of formaldehyde in aqueous solution, hydrated monomer and oligomers, participate equally in the reaction.[16] Smissman and coworkers have examined the kinetics of the Prins reaction of anethole in acetic acid solution as a function of the formaldehyde concentration.[17] They interpreted the results to indicate that the reaction proceeds *via* an initial fast complexation of formaldehyde and olefin followed by a slow reaction of the complex.

The present study was undertaken in an effort to provide additional evidence concerning possible alternative reaction mechanisms and the proposed intermediates (**1**–**3**). We have measured the pseudo-first-order rate constants of the Prins reaction of styrene in aqueous sulfuric acid. In addition, we have measured the Prins reaction rates and the hydration rates of a number of *para*-substituted styrenes in water solution. The rates were measured by following the styrene disappearance spectroscopically in a thermostated cell. The formaldehyde concentration was varied to determine the dependence of the reaction rate on formaldehyde species. We find that the Prins reaction of styrene in water has a first-order dependence upon the total concentration of formaldehyde species and *not* on either formaldehyde monomer or dimer concentration. We also find that reaction rates of the *para*-substituted styrenes give an excellent Hammett plot using the σ^+ values of Brown.[18]

The formaldehyde concentration dependence data are presented in Table I.

If these rates are plotted *vs.* either formaldehyde monomer concentration or *vs.* formaldehyde dimer concentration, a pronounced curvature is found at higher concentrations. This observed upward curvature, illustrated in Figures 1 and 2, shows that the rate is increasing more rapidly than expected on the basis of first-order dependence on monomer concentration or on dimer concentration. One possible interpretation of this result is that all forms of formaldehyde present are reacting with the styrene substrate. Support for this idea is found in Figure 3. This plot of the rate constant *vs.* ΣF shows an excellent linear correlation with concentration. The formaldehyde concentration, ΣF, as defined previously[19] is the sum of the molar concentrations of methylene glycol, the dominant form of monomeric formaldehyde in aqueous solutions, and all of its oligomers. Figure 4 demonstrates that the rate does not show first-order dependence upon analytical formaldehyde. The analytical formaldehyde con-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This investigation was supported in part by a Public Health Service Research Career Development Award Number 1-K3-NB-28-105 from the National Institute of Neurological Disease and Blindness.

(2) Alfred P. Sloan Research Fellow, 1965–1967.

(3) National Defense Education Act Predoctoral Fellow, 1964–1967.

(4) P. S. Portoghese and E. E. Smissman, *J. Org. Chem.*, **27**, 719 (1962).

(5) L. Bernardi and A. Leone, *Tetrahedron Lett.*, 499 (1964).

(6) E. E. Smissman, R. A. Schnettler, and P. S. Portoghese, *J. Org. Chem.*, **30**, 797 (1965).

(7) L. J. Dolby, C. Wilkins, and T. G. Frey, *ibid.*, **31**, 1110 (1966).

(8) A. T. Blomquist and J. Wolinsky, *J. Amer. Chem. Soc.*, **79**, 6025 (1957).

(9) E. E. Smissman and D. T. Witiak, *J. Org. Chem.*, **25**, 471 (1960).

(10) L. J. Dolby, C. N. Lieske, D. R. Rosencrantz, and M. J. Schwarz, *J. Amer. Chem. Soc.*, **85**, 47 (1963).

(11) N. A. LeBel, R. N. Liesemer, and E. Mehemedbasich, *J. Org. Chem.*, **28**, 615 (1963).

(12) M. Hellin, M. Davidson, D. Lumbroso, P. Guiliani, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 2974 (1964).

(13) K. H. Engel, U. S. Patent 2,417,548 (1947); *Chem. Abstr.*, **41**, 3493*a* (1947).

(14) M. G. J. Beets, *Rec. Trav. Chim. Pays-Bas*, **70**, 20 (1951).

(15) A. Heslinga, *ibid.*, **79**, 222 (1960).

(16) M. Hellin, J. Gaillard, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 3360 (1967).

(17) K. B. Schowen, E. E. Smissman, and R. L. Schowen, *J. Org. Chem.*, **33**, 1873 (1968).

(18) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(19) See Table I, footnote *d*.

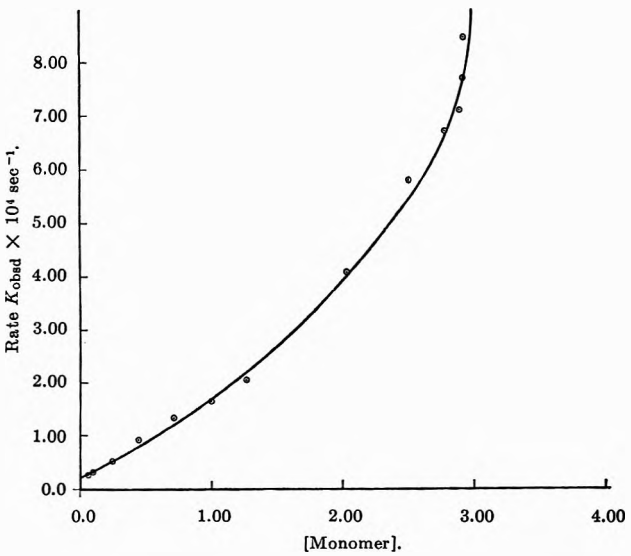


Figure 1.—Rate K_{obsd} of Prins reaction *vs.* [monomer] at 60.5° in 0.97 *N* (average) sulfuric acid–water. Styrene is 1×10^{-4} *M*.

TABLE I

PRINS REACTION OF STYRENE AT 60.5° IN WATER SOLUTION[a,b]

Formaldehyde concentrations						
Analytical, *M*	ΣF[c,d]	Monomer, M^{e-g}	Dimer, M^{e-g}	Other, M^{e-h}	K_{obsd} × 10^4, sec^{-1}	*n*[i]
0.0537	0.05	0.05	0.002	0.0000	0.266 ± 0.007	1
0.1273	0.12	0.11	0.009	0.0000	0.301 ± 0.006	1
0.2904	0.27	0.24	0.025	0.0004	0.532 ± 0.039	3
0.5366	0.48	0.44	0.047	0.0026	0.908 ± 0.407	2
0.8924	0.80	0.72	0.083	0.0094	1.347 ± 0.157	3
1.273	1.12	1.00	0.128	0.017	1.652 ± 0.062	4
1.712	1.45	1.27	0.186	0.070	2.032 ± 0.009	2
3.546	2.74	2.04	0.485	0.530	4.090 ± 0.243	4
5.360	3.75	2.51	0.780	1.29	5.781 ± 0.245	2
7.328	4.63	2.78	1.028	2.49	6.711 ± 0.273	6
8.821	5.18	2.89	1.140	3.65	7.091 ± 0.375	10
9.723	5.46	2.92	1.167	4.49	7.673 ± 0.498	10
10.72	5.73	2.93	1.195	5.40	8.521 ± 0.746	14

[a] Average sulfuric acid concentration 0.97 *N*. Styrene concentration 1×10^{-4} *M*. [b] Rate constants are not corrected for hydration which is 0.2×10^{-4} sec^{-1} at 60.5° in 0.97 *N* sulfuric acid. [c] Sum of the concentrations of formaldehyde hydrate and its oligomers, *i.e.*, the total concentration of formaldehyde species. [d] M. Hellin, J. Delmac, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 3355 (1967). [e] Determined by nmr methods as described by Moedritzer and Van Wazer,[f] Hellin, Delmac, and Coussement,[d] and Skell and Suhr.[g] [f] K. Moedritzer and J. R. Van Wazer, *J. Phys. Chem.*, 70, 2025 (1966). [g] P. Skell and H. Suhr, *Ber.*, 94, 3317 (1961). [h] Includes trimer and other oligomers as well as trioxane and is presented as analytical formaldehyde and not as the sum of the molar concentrations of the individual species. [i] Number of determinations averaged to give the reported rate constant.

centration is the total molar concentration of $-CH_2O-$ units which is determined titrimetrically.

The change of solvent from deuterium oxide to water, *i.e.*, from the analytical solutions to the kinetic solutions, might be expected to produce a solvent effect such that the equilibrium distribution of formaldehyde polymers would differ in the two systems. Such an effect has been considered and dismissed as negligible to the over-all distribution.[20] Again, a small difference in temperature (from 60.5 to 75.5°) has little effect on the polymer distribution since the formaldehyde chain–

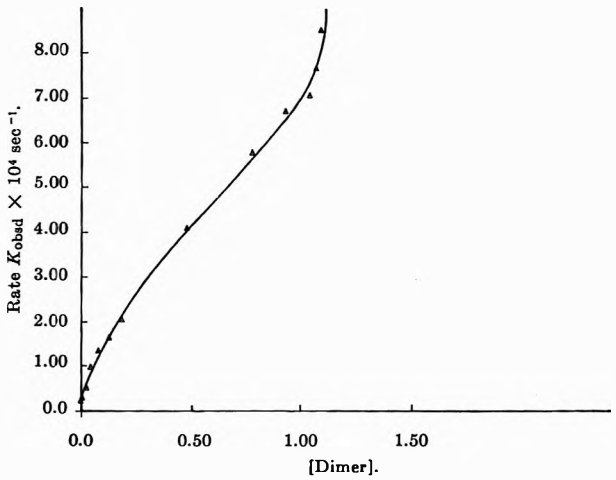


Figure 2.—Rate K_{obsd} of Prins reaction *vs.* [dimer] at 60.5° in 0.97*N* (average) sulfuric acid–water. Styrene is 1×10^{-4} *M*.

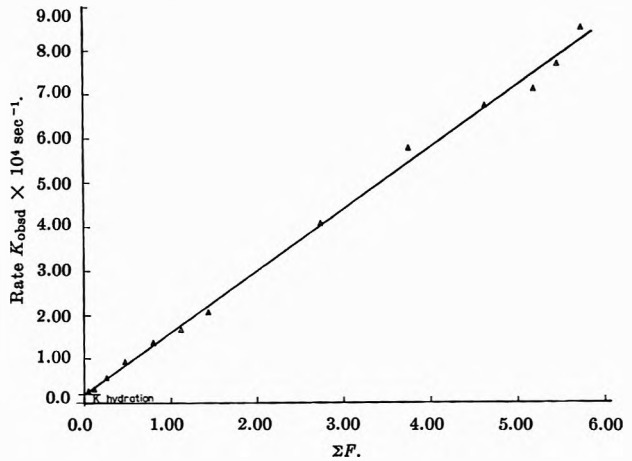


Figure 3.—Rate K_{obsd} of Prins reaction *vs.* ΣF at 60.5° in 0.97 *N* (average) sulfuric acid–water. Styrene is 1×10^{-4} *M*. Slope = 1.41 ± 0.03; intercept = 0.16 ± 0.08.

chain equilibria have a negligible temperature dependence.[21]

The rates of hydration of a number of styrenes used in the present study were determined at the same temperature and acid concentration used for the studies of the Prins reaction. These data show that the disappearance of styrene in the studies of the Prins reaction is indeed primarily due to the Prins reaction and not to the competing hydration reaction. Moreover, these data provide a ρ value for comparison with the ρ obtained for the Prins reaction of styrenes.

The study of the Prins reaction of α-methylstyrene suggests that the acidity dependences for hydration and the Prins reaction are the same. Considering this and that the highest value of the rate constant for hydration in our studies is less than one-seventh that for the Prins reaction, we can conclude that the observed rate is essentially only that of the Prins reaction. The results of the kinetic measurements for the hydration and Prins reaction of a number of styrenes are summarized in Table II.

From the Prins and hydration reaction constants in Table II it is possible to determine the Hammett ρ values for the reactions in water solution at 75.5°. The Hammett plots (using σ^+) are presented in Figure 5.

(20) See Table I, footnote *g*.

(21) See Table I, footnote *f*.

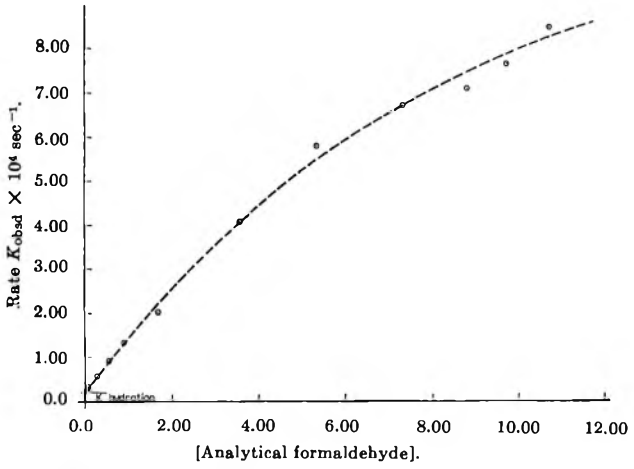


Figure 4.—Rate K_{obsd} of Prins reaction *vs.* [analytical formaldehyde] at 60.5° in 0.97 *N* (average) sulfuric acid–water. Styrene is 1 × 10^{-4} *M*.

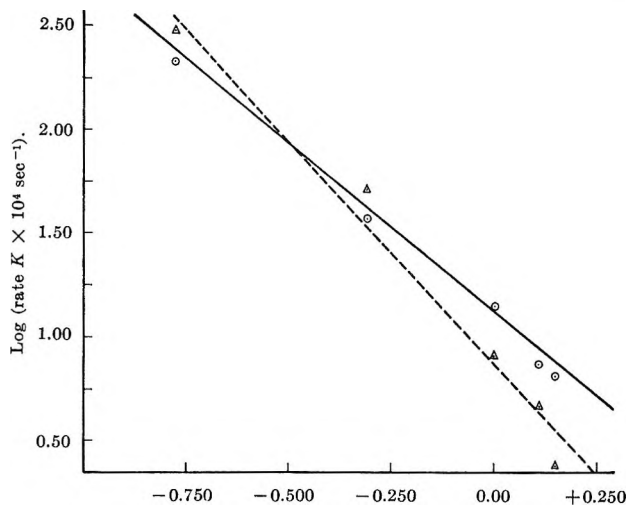


Figure 5.—Log rate K *vs.* σ^+ at 75.5°: – – – –, △, rate K_{hydrn}, ρ = −2.12 ± 0.14; ———, ⊙, rate K_{Prins}, ρ = −1.61 ± 0.07.

TABLE II

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE HYDRATION AND PRINS REACTIONS OF STYRENES[a,b]

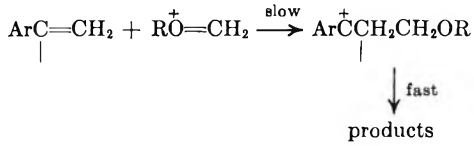
p-X	Solvent	Temp, °C	*n*[c]	K_{obsd} × 10^4, sec^{-1}	K_{hydrn} × 10^4, sec^{-1}
H	H_2O	75.5	2	15.67 ± 0.23	
		60.5	3	4.19 ± 0.05	
		60.5	1		0.19 ± 0.003
		75.5	1		0.78[d] ± 0.02
Br	H_2O	75.5	2	6.99 ± 0.20	
		60.5	2	1.49 ± 0.05	
		75.5	1		0.24[d] ± 0.01
Cl	H_2O	75.5	3	7.41 ± 0.27	
		60.5	3	1.96 ± 0.07	
		75.5	1		0.42[d] ± 0.02
CH_3	H_2O	75.5	3	43.62 ± 4.21	
		60.5	2	13.03 ± 0.42	
		75.5	1		5.2[d] ± 0.01
OCH_3	H_2O	75.5	*e*	199.79	
		60.5	*e*	61.81	
		40.0	3	10.38 ± 0.41	
		32.7	3	5.22 ± 0.29	
		75.5	2		28.11[d] ± 1.23

[a] Prins reaction solvent was water containing 3.2 *M* formaldehyde and 0.89 *N* sulfuric acid. Styrene concentration 1 × 10^{-4} *M*. [b] Plotted as rate *vs.* σ^+ in Figure 5. [c] Number of determinations which were averaged to give reported rate constant. [d] The hydration solution was 0.96 *N* sulfuric acid. Infinity points were calculated using Guggenheim plots. [e] Extrapolated from measurements made at a lower temperature.

The small negative ρ of −2.1 that we observe for the hydration of styrenes requires comment. This value is substantially different from the ρ of −3.42 for the hydration of styrenes in 3.83 *N* perchloric acid at 25° determined by Schubert, Lamm, and Keefe in the course of their elegant studies on the hydration of styrenes.[22] As a check on our experimental methods, we repeated some of the hydration measurements in 3.83 *N* perchloric acid at 25°, and these results were in excellent agreement with those reported by Schubert and coworkers. Perhaps the combination of higher temperature and lower acid concentration used in the present study is enough to account for the change in ρ.

Although it is difficult to compare reaction constants for reactions done under quite different conditions of solvent and temperature, it is interesting to note that Okamoto and Brown[23] find ρ = −2.34 (using σ^+) for the stannic chloride catalyzed polymerization of styrenes in carbon tetrachloride–nitrobenzene solution (1:1).[23] Similarly, the cationic polymerization of a number of α-methylstyrenes shows ρ = −1.7[23] in carbon tetrachloride solution,[24] whereas our data indicate a maximum negative ρ of −1.61 for the Prins reaction of styrenes. Any correction for hydration would only decrease this value since the ρ for hydration is more negative than that observed for the Prins reaction. The cationic polymerization of styrenes has one major feature in common with the Prins reaction of styrenes. They both involve formation of a carbon–carbon bond as a result of electrophilic attack upon the styrene double bond.

The reaction constant for the Prins reaction of styrenes is less negative than might be anticipated for a reaction in which a full positive charge is placed on the benzylic carbon at the transition state. However, the value is not so grossly different from that observed for the hydration of styrenes under similar conditions. We conclude that the reaction constant observed for the Prins reaction of styrenes does not rule out a simple carbonium-ion mechanism and clearly does not make it necessary to propose a four-membered cyclic oxonium-ion structure for the transition state. Moreover, the lack of stereoselectivity observed for the Prins reaction of 1-phenylpropene in aqueous medium is consistent with a simple carbonium-ion mechanism.[7] The accumulated data lead us to conclude that the major pathway for the Prins reaction of styrenes in aqueous solution involves the rate-determining transfer of a positive formaldehyde species to styrene to give an intermediate carbonium ion.



(22) W. M. Schubert, B. Lamm, and J. R. Keefe, *J. Amer. Chem. Soc.*, **86**, 4727 (1964).

(23) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957).

(24) C. F. Overberger, L. H. Arond, D. Tanner, J. J. Taylor, and T. Alfrey, Jr., *J. Amer. Chem. Soc.*, **74**, 4848 (1952).

This mechanism is similar to that proposed for the hydration of styrenes,[22] and the same conclusion was reached by Hellin, Gaillard, and Coussemant from their study of the Prins reaction with α-methylstyrene.[16] A mechanism specifically involving a dimer of formaldehyde is not indicated by any of the data.

Experimental Section

Materials.—Chemicals were stored under refrigeration and used without further purification except where otherwise noted. *p*-Methyl-, *p*-chloro-, and *p*-bromostyrene were purchased from Aldrich Chemical Co. Reagent grade styrene and trioxane (>99%) were obtained from Matheson Coleman and Bell. *p*-Methoxystyrene was prepared from 1-(*p*-methoxyphenyl)-ethanol by the method of Brooks.[25]

Solvents were distilled water and 99.85 atom % deuterium oxide (Calbiochem), while the acids were reagent grade sulfuric (>98%) or 99 atom % deuterated sulfuric acid (Stohler Isotope Chemicals).

Apparatus.—The ultraviolet spectral measurements were obtained with a thermally regulated Cary 15 spectrophotometer; the temperature was read (±0.2°) at the sample cell. The sample cell consisted of the usual 10-mm quartz cuvette to which was fused a Teflon stopcock.

The nmr spectral measurements were made in sealed tubes using a Varian A-60 spectrometer in analogy with earlier work.[19-21]

Preparation of Formaldehyde Solutions.—The aqueous and deuterium oxide solutions of formaldehyde were prepared by dilution of a standard formaldehyde–sulfuric acid–water solution or a standard formaldehyde–deuteriosulfuric acid–deuterium oxide solution. These standard solutions were prepared by the depolymerization of trioxane.

All solutions were analyzed for total formaldehyde content using the iodometric method cited by Walker.[26] The acid content was determined by titration with standard base. The densities of the aqueous solutions were taken as equivalent to those presented by Natta and Baccaredda[27] while those of the deuterium oxide solutions were obtained by extrapolation from the density measurements of Hellin, *et al.*[19]

All solutions were allowed to equilibrate at least 1 week prior to use. Solutions above 20% w/w formaldehyde were maintained above room temperature to prevent precipitation.

Kinetic Measurements.—The reactions were followed by observing the decrease in the π–π^* absorption for the styrene and substituted styrene solutions. A typical run was performed as follows: To 10 ml of formaldehyde solution was added 0.1 to 0.2 μl of styrene, and the solution was agitated. Approximately 5 ml of the solution was then transferred to a 13 × 100 mm Pyrex test tube which was sealed and placed in an oil bath for later use as an infinity point sample. The uv sample cell was then filled to a mark with the remaining solution.

The Cary 15 spectrophotometer which had equilibrated for 2 hr at 60.5° ± 0.2° was adjusted using two matched water-filled 10-mm quartz cells to provide a base line of zero at 248 mμ. The instrument was set to a "sync" operation of 50 sec/div. The sample cell was preheated for 2–3 min in a 55–60° oil bath, then cleaned, and immediately transferred to the cell compartment. The disappearance of styrene was followed for at least 1 half-life. The base line was checked with the matched cells at the completion of the run to ascertain instrument stability. After at least 10 half-lives, the contents of the test tube which had been previously placed in the oil bath were cooled, transferred to the sample cell, and allowed to temperature equilibrate. The infinity value was recorded.

The rate constants were calculated using a linear least-squares fit of the integrated form of the first-order rate equation. The rate *vs.* concentration plots and the log rate *vs.* σ^+ plots were similarly calculated using a linear least-squares method, assuming variance in the rate constants only. All calculations were performed with an IBM 360, Model 50, computer.

Registry No.—Styrene, 100-42-5; *p*-bromostyrene, 2039-82-9; *p*-chlorostyrene, 1073-67-2; *p*-methylstyrene, 622-97-9; *p*-methoxystyrene, 637-69-4.

Acknowledgment.—We wish to thank Dr. C. E. Klopfenstein for his valuable assistance in writing the Fortran programs which we used for the calculations.

(25) L. A. Brooks, *J. Amer. Chem. Soc.*, **66**, 1295 (1944).

(26) J. F. Walker, "Formaldehyde," 3rd ed. Reinhold Publishing Corp., New York, N. Y., 1964, p 480.

(27) G. Natta and M. B. Baccaredda, *Giorn. Chim. Appl.*, **15**, 273 (1933), as cited in ref 26, p 110.

Alkanesulfonate Synthesis. I. Ion Catalysis of Sulfite Radical-Ion Addition to Olefins

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Certain nitrate salts have unusual, significant, and practical catalytic effects on the selective addition of the sulfite radical ion in the presence of oxygen to unsaturated bonds. Specific cations and anions have selective coinitiation catalytic effects with oxygen on the conversions of olefins into alkanesulfonates. The relative reactivities of homologous 1-alkenes, mixed 1-alkenes, internal *n*-alkenes, branched olefins, monocyclic olefins, bicyclic olefins, dienes, and acetylenes with potassium nitrate catalysis are compared. The competition conversion of hexene isomers indicates a *cis* effect inherent in the olefin activation for addition. The mechanism of the potassium nitrate catalysis and the stereochemistry of the sulfite radical-ion addition are discussed. A mechanism involving (1) the production of sulfite radical ion, directly or indirectly, by nitrate-ion oxidation of sulfite ion, (2) bisulfite ion in the chain-transfer reaction, and (3) termination by sulfite radical-ion oxidation and radical coupling is proposed. The product mixtures containing predominantly 1-alkanesulfonates have been analyzed and characterized. The presence of nitrogen in the organic sulfonate product indicates the incorporation of nitrogen-containing radical species.

Olefin-derived 1-alkanesulfonates have excellent biodegradability and also good surfactant properties[1-4] and hold promise of new markets for 1 olefins from cracked paraffin wax. They may directly reduce pollution problems and indirectly make more natural fats and oils available for human nutrition. These social and economic considerations, as well as organic chemical interests, make the bisulfite addition to olefins

(1) J. Rubinfeld and H. D. Cross, III, *Soap Chem. Spec.*, **43** (3), 41 (1967).

(2) "Chevron Alpha-Olefins for—Primary Paraffin Sulfonates—Secondary Alkyl Sulfates," Technical Bulletin, Oronite Division, California Chemical Co., Richmond, Calif., 1963.

(3) "Alkane Sulfonate Surfactants," Technical Bulletin 2-4-0664, Esso Research and Engineering Co., Linden, N. J. (about 1964).

(4) M. C. Fuerstenau and J. D. Miller, *Trans. Mining Soc. AIME*, 153 (1967).

a challenging and attractive reaction for review and research investigation.

The addition of bisulfite to unsaturated bonds is very old[5] in the art, but the reaction is still not well understood.

$$R{-}CH{=}CH_2 + NaHSO_3 \xrightarrow{\text{radical initiation}} R{-}CH_2CH_2SO_3Na \quad (1)$$

This reaction was reviewed by Kharasch, Mayo, and coworkers[6-8] who established (1) that the reaction requires an "oxidizing agent" for initiation, (2) that the reaction goes anti-Markovnikov giving 1-alkanesulfonate as the major product from 1 olefin, and (3) that the reaction is susceptible to radical-inhibiting reagents.

Mayo and Walling[9] proposed the reaction mechanism outlined below.

$$\text{initiation: } SO_3^{2-} + \text{oxidant} \longrightarrow \cdot SO_3^- + \text{oxidant}^- \quad (2)$$

$$\text{addition: } \cdot SO_3^- + RCH{=}CH_2 \longrightarrow R{-}\dot{C}HCH_2SO_3^- \quad (3)$$

$$\text{chain transfer: } R{-}\dot{C}HCH_2SO_3^- + HSO_3^- \longrightarrow RCH_2CH_2SO_3^- + \cdot SO_3^- \quad (4)$$

This reaction has received little critical study since the works cited above. The exact nature of the chain-carrying species has not been established since a bisulfite radical could also be involved.[10] Subsequent research has been largely reported in the patent literature.[11-19] Little attention has been given this reaction in subsequent reviews.[20,21]

Investigations in this area have been recently restimulated by the interest in converting readily available commercial 1 olefins into 1-alkanesulfonates, which have good detergent properties[1] and superior biodegradability properties,[2,3] but to date no one has carried this reaction to commercial production.

For practical purposes, the major problem has been to produce the organic sulfonates selectively under conditions which use close to stoichiometric amounts of sodium bisulfite reagent so as to obtain both good sulfonate yields and high sulfonate concentrations (*i.e.*, high activities) in the product mixtures. Initiations with peroxide reagents have been prohibitively expensive and have not been commercialized. Air initiation is often slow and wasteful of bisulfite owing to its by-product oxidation to sulfate. Efforts have been made to improve the rate of reaction, yield, and economics by cosolvents, surfactants, and slow dilute addition, but these modifications have not been entirely satisfactory.

It is not surprising that the reaction shows some improvement with solvent manipulation since the postulated addition species is a polar radical ion. Russell's[22] investigations of polar effects on radical reactions suggested to us that there might be some promise for specific salt catalysis on the reaction. With this purpose in mind, we undertook an extensive catalyst screening program.

Experimental Section

Reagents.—The sodium bisulfite used was Mallinckrodt reagent grade. 1 olefins were obtained from several sources, but primarily as follows. Propene, 2-methylpentene-1, 2-ethylbutene-1, 2,3-dimethylbutene-2, a mixture of *cis*-hexene-2 and *trans*-hexene-2, cyclohexene, and octene-2 (all of >98% purity) were obtained from the Phillips Petroleum Co. Octene-1, nonene-1, decene-1, undecene-1, dodecene-1, tetradecene-1, hexadecene-1, octadecene-1, eicosene-1, and docosene-1 (all of 95–99% purity) were obtained from the Humphrey Chemical Co.

The norbornene was synthesized from dicyclopentadiene and ethylene by the Diels–Alder addition reaction and fractionally distilled to obtain a cut of >95% purity.

Commercial mixtures of 1 olefins of 85–90% purity were obtained from The California Chemical Co.[23,24]

Reagent grade salts were investigated as catalysts.

Parr Autoclave Reaction Procedure.—The reactions of olefins were carried out in a Parr rocking autoclave apparatus. The 500-ml reaction vessel stopper was equipped with an oxygen inlet line and a glass thermocouple well. A typical procedure given below was used throughout the study.

Sodium bisulfite (21.0 g, 0.20 mol), potassium nitrate (2.2 g, 0.020 mol), 50.0 ml of distilled water, 50.0 ml of 2-propanol, and 1-hexadecene (24.4 g, 0.10 mol, 24.0 ml) were placed in a 500-ml Parr reaction vessel and assembled in the rocking apparatus. All valves were closed and a thermocouple was inserted into the thermocouple well in the rubber stopper which sealed the vessel. The apparatus heater and auxiliary heating jacket were turned on and allowed to warm for approximately 1 hr to 110° and 40–42-psig vessel pressure at equilibrium. The oxygen line pressure was adjusted to equal the equilibrium pressure. The vessel inlet valve was opened, and the applied oxygen pressure was increased to 1.0–2.0 psig in excess of the vessel pressure. The reaction was continued for 3 hr, then cooled.

The following procedure was used for the work-up: (1) the cooled vessel was depressurized by closing the oxygen valve and slowly opening the exhaust tank valve; (2) the cooled reaction mixture was transferred to a separatory funnel and the pH noted, 500 ml of distilled water was added, and the phase was allowed to separate; (3) a measured volume of standardized sodium hydroxide solution was added to adjust the pH to 8 in the aqueous phase; (4) the separated and neutralized aqueous phase was evaporated carefully to near dryness on a hot plate using a controlled air stream; (5) complete drying of the product was effected in a vacuum oven at partial vacuum at 80°; (6) the dried product was deoiled in a Soxhlet extraction thimble in which ether or acetone was refluxed for 4 hr; (7) dried products from steps 5 and/or 6 were submitted for sulfonate analyses, carbon, hydrogen, sulfur, and sodium, and in some cases nitrogen; and (8) recovered hydrocarbons from extraction and phase separation were analyzed by gas–liquid partition chromatography (glpc).

Analytical Procedures.—Glpc analyses confirmed the purity of the olefin reagents used and were used to check the composition of recovered oils.

In our early work ir spectra were used to characterize the alkanesulfonates and to estimate the amounts of sodium sulfate in the alkanesulfonate samples. Spectroscopic analyses for alkanesulfonate by the methylene blue complex absorption in

(5) I. Kolker and A. Lapworth, *J. Chem. Soc.*, **127**, 307 (1925).
(6) M. S. Kharasch, R. T. E. Schenck, and F. R. Mayo, *J. Amer. Chem. Soc.*, **61**, 3092 (1939).
(7) M. S. Kharasch, E. M. May, and F. R. Mayo, *J. Org. Chem.*, **3**, 175 (1939).
(8) R. T. E. Schenck, Ph.D. Thesis, University of Chicago, Chicago, Ill., 1940.
(9) F. R. Mayo and C. Walling, *Chem. Rev.*, **27**, 394 (1940).
(10) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, pp 326–328.
(11) J. H. Werntz, U. S. Patent 2,318,036 (1943).
(12) D. Harman, U. S. Patent 2,504,411 (1950).
(13) C. van Bylandtlaan, British Patent 682,207 (1952).
(14) W. A. Fessler, U. S. Patent 2,653,970 (1953).
(15) E. Clippinger, U. S. Patent 3,084,186 (1963).
(16) E. E. Johnson, U. S. Patent 3,150,169 (1964).
(17) E. Clippinger and R. G. McKee, U. S. Patent 3,168,555 (1965).
(18) W. A. Fessler, U. S. Patent 3,231,606 (1966).
(19) R. T. Adams, E. E. Johnson, and J. M. Salmela, U. S. Patent 3,306,931 (1967).
(20) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The Macmillan Co., New York, N. Y., 1964, pp 89–91.
(21) E. Clippinger, *Ind. Eng. Chem. Prod. Res. Develop.*, **3**, 3 (1964).
(22) G. A. Russell and R. C. Williamson, *J. Amer. Chem. Soc.*, **86**, 2357 (1964).
(23) "Chevron Alpha-Olefins," Technical Bulletin, Oronite Division, California Chemical Co., Richmond, Calif., 1963.
(24) *Oil Gas J.*, **63**, 102 (1965).

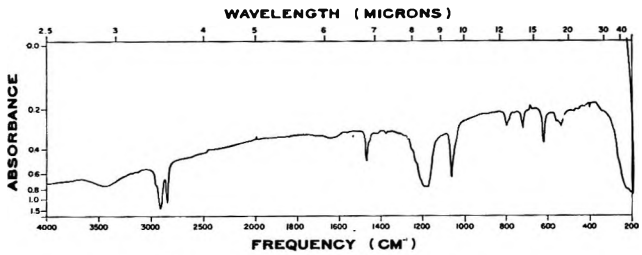


Figure 1.—Infrared spectrum of 1-hexadecanesulfonate.

the uv region and by ir absorption were often inconsistent with each other and elemental analyses. A barium alkanesulfonate precipitation procedure or inorganic salt precipitation procedure with methanol, followed by elemental analysis, was developed to characterize better the reaction products.

Calculations.—Olefin conversion based upon unrecovered olefins gives an estimate of the conversion (eq 5). Although

$$\text{Conversion} = \frac{[\text{input olefin vol.} - \text{recovered olefin vol.}]}{[\text{input olefin vol.}]} \times 100\% \quad (5)$$

often given in the literature, this conversion value is subject to errors due to olefin solubilization in the product surfactant solution at high conversion levels and some olefin loss on evaporation in the work-up. Conversions calculated on the basis of weight increase in the dried solid is more reliable, but the vacuum oven-dried sulfonates may contain 1–5 wt % oil. To get precise olefin conversion values, it is necessary to extract the dried product and correct the recovered oil therefrom.

The yield of deoiled alkanesulfonate is calculated from the eq 6.

$$\text{sulfonate yield} = \frac{\begin{array}{c}[\text{total weight of product mixture after drying and extraction to constant weight} - \text{weight of sodium bisulfite input (no correction for oxidation to sodium sulfate)}]\end{array}}{\begin{array}{c}[\text{theoretical alkanesulfonate weight calculated for the unrecovered oil on reaction with the stoichiometric amount of sodium bisulfite}]\end{array}} \times 100\% \quad (6)$$

The sodium sulfate formation would cause only a 5 wt % error in the sulfite weight if all of the bisulfite were oxidized to sulfate at 0% olefin conversion. The error is less at significant conversion levels.

Results

Results of screening a wide range of nitrate salts are summarized in Table I. The estimates of conversions based on the olefin recovery are contrasted with the more reliable conversions calculated by the weight increase of the recovered solid in the third and fourth columns. Theoretical yields were calculated based upon the unrecovered olefin and are valid for relative comparisons.

Table II summarizes results from a study of a variety of potassium salts. These screening conditions of Table II are different from those used for the data of Table I. In the column headed "Product composition," an analysis for the added potassium salt, the unused sodium sulfite, by-product sodium sulfate, and sodium alkanesulfonate is given for several of the products. (The alkanesulfonates are calculated from the organic carbon incorporated in the deoiled solid product. This carbon is assumed to be alkanesulfonate, although small amounts of the carbon may be present as organic by-products.) It is apparent that potassium nitrate gives the highest conversion and yield for production of alkanesulfonate and these results are confirmed by the product analysis.

TABLE I

SALTS SCREENED FOR CATALYSIS OF THE ADDITION OF SODIUM BISULFITE TO 1-DODECENE[a]

Run	Salt added	pH_o/pH_f[b]	Conversion, Based on unrecovered olefin, wt %	Conversion, Based on dried product,[c] wt %	Selectivity, theor yield based on unrecovered olefin,[d] mol
	None	5.4/3.4	24	22.5	86
	A. Cation Effect with Various Nitrates				
1	$Zn(NO_3)_2$, repeated	4.8/3.3, 1.6	55, 54	66.5, 58.4	100, 99
2	$Be(NO_3)_2$	4.9/5.3	48	50.0	95
3	$Bi(NO_3)_3$	4.2/3.0	54	54.8	93
4	$Hg_2(NO_3)_2$	5.4/6.0	49	49.6	92
5	$[Ce(NH_4)_2](NO_3)_6$	2.9/2.2	56	54.0	88
6	NH_4NO_3	5.5/9.6	56	54.0	88
7	$LiNO_3$	5.7/4.7	56	52.4	86
8	KNO_3	5.8/3.6	64	59.9	86
9	$Hg(NO_3)_2$	4.4/1.0	46	43.2	86
10	$Cd(NO_3)_2$	4.9/4.6	61	56.0	85
11	$Fe(NO_3)_3$	4.0/2.0	56	51.8	85
12	$Cr(NO_3)_3$	4.2/1.6	60	54.5	83
13	$Mg(NO_3)_2$	5.0/1.4	52	44.1	78
14	$Pb(NO_3)_2$	5.0/1.4	44	37.4	78
15	$Ni(NO_3)_3$	5.1/1.6	55	46.5	77
16	$AgNO_3$	5.8/3.6	44	35.9	75
17	Arqua[e] 12–50	5.2/1.3	40	32.0	75
18	$NaNO_3$	5.6/8.4	54	43.2	73
19	$Co(NO_3)_2$	5.0/1.9	58	43.5	69
20	$Al(NO_3)_3$, repeated	5.0/3.3, 3.0	Emulsion	51.6, 53.6	50, 61
21	$Cu(NO_3)_2$	4.5/1.0	11	0.0	0
	B. Anion Effects				
22	AgOAc	5.5/5.0	33	29.4	81
23	$AgNO_3$	5.8/3.6	44	35.9	75
24	$Zn(NO_3)_2$	4.8/3.3	55	66.5	100
25	ZnF_2	5.4/2.1	42	40.4	88
26	$Zn(OAc)_2$	5.2/5.7	53	48.3	83
27	$ZnBr_2$	4.9/3.0	50	43.2	79
28	$ZnSO_3$	5.4/5.2	14	11.4	74
29	$ZnSO_4$	5.0/3.1	45	34.5	70
30	$ZnCl_2$	4.8/3.9	20	14.3	66
31	ZnO	5.6/4.4	57	34.1	55
32	ZnI_2	4.8/1.7	6	0.3	5

[a] Conditions: 0.20 mol of $NaHSO_3$; 0.22 mol of 1-dodecene; 0.010 mol of salt; 50.0 ml of H_2O; 50.0 ml of 2-propanol; 1.0 psig of O_2 in Parr vessel at 80° for 2 hr. Product neutralized to pH 8.0. [b] All product mixtures were adjusted to pH 8 with standard base before work-up. [c] According to eq a. [d] According to eq b.

$$\text{wt \% conversion} = \frac{\text{solid wt increase, g}}{\text{33.6 g (0.2 mol) of } C_{12}H_{24} \text{ theor max wt increase}} \times 100\% \quad (a)$$

$$\text{mol theor yield} = \frac{\text{solid wt increase, g}}{\text{theor wt of } C_{12}H_{25}SO_3Na \text{ for olefin unrecovered}} \times 100\% \quad (b)$$

[e] 50% active solution of dodecyl trimethylammonium chloride.

Superficially, the ir spectra of the recrystallized products obtained by potassium nitrate catalysis with 1 olefins compare closely with spectra of alkanesulfonates in the literature.[25,26] The spectrum of 1-hexadecane sulfonate is given in Figure 1.

Table III summarizes the elemental analysis of a homologous series of alkanesulfonate products obtained using potassium nitrate catalyst.

These alkanesulfonates were isolated from the product mixture by recrystallization from aqueous alcohol solution one or more times. The empirical carbon values are all lower than theory for 1-alkanesulfonates, and the empirical sulfur values and most of the sodium values are higher than theory for 1-alkanesulfonates, suggesting the presence of alkanedisulfonate. This

(25) D. Hummel, "Identification and Analysis of Surface-Active Agents by Infrared and Chemical Methods," E. A. Wulkow, translator, Interscience Publishers, New York, N. Y., 1962.

(26) K. Fujimori, *Bull. Chem. Soc. Jap.*, **32**, 850 (1959).

TABLE II

POTASSIUM SALT CATALYST STUDY[a]

Salt added	pH_o/pH_f	Product composition, wt %: Added salt	Na_2SO_3	Na_2SO_4	RSO_3Na	Conversion based on unrecovered 1-dodecene, wt %	Theor yield based on 1-dodecene input, mol %
Blank (none)	4.9/3.8		57.14	30.27	7.0	10	2.9
KNO_3	5.0/2.4	0.58	0.00	26.59	72.12	51	51.3
KNO_2	5.5/3.5	0.00	33.31	52.24	13.15	17	6.2
KNO_2/KNO_3 (50:50)						42 (interpolated 34)	
KBr	4.6/3.4	6.90	10.54	61.86	20.72	25	13.5
KCl	4.8/4.1	5.11	15.37	69.69	9.84	31	4.7
KI	4.4/3.5	11.84	55.86	26.20	4.74	22	1.4
KF	4.8/3.8		43.87	42.65	13.48	13	6.8
K_2SO_4						22	
KOAc						20	
$KBrO_3$						13	
KSCN						21	
K_2CO_3						34	
K_2HPO_4						19	

[a] Conditions: 0.20 mol of $NaHSO_3$; 0.20 mol of 1-dodecene; 0.020 mol of salt; 50.0 ml of water; 50.0 ml of 2-propanol; and 2.0 psig of O_2 in Parr vessel with shaking at 110° for 3 hr.

TABLE III

ELEMENTAL ANALYSES OF RECRYSTALLIZED[a] ALKANESULFONATES PREPARED FROM 1-ALKENES[b]

Carbon no.	Conversion, wt %	Yield, mol %		% C	% H	% Na	% S	% N	% O (by difference)
6	100.0	100.0	Calcd	38.29	6.96	12.21	17.04	0.00	25.50
			Found	31.56	5.73	13.19	17.65	0.42	31.45
6 (2-ethyl-1-butyl)	100.0	100.0	Calcd	38.29	6.96	12.21	17.04	0.00	25.50
			Found	37.24	7.05	12.18	17.11	0.26	26.16
8	91.6	92.6	Calcd	44.43	7.92	10.63	14.83	0.00	22.19
			Found	38.75	7.02	11.22	19.82	0.27	22.92
9	95.2	95.7	Calcd	46.94	8.32	9.98	13.92	0.00	20.84
			Found	39.86	7.23	10.84	15.44	0.30	26.33
10	97.8	89.3	Calcd	49.16	8.66	9.41	13.12	0.00	19.65
			Found	47.68	8.51	8.89	12.89	0.39	21.64
10 (repeat)			Calcd	49.16	8.66	9.41	13.12	0.00	19.65
			Found	37.99	7.09	11.99	16.71	0.49	25.73
12	97.7	78.0[c]	Calcd	52.91	9.19	8.46	11.74	0.00	17.70
			Found	52.74	9.09	8.23	11.48	0.50	17.96
14	97.0	97.3	Calcd	55.96	9.75	7.65	10.67	0.00	15.97
			Found	55.36	9.78	7.92	10.95	0.50	15.49
16	95.1	84.2	Calcd	58.50	10.12	7.00	9.76	0.00	14.62
			Found	56.59	9.92	7.68	10.88	0.70	14.23
18	94.8	91.9	Calcd	60.63	10.46	6.45	8.99	0.00	13.47
			Found	58.69	10.07	6.54	9.13	0.50	15.07
20	93.9	96.7	Calcd	62.46	10.74	5.98	8.34	0.00	12.48
			Found	61.03	10.59	6.07	8.84	0.70	12.77
22	72.8	73.8	Calcd	64.03	10.99	5.57	7.77	0.00	11.64
			Found	62.29	10.80	5.48	8.08	0.10	13.25

[a] Recrystallized from aqueous 2-propanol. [b] Conditions: 0.20 mol of $NaHSO_3$; 0.10 mol of olefin; 0.020 mol of KNO_3; 50.0 ml of H_2O; 50.0 ml of 2-propanol; 2.0 psig of O_2 in Parr vessel with shaking at 110° for 3 hr. [c] Lower yield due to use of 0.10 mol of $NaHSO_3$ and 0.010 mol of KNO_3.

interpretation has been explicitly confirmed by subsequent analyses.[27]

A variety of olefins of differing molecular weight and structure was reacted using potassium nitrate catalyst. Conditions and results are summarized in Table IV. A more accurate and reliable comparison of molecular weight and structural effects upon reactivity was made under conditions of competitive reaction summarized in Table V and Figure 2.

Discussion

A radical-ionic character of this reaction is well established.[6] Therefore, in light of the fact that even nonionic radical reactions have been shown by reinvestigation[22] to be very susceptible to solvent and salt effects, it is not surprising that this reaction should show considerable susceptibility to polar effects as well.

Solvent Effects.—The starting reaction mixture has three liquid phases; a nearly complete conversion gives a single liquid phase at the reaction temperature. So solvent effects are critical, complicated, and vary over the course of the reaction. Kohler and Lapworth[5] in their early work claim that dilution favors the reaction. Mayo and Walling[9] state, "The yields of addition products from the less reactive alkenes are decreased by the use of either alcohol or hydrocarbon solvent and slightly increased by the use of ethylenediamine." Clippinger's[21] studies and our investigations of aqueous alcohol solvents, summarized in Table VI, show that 1-propanol is the best alcohol solvent

(27) C. J. Norton, unpublished results.

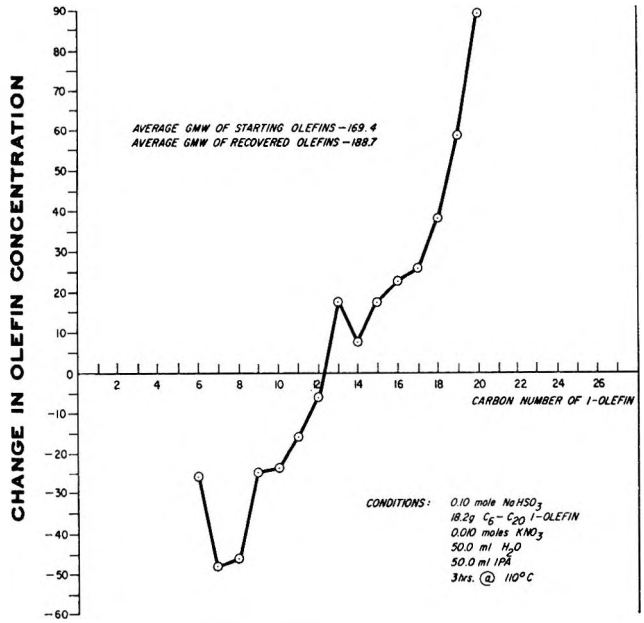


Figure 2.—Competitive reaction of 1-olefin homologs for bisulfite addition.

TABLE IV

THE EFFECTS OF OLEFIN STRUCTURE ON CONVERSIONS INTO ALKANESULFONATE[a]

Hydrocarbon reactant	Conversion, wt%
A. Effect of Isomeric Olefins	
2-Methylpentene-1	99.0
2-Methylpentene-2[b]	88.7
2,3-Dimethylbutene-2[b]	71.0
Hexene-1[b]	52.8
Hexene-2[b] (92.5% *cis*, 7.5% *trans*)	38.4
B. Effect of Molecular Weight	
Hexene-1	97.0
Octene-1	92.5
Nonene-1	95.5
Decene-1	97.8
Dodecene-1	94.6
Tetradecene-1	97.3
Hexadecene-1	95.0
Octadecene-1	94.9
Eicosene-1	81.8
Docosene-1	69.6
Equimolar mixture of C_6–C_{16} 1 olefins	54.7
C. Effect of Cyclic Structure	
Cyclohexene	37.1
Cyclododecene[c]	23.7
Norbornene[c]	83.0
D. Miscellaneous Olefins	
1,7-Octadiene[c]	100.0
Styrene[c]	100.0
1-Decyne	22.9

[a] Conditions: 0.20 mol of $NaHSO_3$; 0.10 mol of olefin; 0.02 mol of KNO_3; 50.0 ml of 2-propanol; 50.0 ml of water; 2.0 psig of O_2 in Parr vessel with shaking at 3 hr at 110°. [b] Run at 1:1 bisulfite to olefin ratio at 80°. [c] 0.02 mol of KNO_3 used.

and is very much superior to water. Ethylenediamine is not a good solvent under our reaction conditions. For practical synthetic reasons most of our work employed the cheaper 2-propanol.

Under conditions of photoinitiation, spectacular solvent effects have been demonstrated,[28] but we find solvent effects are not so large in the absence of photoinitiation.

TABLE V

COMPETITIVE ADDITION OF SULFITE TO HEXENE ISOMERS[a]

Hexene isomer	Conversion,[b] wt %
2-Methylpentene-1	95.8
Hexene-1	86.5
2,3-Dimethylbutene-2	72.8
Cyclohexene	69.1
Hexene-2, *cis* (2.3 g input, 0.39 g recovered)	
Hexene-2, *trans* (0.19 g input, 1.00 g recovered)	44.2
Total mixture	74.6

[a] Conditions: 0.20 mol of $NaHSO_3$; 0.10 mol of hexene; 0.020 mol of KNO_3; 50.0 ml of H_2O; 50.0 ml of 2-propanol; 2.0 psig of O_2 in Parr vessel with shaking at 95° for 3 hr. [b] Determined by weight and gas–liquid partition chromatographic analysis of recovered olefins.

TABLE VI

SOLVENT EFFECTS ON SULFITE ADDITION[a] TO 1-DODECENE

Solvent	Conversion, wt %
Water	7.0
Methanol	51.6
Ethanol	68.5
1-Propanol	85.4
2-Propanol	58.9
1-Butanol	16.8
2-Butanol	2.7
2-Methyl-2-propanol	4.0
1,4-Butanediol	10.3
Ethylenediamine	4.9

[a] Conditions identical with those in Table II except for the variation in solvents. Oxygen partial pressure fixed at 5% over the solvent pressure at 110°. Recovered and washed olefin analyzed by gas–liquid partition chromatography.

pH Effects.—Reported optimums in the literature range widely from pH 5 to 9. Mayo[9] reports that the optimum pH for the reaction is 5.1–6.1. The more recent literature[19] indicates that the optimum is near pH 7. In our research, we found the reaction proceeds best within the pH range 5–7 where there is a good proportion of both sulfite and bisulfite ions (Table VII). These pH observations suggest that both ions may be involved in the propagation phase of the reaction.

TABLE VII

EFFECT OF pH ON SULFITE ADDITION[a] TO 1-DODECENE

Reaction time, hr	Initial pH	Final pH	Conversion, wt %
0.5	4.5	3.7	18.2
3.0	4.5	1.3	45.5
3.0	6.1	3.7	74.1
3.0	7.0	10.0	73.5
3.0	7.1	12.1	86.7
3.0	8.0	9.3	32.2

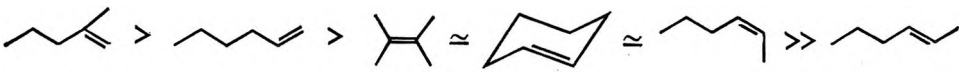
[a] Conditions identical with those in Table II. Initial pH adjusted with 40% aqueous potassium hydroxide and water to give a total water volume of 50.0 ml.

The pH and ionization constants determine the ion species distribution of the sulfite–bisulfite reagent as indicated on Figure 3.[29] The addition of 2-propanol shifts the pH of the reaction solution by only +0.2 of a unit. At an initial pH of 5, the reagent is present as about 30% sulfite and 70% bisulfite; at an initial pH

(28) C. L. Furrow and C. E. Stoops, *Div. Petrol. Chem., Preprints*, **12**, D-107 (1967).

(29) "Sodium Metabisulfite," Technical Bulletin 1-250, Monsanto Corp., St. Louis, Mo. (about 1965).

CHART I



of 6, the reagent is present as about 85% sulfite and 15% bisulfite. The desired reaction (eq 1) has the net effect of removing bisulfite protons from the solution and, therefore, produces a net basic reaction. The undesired side reaction is the two-electron oxidation of bisulfite to bisulfate which produces an acidic reaction. The change of the pH during the course of the reaction can be diagnostic and depends upon the proportions of these two reactions. If the addition reaction predominates, there is generally a drift to higher pH's, whereas if the acid-producing by-product reaction predominates, the drift is to lower pH's. The initial and final pH's of our reaction solutions are recorded in Tables I, II, and VII. Unfortunately, the Parr apparatus was not amendable for recording and controlling the pH during the course of the reaction. Since our screening runs in Table I contain excess sulfite reagent which is ultimately oxidized to sulfate, the reactions usually go acid even under conditions of good conversion into sulfonate; so the over-all changes are of no interpretive value in these screening experiments. When a 1:1 sulfite to olefin ratio is used, as in Table VII, the best conversions are accompanied by drifts to high final pH's. Obviously, a high concentration of sulfite ion favors the reaction, but initial pH's of 8.0 or above are unfavorable for the reaction, presumably because the concentration of bisulfite is too low to sustain the chain-transfer reaction step.

Effect of Olefin Molecular Weight and Structure.—Very high conversions and yields can be obtained with 1 olefin ranging from hexene-1 to docosene-1 under conditions of potassium nitrate catalysis. When an approximately equimolar mixture of olefins reacts competitively, but incompletely, the differences in olefin reactivity are well demonstrated by comparing the analysis of the initial olefin mixture with that of the recovered olefin mixture. The per cent changes for each olefin concentration are plotted against carbon number in Figure 3. The lower molecular weight olefins are more reactive than the higher molecular weight olefins owing to their greater solubility in the aqueous phase of reaction emulsion.

The effects of the olefin structures are compared individually in Table IV and competitively for isomeric hexenes in Table V. The order of hexene reactivities observed is shown in Chart I. The greater reactivity of *cis* over *trans* olefinic structures is indicated by the fact that, when a mixture of 76.5% *cis*- and 23.5% *trans*-hexene-2 reacts, the recovered hexene-2 is greatly enriched in *trans* over its original concentration. Indeed, more *trans*-hexene-2 is recovered than was put into the reaction owing to the rapid isomerization of *cis*-hexene-2 to *trans*-hexene-2 by the reversible addition of sulfite radical ion to the olefin. The *cis* olefins are more reactive than the *trans* olefins owing to higher energy ground states—the so-called *cis* effect. The reactivity order of norbornene, cyclohexene, and cyclododecene is also consistent with increasing *cis*-double-bond strain (Table IV).

The substitution of the terminal double bond with a methyl group at the 1 position reduces reactivity for

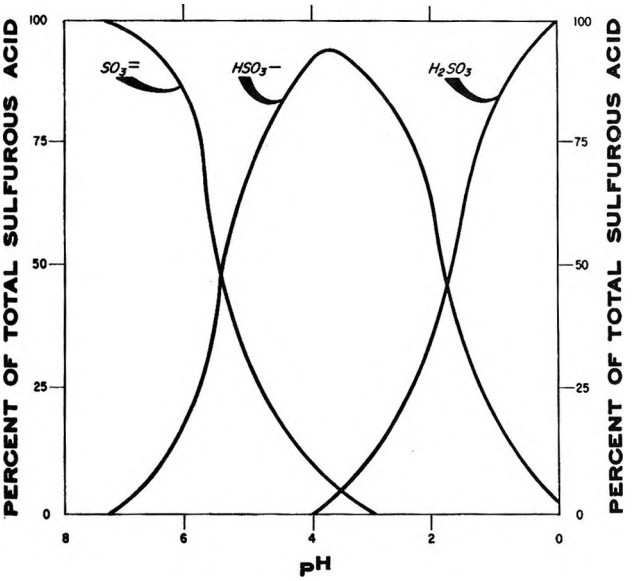


Figure 3.—Effect of pH on distribution of sulfurous acid in solution.[23]

sulfite radical-ion addition for electronic reasons, while, conversely, methyl substitution at the 2 position enhances reactivity, possibly by stabilizing the alkanesulfonate radical-ion intermediate. Steric inhibition for the addition by one, two, or three methyl group on the double bonds appears to be small relative to the electronic effects. These small steric effects are consistent with the interpretation that the sulfite radical ion approaches in the plane of the π bond rather than in the plane of the σ bond and alkyl groups.

Nitrate Catalysis.—Copper nitrate gives very poor results owing to efficient catalysis of cupric ion for the oxidation of the bisulfite to sulfate. Most of the metal nitrates, which do not accelerate bisulfite oxidation to sulfate,[30] are beneficial to the reaction, largely owing to the nitrate effect. Ammonium, alkali, and alkaline earth nitrates give good catalysis because the cations are not catalytic for the oxidation of sulfite to sulfate.

The over-all catalytic effect of potassium nitrate is due to the nitrate ion. This is demonstrated by varying the anions associated with nitrate in Table II. The product analysis confirms that the nitrate is very selective for high conversions and yields of alkanesulfonate. Lithium and ammonium nitrates are very effective, but potassium is more practical for our synthetic interests.

Kharasch, May, and Mayo[7] reported that the system sodium nitrite–sodium nitrate is an effective "oxidizing agent" in the absence of air for initiating the addition of bisulfite to olefins. We find potassium nitrite with oxygen to be an inferior catalyst when compared with potassium nitrate. Table II shows that a 50:50 mixture of potassium nitrate and potassium nitrite is more effective than anticipated for the average but not so good as potassium nitrate alone. No nitrite could be detected in the product mixture. The

(30) M. Gerendas, *Z. Physiol. Chem.*, **254**, 184 (1938).

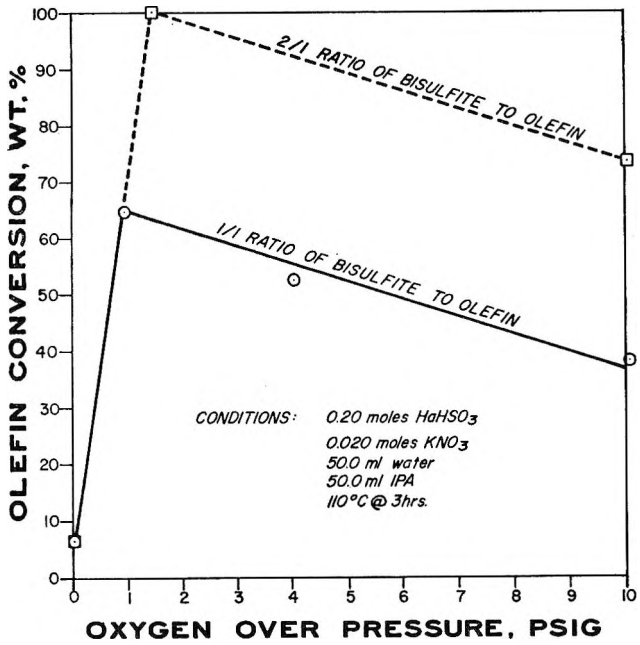


Figure 4.—Optimum oxygen pressure depends on bisulfite to olefin ratio.

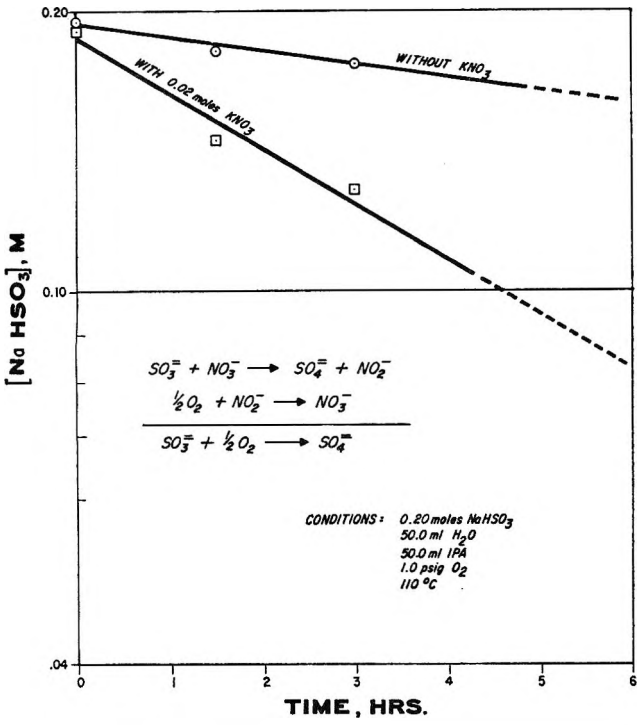


Figure 5.—Potassium nitrate catalyzes the oxidation of bisulfite.

nitrite ion is oxidized to nitrate under these reaction conditions and the effective anion is the nitrate anion. Nitrite is probably less effective than nitrate, because it consumes oxygen and it takes time to oxidize it to nitrate.

Only about 10% of the potassium nitrate is accounted for by direct analysis of the product mixture. Some nitrogen is incorporated into the organic product (Table III).

The effect of potassium nitrate concentration was also investigated. An adequate relative concentration of the nitrate is about 10 mol % of the bisulfite concentration. The oxygen partial pressure used in conjunction with the nitrate promoters is also important; 1.0 psi is optimum for a 1:1 bisulfite to olefin ratio and 2.0 psi is optimum for a 2:1 bisulfite to olefin ratio (Figure 4). Too much oxygen inhibits formation of alkanesulfonate.

The effect of potassium nitrate on the oxidation of bisulfite in the absence of olefin was investigated, and results are presented in Figure 5, wherein it is demonstrated that potassium nitrate exerts its function by catalyzing the air oxidation of sodium bisulfite. Sulfite is more readily oxidized by air at pH 7.4 than at lower pH's.[30] The nitrate ion is a catalyst for the oxidation of sulfite under acidic conditions.[31] Apparently, it is also more selective in effecting the one-electron transfer oxidation of a sulfite anion to a sulfite radical ion than oxygen alone.

In summary, a proposed mechanism for this reaction is outlined below.

initiation: $\left[:\ddot{O}:\right]^- + \left[\begin{matrix}:\ddot{O}:\\ :\ddot{O}:\ddot{N}\\ :\ddot{O}:\end{matrix}\right]^- \longrightarrow \left[\begin{matrix}:\ddot{O}:\\ :\ddot{O}:\ddot{N}\cdot\\ :\ddot{O}:\end{matrix}\right]^- + \left[\begin{matrix}:\ddot{O}:\\ \cdot\ddot{S}:O:\\ :\ddot{O}:\end{matrix}\right]^-$ (7)

$$\cdot NO_2 + SO_3^{2-} \longrightarrow NO_2^- + \cdot SO_3^- \quad (8)$$

$$O_2 + SO_3^{2-} \longrightarrow [\cdot O_2^-] + \cdot SO_3^- \quad (9)$$

propagation: $\cdot SO_3^- + RCH{=}CH_2 \rightleftharpoons R\dot{C}HCH_2SO_3^-$ (10)

$$R\dot{C}HCH_2SO_3^- + HSO_3^- \longrightarrow RCH_2CH_2SO_3^- + \cdot SO_3^- \quad (11)$$

termination: $\cdot SO_3^- + {}^1/_2O_2 \longrightarrow SO_4^{2-}$ (12)

$$R\dot{C}HCH_2SO_3^- + \cdot SO_3^- \longrightarrow \underset{\displaystyle SO_3^-}{RCHCH_2SO_3^-} \quad (13)$$

$$R\dot{C}HCH_2SO_3^- + \cdot X \longrightarrow \underset{\displaystyle X}{RCHCH_2SO_3^-} \quad (14)$$

Initiation may be effected by a number of "oxidizing agents." Nitrate is known to initiate the reaction in the absence of oxygen.[7,12] Obviously, under the conditions we studied, nitrate anion is directly or indirectly an initiator. But the precise mechanism by which nitrate manifests its initiation is debatable. Direct reaction of a nitrate anion with a sulfite anion is appealing for the isoelectronic simplicity (eq 7), but unlikely because of the strong electrostatic repulsion between the negatively charged ions. A more likely mechanism of nitrate catalytic initiation is its decomposition to nitrogen dioxide, a stabile free radical, which is present at low concentration in equilibrium with nitric acid[31] under the reaction conditions (eq 8). The nitrite ion is reoxidized slowly by oxygen to nitrate under the reaction conditions. This explains why nitrite is a less effective initiator than nitrate. There is also a significant amount of oxygen coinitiation under these conditions as well (eq 9). The easiest sulfite ion from which to remove an electron would be the divalent sulfite, giving rise to a sulfite radical ion.

Propagation (eq 10 and 11) is effected by the addition of the sulfite radical ion to the olefin to give a radical intermediate which rapidly chain transfers with bisulfite

(31) W. M. Latimer and J. H. Hildebrand, "Reference Book of Inorganic Chemistry," rev ed, The Macmillan Co., New York, N. Y., 1940, pp 195–207, 247–248.

ion in solution, one of the sources of labile hydrogen, to regenerate the sulfite radical ion.

Termination (eq 12–14) of the reaction may result by a number of processes. One is the consumption of the sulfite by oxidation to sulfate or bisulfate ion—an undesirable side reaction which is catalyzed by many transition metals.[30] Several coupling reactions may be postulated from analogy to radical reactions in general. As the concentration of the radical species becomes appreciable, alkanesulfonate radical may couple with sulfite radical ion to produce a disulfonate. We have analytical results that show substantial amounts of disulfonate of these molecular proportions are produced.[27] Conceivably, two of the alkanesulfonate radicals may couple to produce a higher molecular weight disulfonate for which we have no evidence.

Registry No.—Table I—1, 7779-88-6; 2, 13597-99-4; 3, 10361-44-1; 4, 10415-75-5; 5, 10139-51-2; 6, 6484-52-2; 7, 7790-69-4; 8, 7757-79-1; 9, 10045-94-0; 10, 10325-94-7; 11, 10421-48-4; 12, 13548-38-4; 13, 10377-60-3; 14, 10099-74-8; 15, 15099-34-0; 16, 7761-88-8; 17, 112-00-5; 18, 7631-99-4; 19, 10141-05-6; 20, 13473-90-0; 21, 3251-23-8; 22, 563-63-3; 25, 7783-49-5; 26, 557-34-6; 27, 7699-45-8; 28, 13597-44-9; 29, 7733-02-0; 30, 7646-85-7; 31, 1314-13-2; 32, 10139-47-6; 1-dodecene, 112-41-4; 1-hexadecanesulfonate, 6140-88-1; sodium bisulfite, 7631-90-5.

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Neighboring-Group and Substituent Effects in the Solvolysis of Substituted α-Bromophenylacetate Ions[1]

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A study of the rates of solvolysis of *meta*- and *para*-substituted α-bromophenylacetate ions was made in an attempt to help clarify the nature of the intermediate in the solvolysis of α-halocarboxylate ions. The first-order rate constants were correlated with the Hammett equation and ρ was found to be −2.66 at 25.0° and −2.74 at 35.6°, the solvent being 0.681 *M* aqueous acetone; in 80% methanol, ρ was −2.33 at 25.0°. The reaction does not appear to be very sensitive to base concentration, ionic strength, or solvent effects. A striking similarity is noted between the α-bromophenylacetate and α-bromopropionate ions in terms of salt and solvent effects as well as the values of the activation parameters. It is suggested that the similarities in the ρ value for the solvolysis of the α-bromophenylacetate ions with those for the solvolysis of benzyl derivatives in nucleophilic solvents is a consequence of neighboring carboxylate participation. The value of ρ suggests that the intermediate is an α-lactone with much ionic character.

One of the earliest known examples of the neighboring-group effect is that involving carboxylate participation.[3-6a] The classical work of Cowdrey, Hughes, and Ingold suggested the existence of an α-lactone intermediate during the solvolysis of α-bromopropionate ion. Although β-lactones and larger membered ring lactones have been isolated from the solvolysis of the corresponding halocarboxylate ions,[6a,7] the unstable α-lactone has not, and, as Streitwieser points out, the intermediate has been described as a zwitterion, an α-lactone with much ionic character, and simply an α-lactone. The nature of this intermediate has been thoroughly studied by Grunwald and Winstein[4] in terms of the effects of ionic strength and solvent upon the rate of solvolysis of α-bromopropionate. Their results indicate the creation of a small amount of additional charge in the transition state relative to the ground state.

The present account reports another approach designed to obtain additional information about the "α-lactone" intermediate. The Hammett reaction constant ρ has been evaluated for the solvolysis of several substituted α-bromophenylacetate ions since ρ can be interpreted as a measure of the change in the electron density between the ground state and the transition state at the reaction site.[8] Moreover, a reasonable extension of the Hammond postulate[9] suggests that a reactive intermediate and the transition state leading to it should closely resemble one another. The magnitude of ρ, according to Swain and Langsdorf,[8] can be interpreted in terms of bond making and bond breaking and should therefore be a measure of the electronic structure of the "α-lactone" intermediate.

The kinetics of the solvolysis of *p*-OCH_3-, *p*-H-, *p*-Cl, *m*-NO_2-, and *p*-NO_2-α-bromophenylacetates were determined, as well as the activation parameters for several of the compound. Salt and solvent effects were also studied to a limited extent.

Results and Discussion

Kinetics.—First-order rate constants for the hydrolysis of several substituted sodium α-bromophenylacetates in 0.681 *M* aqueous acetone are presented in Table I. The hydrolyses were carried out on the sodium salts of the bromo acids in the presence of an equivalent amount of sodium hydroxide and at

(1) (a) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract S97. (b) Based in part on the M.S. Thesis of D. Metzger, 1967.

(2) National Science Foundation Cooperative Fellow, 1964–1966.

(3) W. Cowdrey, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1028 (1937).

(4) E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, **70**, 841 (1948).

(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp 383–386.

(6) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y.: (a) pp 116–119; (b) pp 75,76.

(7) B. Capon, *Quart. Rev.* (London), **18**, 45 (1964).

(8) C. G. Swain and W. P. Langsdorf, *J. Amer. Chem. Soc.*, **73**, 2813 (1951).

(9) G. S. Hammond, *ibid.*, **77**, 334 (1955).

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF SUBSTITUTED α-BROMOPHENYLACETATE IONS IN 0.681 *M* AQUEOUS ACETONE[c]

Substituent	$k_1 \times 10^4$,[b] sec^{-1} 25.03°	$k_1 \times 10^4$,[b] sec^{-1} 35.6°	ΔH^*, kcal/mol	ΔS^*, eu
p-OCH_3	293[e]			
p-H	3.12[d]	15.0[e]	26.6	14.2
p-Cl	1.66	7.95	26.5	13.1
m-NO_2	0.0415	0.222	28.4	14.9
p-NO_2	0.0222			

[a] Reproducibility based upon the average of two or more runs is about 2% or better. [b] [Base] = [acid salt] = 0.02543 *M*; *I* = 0.551. [c] Evaluated at pH = 2.0. [d] Lit. $k_1 = 2.45 \times 10^{-4}$ sec^{-1} [G. Senter and S. H. Tucker, *J. Chem. Soc.*, **109**, 690 (1916)]. The literature value is probably lower because base was not present to neutralize the HBr produced. [e] Calculated from measurements at 25.03 and 15.6°.

constant ionic strength. Sodium perchlorate was used as the inert salt. Under these conditions linear first-order plots were obtained, the reactions being followed to about 80% completion. The reactivity of the compounds corresponds to the anticipated trend for the solvolysis of benzyl derivatives; *i.e.*, the susceptibility toward hydrolysis decreases as the electron-withdrawing power of the substituent increases.

Even though excellent first-order plots were obtained when the reactions were carried out in the presence of an equivalent amount of base, hydrolyses were also studied using a ninefold excess of base to determine the possible importance of a second-order reaction between hydroxide and substrate. Linear first-order plots were obtained to approximately 75% reaction for the unsubstituted, *p*-chloro-, and *m*-nitro-α-bromophenylacetates. Excess base was found to have no effect upon the rate of hydrolysis of the unsubstituted acid, and only a small rate enhancement was noted for the *p*-chloro- and *m*-nitro-α-bromophenylacetates. These observed first-order rate constants are given in Table II along with second-order rate constants which were evaluated as discussed below. If the hydrolysis were first order in solvent as well as substrate, the presence of excess hydroxide ion, which is a much better nucleophile than water, should cause a significant increase in the rate of hydrolysis. Accordingly, the data in Table II suggest the reaction is not first order in solvent.

TABLE II

KINETICS OF HYDROLYSIS OF SODIUM α-BROMOPHENYLACETATES IN 0.2089 *N* SODIUM HYDROXIDE[a]

Substituent	$k_{obsd} \times 10^4$, sec^{-1}	$k_1 \times 10^4$, sec^{-1}	$k_2 \times 10^4$, l./(mol sec)
p-H	3.10	3.12	0.0
p-Cl	1.80	1.66	0.67
m-NO_2	0.0728	0.0415	0.15

[a] Solvent 0.681 *M* aqueous acetone; [acid salt] = 0.02543 *M*; temp, 25.03°; *I* = 0.551.

If it is assumed that the hydrolysis occurs both by first- and second-order processes in the presence of excess base, the rate expression may be represented as

$$-dA/dt = k_1A + k_2A[OH] \quad (1)$$

where *A* and [OH] refer to the substrate and hydroxide concentrations, respectively. If the hydroxide concentration is essentially constant, eq 1 becomes

$$-dA/dt = k_{obsd}A \quad (2)$$

where

$$k_{obsd} = k_1 + k_2[OH] \quad (3)$$

The values of k_2 in Table II were obtained from eq 3 and the values of the first-order constants from Table I. Because the rate enhancements in excess base are relatively small, the values of k_2 are subject to considerable error and are considered as approximations. Under the conditions which k_1 was evaluated, *viz.*, equal substrate and base concentrations, the half-life for the second-order process for the *p*-chloro compound is 145 times greater than the half-life for the first-order reaction. For the *m*-nitro compound the corresponding factor is 17. This, in conjunction with the linearity of the first-order plots, suggests that first-order constants of Table I are reasonably reliable and do not contain significant contribution from the bimolecular process.

Reliable results for *p*-nitro-α-bromophenylacetate ion at the high base concentrations could not be obtained. The solutions darkened almost immediately; this may be a consequence of an oxidative coupling reaction.[10]

The relatively large activation parameters for these α-bromophenylacetates (see Table I) are quite comparable with the values for the hydrolyses of other α- and β-bromocarboxylate ions.[6a] For example, the enthalpy and entropy of activation for α- and β-bromopropionate[11] ions are 29.7 kcal/mol and 11.4 eu and 28.7 kcal/mol and 12.7 eu, respectively. These relatively large activation parameters have been attributed to solvation effects. In particular, the large entropy has been associated with the desolvation of the carboxylate group in the transition state. A recent study of Kingsbury[12] of the solvolysis of bromo acids in dimethylsulfoxide (DMSO)–water solutions supports this interpretation.

Medium Effects.—The sensitivity of the solvolyses to salt and solvent effects for the unsubstituted, *p*-Cl, and *m*-NO_2 derivatives were studied, and the results are summarized in Table III. The ratio $k_{0.5}/k_{0.05}$ refers to

TABLE III

SALT AND SOLVENT EFFECTS FOR THE SOLVOLYSIS OF α-BROMOPHENYLACETATES AT 25.03°

Substituent	$k_{0.5}/k_{0.05}$	k_{H_2O}/k_{MeOH}
p-H	1.13	4.52
p-Cl	1.12	5.68
m-NO_2	1.04	1.97

the ratio of the first-order rate constants at ionic strengths of 0.551 and 0.0509, the solvent being 0.681 *M* aqueous acetone. Similarly, k_{H_2O}/k_{MeOH} refers to the ratio of first-order rate constants for the solvents 0.681 *M* aqueous acetone and 80% (v/v) methanol, the ionic strength being 0.551. The data showed that the reaction is not very sensitive either to ionic strength or to solvent effects. These results are remarkably similar to those reported for the α-bromopropionate ion by Grunwald and Winstein.[4] An increase of approximately 6% was noted for the first-order rate constant

(10) G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, **89**, 300 (1967).
(11) J. F. Lane and H. W. Heine, *ibid.*, **73**, 1348 (1951).
(12) C. A. Kingsbury, *ibid.*, **87**, 5409 (1965).

for α-bromopropionate ion when the ionic strength was increased from 0.06 to 0.99, while the rate of solvolysis in water was approximately twice that in methanol. These effects are slightly less than those observed for the α-bromophenylacetates, but not markedly so. In general, the change from water to methanol decreases the rate of solvolysis of halocarboxylate ions by a factor of less than ten.[6a]

Salt and solvent effects are minimal for the m-NO_2 derivative. Since the nitro group does not stabilize the developing charge at the benzyl position, participation by the carboxylate group should be more extensive for this derivative than for the unsubstituted acid and thus produces a less ionic transition state. It may seem, at first, that this participation should manifest itself in a discernible manner in the entropies of activation for this series; however, there are two opposing effects which tend to offset one another. The more extensive the participation, the larger the number of solvent molecules freed, while on the other hand, the greater is the constraint imposed upon the bromo acid. This may account for the near constancy of the entropies noted in Table I. This interpretation is in accord with the results of the studies of Kingsbury[12] on the solvolysis of 3-bromopropionate in DMSO–water solutions. As the concentration of DMSO was increased, the carboxylate group became a more effective nucleophile because of decreased solvation. The solvolysis rate in 80% (v/v) DMSO was 290 times greater than in water. The entropy of activation decreased from +4.6 eu in water to −6.5 eu in 80% DMSO, apparently because there were fewer solvent molecules to be released by the carboxylate group.

Hammett Relationship.—A Hammett plot for the first-order rate constants using σ^+ is presented in Figure 1. The values of ρ at 25.03° are −2.66 in aqueous acetone and −2.33 in 80% (v/v) methanol. In many cases benzylic systems do not give linear plots because of competition of unimolecular with bimolecular reaction mechanisms.[6b,13] The linearity displayed in Figure 1 is probably fortuitous, since the point corresponding to the p-methoxy acid is based on a first-order constant obtained at pH 2. Because the hydrolysis was too rapid to follow at any higher pH, this point represents a lower limit for the rate constant and should lie above the line. A good straight line is obtained using the other four points, however, indicating that the same reaction mechanism is operative for these compounds.

It is interesting to compare the reaction constants of the α-bromophenylacetate ions with those of other benzylic systems. Reaction constants for the solvolyses of several benzylic derivatives are summarized in Table IV. The reaction constants for the formolysis of benzyl bromides[14] and tosylates[15] are relatively large in the negative sense, −5 to −6, while the reaction constants for solvolysis of benzyl tosylates in aqueous acetone[16] and benzyl chlorides in aqueous ethanol or aqueous acetone[17] are only about −2. The difference

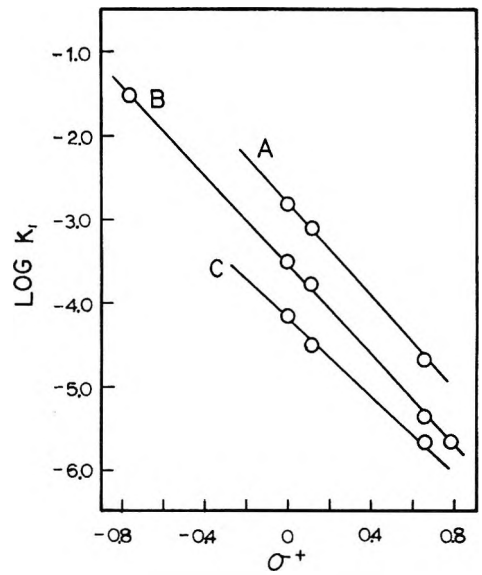

Figure 1.—Hammett plot for the solvolysis of substituted α-bromophenylacetate ions (I = 0.551): A, ρ = −2.74, 35.6°, 0.681 M aqueous acetone; B, ρ = −2.66, 25.0°, 0.681 M aqueous acetone; C, ρ = −2.33, 25.0°, 80% (v/v) methanol.

TABLE IV
REACTION CONSTANTS FOR SOLVOLYSES OF SEVERAL BENZYLIC SYSTEMS[a]

Reaction	ρ
Formolysis of benzyl bromides[b]	−5.55
Formolysis of benzyl tosylates[c]	−6.04
Solvolysis of benzyl chlorides	
48% aq ethanol, 30°[d]	−2.19
50% aq acetone, 30°[d]	−1.82
Solvolysis of benzyl tosylates	
76.6% aq acetone[e]	−2.2
Hydrolysis of α-bromophenylacetates	−2.66

[a] Temperature 25° unless specified. [b] Calculated from data in ref 14. [c] Reference 15. [d] Reference 17. [e] Reference 16.

in these reaction constants no doubt reflects the different extent of solvent participation, the formolysis reactions being the more limiting cases. In more nucleophilic solvents, bonding with the entering solvent molecules tends to diminish the charge on the incipient benzyl cation and thus renders the reaction less sensitive to substituent effects. The ρ value of −2.66 for hydrolysis of the α-bromophenylacetate ions (0.681 M aqueous acetone) is comparable with the ρ for solvolysis of these benzyl derivatives in more nucleophilic solvents. However, in the α-bromophenylacetate system it is participation of the negatively charged oxygen atom of the neighboring carboxylate group rather than bonding with the entering solvent molecule which tends to influence the magnitude of ρ. The lack of rate dependence on base concentration and the absence of salt and solvent effects, as well as the close similarity to the α-bromopropionate ion, strongly indicate such participation.

It may seem that an even less negative value for the reaction constant would be expected as a consequence of this participation. The fact that this is not observed indicates a small charge separation in the transition state and, by the Hammond postulate, in the intermediate as well. Admittedly, the value of such comparison depends on the choice of reference compound. It is difficult to assess the influence of the carboxylate

(13) E. R. Thornton, "Solvolysis Mechanisms," Ronald Press, New York, N. Y., 1964, pp 160, 161.
(14) C. W. Bevan, E. D. Hughes, and C. K. Ingold, *Nature*, **171**, 301 (1953).
(15) H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Schepple, *J. Amer. Chem. Soc.*, **89**, 370 (1967).
(16) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3445 (1953).
(17) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

group in the absence of participation, although its inductive effect as indicated by its substituent constant[17] should be small. Qualitatively, at least, the benzylic derivatives seem to be reasonable models for comparison, and the analogy makes ρ for the α-bromophenylacetate ions plausible.

These results indicate that the intermediates in solvolysis of the α-bromophenylacetates are very similar to that of the α-bromopropionate case. In addition, the magnitude of ρ suggests small charge separation in the intermediate. Just as with earlier results,[4] an unambiguous description of the intermediate cannot be rendered, but it seems best described as an α-lactone with much ionic character.

Experimental Section[18]

Materials. ***p*-Methoxy-α-bromophenylacetic Acid.**—*p*-Methoxyphenylacetic acid was brominated in the benzyl position following the general procedure of Panayotov.[19] This procedure is preferred to the Hell–Volhard–Zelinsky method for it avoids bromination of the reactive aromatic nucleus. A mixture of *p*-methoxyphenylacetic acid (16.6 g, 0.100 mol; Frinton Laboratories) and N-bromosuccinimide (17.8 g, 0.100 mol; Matheson Coleman and Bell) in 400 ml of reagent grade carbon tetrachloride was refluxed for 4 hr. After the mixture cooled, succinimide was filtered from the dark orange solution, and the solvent was removed under vacuum with a rotary film evaporator. The crude product was recrystallized twice from benzene yielding colorless needles of *p*-methoxy-α-bromophenylacetic acid, 12 g (50%), mp 100–102°.

Anal. Calcd for $C_9H_9BrO_3$: C, 44.10; H, 3.71; Br, 32.60. Found: C, 44.06; H, 3.59; Br, 32.58.

The nmr spectrum ($CDCl_3$) showed the expected signals at τ −2.10 (singlet, 1 H), 2.88 (AB quartet, 4 H), 4.77 (singlet, 1 H), and 6.23 (singlet, 3 H).

***p*-Chloro-α-bromophenylacetic Acid.**—The acid was prepared from *p*-chlorophenylacetic acid, mp 107–109° (lit.[20] mp 105–106°) (obtained from hydrolysis of *p*-chlorophenylacetonitrile, Eastman, practical grade), according to the method of Wladislaw and Giora.[21] The crude *p*-chloro-α-bromophenylacetic acid was recrystallized from a ligroin–benzene solution yielding colorless prisms: 56.4 g (97%); mp 96–98°.

Anal. Calcd for $C_8H_6O_2BrCl$: C, 39.41; H, 2.43; Br, 32.03; Cl, 14.21. Found: C, 39.37; H, 2.52; Br, 32.10; Cl, 14.02.

An nmr spectrum showed signals at τ 4.69 (singlet, 1 H), 2.57 (AB quartet, 4 H), and −1.04 (singlet, 1 H).

***p*-Nitro-α-bromophenylacetic Acid.**—*p*-Nitrophenylacetic acid (Columbia Organic Chemicals) was brominated according to reported methods.[21] Several recrystallizations from benzene gave pale yellow crystals: 15.9 g (53.7%); mp 103.0–103.6° (lit.[21] mp 111–112°, lit.[22] mp 113°).

Anal. Calcd for $C_8H_6BrNO_4$: C, 36.87; H, 2.33; Br, 30.73; N, 5.39. Found: C, 37.06; H, 2.35; Br, 31.21; N, 5.37.

The nmr spectrum ($CDCl_3$) and integration were consistent with the structure for this acid. Signals were observed at τ −0.83 (singlet, 1 H), 1.83 (AB quartet, 4 H), and 4.55 (singlet, 1 H).

***m*-Nitro-α-bromophenylacetic Acid.**—This acid was prepared by the same method as the *p*-nitro-α-bromophenylacetic acid. Pale yellow crystals were obtained from recrystallization from benzene: 12.1 g (87%); mp 125.9–127.1°.

Anal. Calcd for $C_8H_6BrNO_4$: C, 36.87; H, 2.33; Br, 30.73; N, 5.39. Found: C, 37.02; H, 2.44; Br, 30.68; N, 5.46.

α-Bromophenylacetic acid was commercially available (Frinton Laboratories). The acid was recrystallized twice from *n*-hexane: mp 81–82°.

Kinetics.—The course of hydrolysis of the substituted α-bromophenylacetates was followed by titrating the acid produced. In each case, 2.543 mequiv of the bromo acid was dissolved in 5.0 ml of redistilled reagent grade acetone in a 100-ml volumetric flask; 25 ml of a stock 2.00 *M* sodium perchlorate solution and 20.0 ml of 0.2543 *N* NaOH were added; and the solution was quickly diluted to volume. All solutions were previously thermostated. The reactants were thoroughly mixed and then returned to the constant-temperature bath at 25.03° ± 0.01° (or 35.60° ± 0.03°). The initial time was taken when half of the volume of the sodium hydroxide had been added. Alliquots of 5 ml were pipetted at appropriate time intervals into ice-cold nitric acid to quench the reaction. The solution was quickly titrated with standard sodium hydroxide. Infinity measurements were made in most instances to check the accuracy of the titrations. The ionic strength of the reaction solution was 0.551.

A similar procedure was used to follow the hydrolyses of the substituted α-bromophenylacetates in the presence of 0.2089 *N* sodium hydroxide. Appropriate adjustments were made in the concentration of the stock sodium perclorate solution so that the ionic strength of the reaction solution was 0.551.

The hydrolysis of *p*-methoxy-α-bromophenylacetate was carried out with a Radiometer TTT-1 titrator at pH 2. This compound was too reactive at 25° to study by the removal and analysis of aliquots, and, in fact the titrator was unable to follow the reaction at higher pH values. *p*-Methoxy-α-bromophenylacetate (0.100 g) was dissolved in 2 ml of acetone. Sodium perchlorate stock solution (6.25 ml, 2 *M*) and hydrochloric acid (15 ml, 0.01 *N*) were quickly added, and the titration was started immediately with 1.051 *N* NaOH. All solutions were previously thermostated, and the reaction vessel was maintained at 25.0° ± 0.5°. Volume of base *vs.* time was automatically recorded.

Product Identification.—Reactions were carried out on a larger scale, under the same conditions employed in the kinetic studies to facilitate the isolation of the expected α-hydroxy acids. Mandelic acid was identified as the hydrolysis product of α-bromophenylacetate on basis of its mp 118–120° and mmp 119–120.5° with authentic mandelic acid. Hydrolysis of *p*-chloro-α-bromophenylacetate gave *p*-chloromandelic acid, mp 120–121° (lit.[23] mp 120.5–121°). The hydrolysis product from *p*-methoxy-α-bromophenylacetate was *p*-methoxymandelic acid. Recrystallization from a benzene–hexane mixture afforded colorless crystals, mp 105–107°.

Anal. Calcd for $C_9H_{10}O_4$: C, 59.31; H, 5.54. Found: C, 58.99; H, 5.54.

Registry No.—*p*-Methoxy-α-bromophenylacetic acid, 17478-44-3; *p*-chloro-α-bromophenylacetic acid, 3381-73-5; *m*-nitro-α-bromophenylacetic acid, 4578-72-7; *p*-methoxymandelic acid, 10502-44-0.

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(18) All melting points are corrected. The nmr spectra were taken with a Varian A-60 spectrometer using TMS as the internal standard.

(19) I. M. Panayotov, *Compt. Rend. Acad. Bulgare Sci.*, **10** (2), 137 (1957).

(20) F. Straus, *Ann.*, **393**, 235 (1912).

(21) B. Wladislaw and A. Giora, *J. Chem. Soc.*, 5747 (1965).

(22) K. Heyns and H. Schultze, *Ann.*, **611**, 55 (1958).

(23) S. S. Jenkins, *J. Amer. Chem. Soc.*, **53**, 2341 (1931).

Fluoro Ketones. IV. Mechanism of Thermal Decomposition of Fluoroacetone Hemiketal Esters[1]

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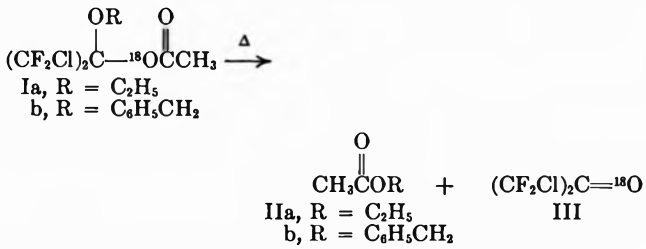
Pyrolysis of oxygen-18-labeled ethyl and benzyl dichlorotetrafluoro hemiketal acetates Ia, b gave labeled fluoroacetone and unlabeled ethyl and benzyl acetates (IIa, b). The sulfur analogs (IVa, b) also decomposed similarly to give the fluoroacetone and the corresponding thiol acetates (Va, b). Solvent studies showed that the rates of decomposition parallel the ionizing power of the solvent. These results are rationalized on the basis of a cyclic four-membered transition state.

The formation of fluoroacetone hemiketal esters *via* acetylation of the corresponding hemiketals[2] proceeds readily and in good yield.[1] We have found these esters to be thermally unstable and suggested a mechanism which is formally analogous to that of normal ester pyrolysis.[3] Since this mechanism was advanced only by analogy, we decided to utilize oxygen-18 as a tracer to provide information on the actual mechanism of the decomposition.

Results and Discussion

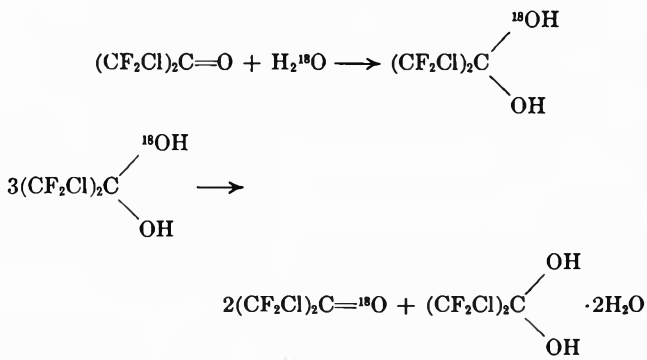
Labeled *sym*-dichlorotetrafluoroacetone was conveniently prepared by the hydration[4] of the unlabeled ketone with oxygen-18-enriched water[5] followed by disproportionation of the monohydrate as shown in Scheme I.[6]

The labeled ketone (2.6 ^{18}O atom %) was treated with the appropriate alcohol to give the hemiketal which was acetylated with acetyl chloride in the manner previously described.[1,2] Pyrolysis of the resultant fluoro ketone hemiketal acetates (I) gave the fluoro ketone (III) and simple nonfluorinated esters (II).



The mass spectra of the ethyl and benzyl acetates (IIa, b) recovered from the pyrolysis of the corresponding oxygen[18]-labeled hemiketal acetates[7] were compared with the spectra of samples of normal isotopic composition and were found to be nearly identical. Relative parent peak heights ($\times 10^3$) for pyrolysate and normal IIa, b were 5.2 and 5.3 for IIa (90/88) and 1.9 and 1.9 for IIb (152/150) (Table I). The fragmentation pattern of III was very complex owing largely to the presence of chlorine isotopes. All of the detectable

SCHEME I



excess oxygen-18 (2.6 ^{18}O atom %)[8] was found to reside in the fluoro ketone (III). The determination was based on the $C_3F_4ClO^+$ fragment corresponding to a loss of Cl from the molecular ion. The intensity of this peak was 20 times that of the parent peak allowing for greater precision. A correction was made for the contribution of the ^{37}Cl isotope to the *m/e* 165 peak by using a ^{35}Cl abundance of 75.7%.[9]

TABLE I

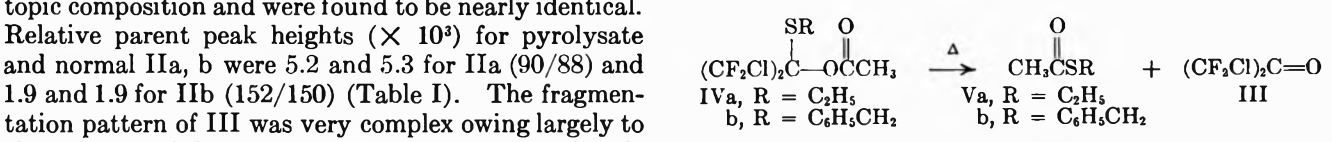
RELATIVE PEAK HEIGHT RATIOS ($^{18}O/^{16}O \times 10^3$)

m/e 90/88		*m/e* 152/150		*m/e* 165/163	
IIa (normal)	5.3[a]	IIb (normal)	1.9[a]	III (normal)	6.50
IIa (pyrolysate)	5.2[a]	IIb (pyrolysate)	1.9[a]	III (labeled) (2.6 atom %)[b]	27.0
				III (pyrolysate) (2.6 atom %)[b]	26.5

[a] Parent peak corrected for 2-^{13}C atoms; reproducibility ±5%. [b] Estimated error ± 0.2 atom %; corrected for ^{37}Cl contribution.[9]

Similarly, the thiohemiketal esters (IVa, b) were prepared by the acetylation of the appropriate thiohemiketal.

An appreciable amount of Vb was obtained on vac-



uum distillation of IVb indicating poorer thermal stability of the sulfur analogs. This was substantiated

(1) Part III: P. E. Newallis and P. Lombardo, *J. Org. Chem.*, **30**, 3834 (1965).

(2) H. E. Simmons and D. W. Wiley, *J. Amer. Chem. Soc.*, **82**, 2288 (1960).

(3) C. H. Depuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(4) C. Woolf, Abstracts, the 132nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1957, p 23M.

(5) Contained 5.15% ^{18}O atom and was purchased from Yeda Research and Development Co., Rehovoth, Israel.

(6) We are indebted to Dr. C. Woolf and W. J. Cunningham for this procedure.

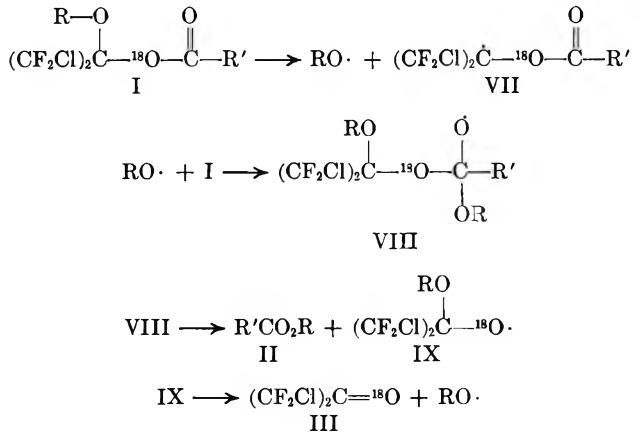
(7) These samples were doubly distilled and checked for purity by gas chromatography on two different columns.

(8) The accuracy of this determination is estimated to be ±0.2 atom %. Since 2.6 ^{18}O atom % was found to be present in III obtained from the pyrolysis of I as well as that used in the synthesis of I, any errors very likely would be canceled. Furthermore, our failure to find any of the excess ^{18}O in II requires that the excess ^{18}O be present in the only other product, namely III.

(9) Determined independently by measuring the $C_3F_4Cl^+$ fragment *m/e* 147/149 from 1,2-dichlorohexafluorocyclobutane which is in good agreement with the previously reported value of 75.8% [S. Meyerson, *Anal. Chem.*, **33**, 964 (1961)].

by the lower temperatures required for the controlled pyrolysis of the sulfur analogs compared with their oxygenated counterparts. It is significant that the thiol esters V were obtained from the pyrolysis of IV, not II. Thus, the sulfur atom serves as a label in this case.

The probability of a clean radical reaction being involved in these decompositions was ruled out based on the following results. We would have expected at least small amounts of radical-type products from the pyrolysis of a wide variety of hemiketal esters[1,10] which included the cyclopropylcarbinol, β-phenethanol, and allylcarbinol derivatives. Evidence for ring opening of cyclopropylcarbinyl radicals[11] and ring closure[11b,12] or isomerization[11b,13] of allylcarbinyl radicals has been reported. The stability of primary, secondary, and tertiary, as well as benzyl, radicals has been discussed and illustrated by many examples.[11b,14] Moreover, no evidence of radicals was observed when the decomposition was followed by esr spectroscopy. Monitoring a neat sample of Ib at 200° over a 30-min period showed only a constant base line.[15] Free-radical mechanisms involving alkyl radicals would place the oxygen label in the ester which is contrary to our results. An interesting radical process involving alkoxy radicals[16a] rather than alkyl radicals is given below.



The attractive feature of this mechanism is that it would give the ^{18}O-enriched ketone (III) which is consistent with our results. However, it would require that this sequence occur within the solvent cage and not abstract hydrogen from hydrocarbon solvent. Considering the reactivity of alkoxy radicals[16b] and the absence of any by-products of any type, this process seems less attractive.

(10) P. Lombardo, unpublished results.

(11) (a) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951); E. Renk, P. R. Shafer, W. H. Graham, R. H. Mazur, and J. D. Roberts, *ibid.*, **83**, 1987 (1961); W. H. Urry, D. J. Strecker, and H. D. Harzler, *J. Org. Chem.*, **29**, 1663 (1964). (b) C. Walling in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963.

(12) T. A. Halgren, M. E. H. Howden, M. E. Medof, and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 3051 (1967).

(13) L. K. Montgomery and J. W. Matt, *ibid.*, **89**, 3050 (1967); L. K. Montgomery, J. W. Matt, and J. R. Webster, *ibid.*, **89**, 923 (1967).

(14) (a) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957; (b) W. H. Urry and N. Nicolaides, *J. Amer. Chem. Soc.*, **74**, 5163 (1952); (c) D. H. Barton, *ibid.*, **82**, 2640 (1960).

(15) Control experiments have shown that the decomposition of Ib does occur at temperatures around 200°; however, the concentration of the radical species may be too low to detect.

(16) (a) Suggested by one of the referees. (b) For a discussion of the fate of alkoxy radicals, see C. Walling, *Pure Appl. Chem.*, **16**, 69 (1967).

A study of the decomposition of 0.1 *M* solutions of Ib in sealed ampoules at 185° showed a significant effect of solvent on the rate of reaction. The decompositions proceeded more rapidly in dipolar aprotic solvents[17] than in nonpolar solvents (Table II).

TABLE II

EFFECT OF SOLVENT ON THE THERMAL DECOMPOSITION OF 0.1 *M* SOLUTIONS OF Ib AT 185°

Solvent	3 hr, % decompn	5 hr, % decompn
Benzene	14	
Cumene	27	
Dioxane	58[a]	65[b]
Tetrahydrofuran	67	
Acetonitrile	97	
Dimethylformamide	100[c]	

[a] 0.65 *M*, 75%; 0.05 *M*, 55%. [b] 0.02 *M*, 60%. [c] Decomposed 75% in 1 hr; indication that generated fluoro ketone may have reacted with the DMF.

Rates of decomposition and the activation parameters for Ib in dioxane were determined gas chromatographically and are recorded in Table III. Good first-order plots were obtained for over 60% reaction.

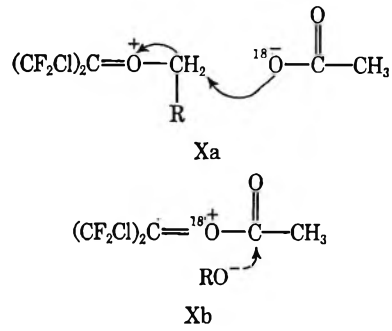
TABLE III

KINETICS OF DECOMPOSITION OF Ib IN DIOXANE

Temp,[a] °C	$k \times 10^{-5}$,[b] sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
177.2	4.74	27.1	−18.9
185.0	8.05		
197.2	18.1		

[a] Temperature variation $\leq \pm 0.2°$. [b] Determined by the method of least-squares analysis.

The entropy of activation is consistent with values obtained for reactions involving cyclic transition states[18] formed from neutral species and may reflect a crowded environment. These results also could be indicative of some charge separation in the transition state, suggestive of the ion pairs (X) or similar ionic pathways.



Xa

Xb

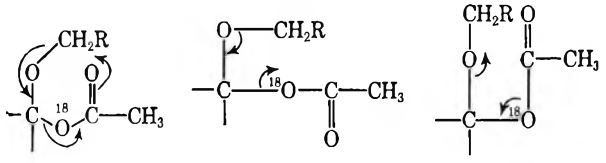
Ion pair Xb would give labeled fluoro ketone as we observed but would invoke a highly destabilized carbonium ion due to the six adjacent halogens. Since acetate is a better leaving group than alkoxide, Xa would be more reasonable. However, in view of the absence of scrambling of oxygen-18 which we would

(17) The solvent studies may have been complicated by the high reactivity of the fluoro ketones. For an excellent review of the reactions of fluoro ketones, see N. P. Gambaryan, E. M. Rokhlin, Y. V. Zeifman, C. Ching-Yun, and I. L. Knunyants, *Angew. Chem. Intern. Ed. Engl.*, **5**, 947 (1966).

(18) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 226 (1968); C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960), and references cited therein.

anticipate,[19] processes such as Xa are untenable. Further support for this view can be found in our studies on the decomposition of thio hemiketal esters (IV). The thio ketone and II would be the expected products from Xa; instead, only III and V were produced. Bimolecular reactions were also considered unlikely based on the labeling experiments and the fact that the decomposition was not significantly dependent upon concentration.

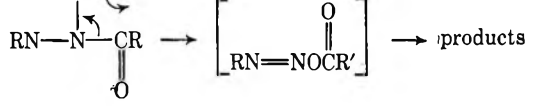
Finally, three cyclic intramolecular mechanisms which would account for this over-all reaction were considered. Path XI invokes a cyclic six-membered transition state similar to that proposed for normal ester pyrolysis and would require that the excess ^{18}O appear in the carbonyl function of the resultant ester.



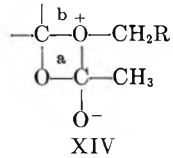
XI XII XIII

If mechanism XII were operative, the excess ^{18}O would be found in the ether oxygen of the ester, while the presence of the excess ^{18}O in fluoro ketone would be in accord with mechanism XIII as the correct pathway for these decompositions. The only mechanism consistent with the mass spectral data is XIII which invokes a cyclic four-membered transition state in which there is probably considerable charge separation in contrast to the nonfluorinated esters.[20] The ease of these decompositions[21] is attributed to the electronegative influence of the halogen atoms on the carbon–oxygen bonds, resulting in the generation of the fluoro ketone.

Mechanistically these pyrolyses are more analogous to the first step in the thermal elimination of N_2 or N_2O from nitroso and nitro amides which have been extensively studied by White,[22] Huisgen,[23] and Hey.[24]



We suggest that the transition state very likely resembles XIV with cleavage of bond a being well advanced.



XIV

Hemiketal esters derived from secondary alcohols decompose in a similar fashion to give II and III and apparently *via* the same mechanism. Pyrolysis of the tertiary alcohol derivatives (*e.g.*, *t*-butyl), however, gave III, olefin, and acid.[1] The effect of structure in determining the products of the decomposition of the hemiketal esters and their mechanistic implications are now under investigation.

Experimental Section

Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer and the esr studies were conducted with a Varian V-4502 instrument. Unless otherwise specified, gas chromatographic analyses were carried out using an F & M Model 700 or 720 instrument with either 0.125- or 0.25-in.-diam, 6-ft columns packed with 10% DC-200 on Chromosorb W.

Preparation of ^{18}O-Labeled Dichlorotetrafluoroacetone.—*sym*-Dichlorotetrafluoroacetone (100 g 0.5 mol) was placed in a 250-ml three-necked flask equipped with stirrer, condenser, thermometer, and addition funnel. The ^{18}O-enriched water,[5] 9.0 g (5.15% ^{18}O, 0.56% ^{17}O), was added dropwise with stirring over 15 min. After completion of the addition, the mixture was stirred for an additional hour and then distilled at atmospheric pressure. A 67% yield (44.0 g) of labeled ketone was obtained.

Preparation of the ^{18}O-Labeled Hemiketal Esters. 1-Benzyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—To 10.0 g (0.05 mol) of ^{18}O-labeled *sym*-dichlorotetrafluoroacetone was added dropwise 5.4 g (0.05 mol) of benzyl alcohol. After the addition was completed, 50 ml of anhydrous ethyl ether was added, and the reaction mixture was cooled to 5°. A solution of 3.9 g (0.05 mol) of acetyl chloride in 10 ml of ether was then added rapidly, followed by dropwise addition of a solution of 3.9 g (0.5 mol) of pyridine in 50 ml of ether. The mixture was then stirred overnight at room temperature. After washing with water and drying over anhydrous magnesium sulfate, the ether was distilled leaving a residue of 16 g of an oil. Distillation of the crude product gave 10.0 g (57%) of a water-white liquid, bp 100–102° (0.9 mm) [lit.[1] bp 106° (0.95 mm)].

1-Ethoxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—Using the procedure described above, a 0.05 *M* run gave 9.7 g (67%) of product, bp 45–46° (2.0 mm) [lit.[1] bp 42–43° (1.2 mm)].

Decomposition of ^{18}O-Labeled 1-Benzyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoromethyl Acetate.—A 5-g sample (0.014 mol) of the above ester was placed in a 10-ml distilling flask attached to a Berl saddle packed, vacuum-jacketed semimicro column and distillation head. The distilling flask was immersed in an oil bath heated to 230°, and 1.8 g (63%) of the fluoro ketone was collected (bp 46–50°). The column was removed, and 1.5 g (70%) of benzyl acetate was collected (bp 220–225°).[25]

Decomposition of ^{18}O-Labeled 1-Ethoxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—Using the procedure and equipment described above, 4.0 g (0.014 mol) of the above ester was decomposed at 130° over a 22-hr period to give 1.8 g (65%) of the fluoro ketone and 0.7 g (57%) of ethyl acetate,[21] bp 75–77°.

1-Benzylthio-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—To 39.8 g (0.2 mol) of *sym*-dichlorotetrafluoroacetone dissolved in 100 ml of anhydrous ether was added dropwise 24.8 (0.2 mol) of benzyl mercaptan with stirring and cooling. After the addition was completed, 15.7 g (0.2 mol) of acetyl chloride was added followed by dropwise addition of 15.8 g (0.2 mol) of pyridine in 100 ml of anhydrous ether. The reaction mixture was stirred overnight, filtered, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed with a rotary evaporator, and the residual oil was distilled. The first fraction distilling at 68–80° (0.5 mm) was benzyl thiolacetate[25] (35%) followed by 6.4 g of an intermediate fraction at 82–114° (0.4 mm) and 22.9 g (31%) of the product

(19) Equilibration of ^{18}O for carboxylate anions has been well documented. See, for example, H. L. Goering and M. M. Pombo, *ibid.*, **82**, 2515 (1960); H. L. Goering and J. F. Levy, *ibid.*, **86**, 120 (1964), and references cited therein. Exceptions have been noted in special cases involving bridged species [D. B. Denney and D. G. Denney, *ibid.*, **79**, 4806 (1957)] and when the generated carbonium ion is of high energy [W. E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, *ibid.*, **76**, 1008 (1953)].

(20) R. Taylor, G. G. Smith, and W. H. Wetzel, *ibid.*, **84**, 4817 (1962).

(21) Electronic effects of acyl substituents on the stability of esters has been demonstrated. See, for example, W. J. Bailey and J. J. Howitt, *J. Org. Chem.*, **21**, 543 (1956); G. L. O'Connor and H. R. Nace, *J. Amer. Chem. Soc.*, **75**, 2118 (1953). For the effect of alkyl substituents, see G. G. Smith, F. D. Bagley, and R. Taylor, *ibid.*, **83**, 3647 (1961); C. H. DePuy and R. E. Leavy, *ibid.*, **79**, 3705 (1957).

(22) E. H. White and L. A. Dolak, *ibid.*, **88**, 3790 (1966); E. H. White and C. A. Aufdermarsh, *ibid.*, **83**, 1179 (1961); E. H. White, *ibid.*, **77**, 6011 (1955).

(23) R. Huisgen, *Ann.*, **574**, 184 (1951); R. Huisgen and H. Reimlinger, *ibid.*, **599**, 161 (1956).

(24) D. H. Hey, J. Stuart-Webb, and G. H. Williams, *J. Chem. Soc.*, 4657 (1952).

(25) The ir spectrum and vpc retention times of this sample were identical to those of an authentic sample.

at 113–115° (0.5 mm): $n^{25}D$ 1.4991; λ_{max}^{film} 5.6 (C=O) and 8.2–9.0 μ (C—F, very broad and intense).

Anal. Calcd for $C_{12}H_{10}Cl_2F_4O_2S$: C, 39.4; H, 2.74; Cl, 19.4. Found: C, 39.5; H, 2.85; Cl, 19.3.

Decomposition of Benzylthio-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—Into a distillation flask attached to a vacuum-jacketed Vigreaux column was placed 7.3 g (0.02 mol) of the ester. The flask was immersed in an oil bath at 170°, and 3.4 g of the fluoro ketone, bp 42–48°, was collected. Vacuum was then applied and the oil bath was heated to 210° until the high-boiling component appeared to be rising in the column. The bath temperature was then adjusted so that a smooth distillation could be carried out. The benzyl thiolacetate[25] (2.5 g) was collected at 50–52° (0.1 mm), leaving a residue of 0.5 g shown to be the undecomposed starting ester by gas chromatography.

1-Ethylthio-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—To a solution of 39.8 g (0.2 mol) of *sym*-dichlorotetrafluoroacetone in 100 ml of anhydrous ether was added 12.4 g (0.2 mol) of ethyl mercaptan all at once with stirring and cooling. After stirring for 1 hr at room temperature, 15.7 g (0.2 mol) of acetyl chloride was added followed by dropwise addition of a solution of 15.8 g (0.2 mol) of pyridine in 50 ml of anhydrous ether. The reaction mixture was stirred overnight and quenched with water, and the organic layer was dried over anhydrous magnesium sulfate. Removal of solvent with a rotary evaporator left 48.2 g of an amber oil, which on distillation gave 46.2 g (76%) of a water-white liquid: bp 42–46° (0.15 mm); $n^{25}D$ 1.4352; λ_{max}^{film} 5.6 (C=O) and 8.2–9.2 μ (C—F, very broad and intense).

Anal. Calcd for $C_7H_8F_4O_2S$: C, 27.8; H, 2.64; Cl, 25.1. Found: C, 27.8; H, 2.57; Cl, 25.0.

Decomposition of 1-Ethylthio-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—A distilling flask attached to a vacuum-jacketed Vigreux column containing 9.1 g (0.03 mol) of ester was placed in an oil bath at 180–215°. The temperature of the bath was maintained so that smooth evolution of the fluoro ketone (1.6 g), bp 44°, occurred. An intermediate fraction (1.7 g), bp 65–90°, consisted largely of ethyl thiolacetate and a third fraction (2.3 g), bp 95–100°, was essentially pure ethyl thiolacetate.[26] The residue (2.1 g) was shown to be a 2:1 mixture of the starting material to ethyl thiolacetate by gas chromatography.

α-Methylbenzyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Propionate.—To a solution of 12.2 g (1.0 mol) of α-methyl benzyl alcohol in 100 ml of anhydrous ether was added 20.0 g (0.1 mol) of *sym*-dichlorotetrafluoroacetone with stirring and cooling. Propionyl chloride, 9.3 g (0.1 mol), was then added all at once followed by dropwise addition of 7.9 g (0.1 mol) of pyridine in 100 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 6 hr. The solid was filtered, and the ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed with a rotary evaporator, and the residual oil distilled to yield 33.0 g (87%): bp 89° (0.15 mm); $n^{20}D$ 1.4606; λ_{max}^{film} 5.6 (C=O) and 8.1–9.1 μ (C—F broad and intense).

Anal. Calcd for $C_{14}H_{14}Cl_2F_4O_3$: C, 44.6; H, 3.73; Cl, 18.8. Found: C, 44.9; H, 3.65; Cl, 18.6.

Decomposition of α-Methylbenzyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Propionate.—A distilling flask attached to a vacuum-jacketed Vigreaux column containing 5.4 g (0.015 mol) of ester was placed in an oil bath at 185°. The fluoro ketone (2.3 g) distilled smoothly over a 2-hr period. After the distillation had subsided, the bath temperature was lowered; vacuum was applied; and 1.8 g of α-methylbenzyl propionate[26] distilled at 64° (0.8 mm). The residue (approximately 0.5 g) was shown to be more undistilled decomposed ester, by ir spectroscopy and gas chromatography.

1-Phenethoxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Propionate.—This compound was made by the method described for Ib. Distillation of the crude product gave a 68% yield of colorless liquid: bp 87° (0.07 mm); $n^{20}D$ 1.4603; λ_{max}^{film} 5.65 (C=O) and 8.1–8.7 μ (C—F, very broad and intense).

Anal. Calcd for $C_{14}H_{14}Cl_2F_4O_3$: C, 44.6; H, 3.73; Cl, 18.8. Found: C, 44.3; H, 3.7; Cl, 18.6.

Decomposition of 1-Phenethoxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Propionate.—A distilling flask attached to a vacuum-jacketed Vigreaux column containing 5.0 g (0.013 mol) of the ester was placed in an oil bath at 140°. The fluoro ketone (2.2 g) distilled smoothly over a 4-hr period. After the distillation had subsided, the bath temperature was lowered; vacuum was applied; and 2.5 g of phenethyl propionate distilled at 104–105° (4.0 mm). There was no residue left.

1-Cyclopropylcarbinyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—This compound was made by the method described for Ib. Distillation of the crude product gave a 33% yield of water-white liquid: bp 55–56° (0.5 mm); $n^{25}D$ 1.4130; λ_{max}^{film} 5.6 (C=O) and 8.1–9.0 μ (C—F, very broad and intense).

Anal. Calcd for $C_9H_{10}Cl_2F_4O_3$: C, 34.5; H, 3.20; Cl, 22.7. Found: C, 34.4; H, 3.4; Cl, 22.4.

Decomposition of Cyclopropylcarbinyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—A 5-g sample (0.016 mol) of ester in a distilling flask attached to a vacuum-jacketed Vigreaux column was placed in an oil bath at 180°. The bath temperature was slowly raised to 225° over a 10-hr period. Four fractions[26] were collected containing 3.3 g of a mixture of fluoro ketone and cyclopropylcarbinyl acetate.[25,27] The residue (1.1 g) consisted of approximately a 3:5 mixture of cyclopropylcarbinyl acetate to starting ester and 0.5 g of black tar.

1-Allylcarbinyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—This compound was made by the method described for Ib. Distillation of the crude product gave a 40% yield of water-white liquid: bp 49° (0.2 mm); $n^{25}D$ 1.4072; λ_{max}^{film} 5.6 (C=O), 6.05 (C=C), and 7.8–9.0 μ (C—F, very broad and intense).

Anal. Calcd for $C_9H_{10}Cl_2F_4O_3$: C, 34.5; H, 3.20; Cl, 22.7. Found: C, 34.4; H, 3.1; Cl, 22.5.

Decomposition of 1-Allylcarbinyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl Acetate.—Six grams (0.019 mol) of esters in a distilling flask aattched to a vacuum-jacketed Vigreux column was placed in an oil bath at 180°. The bath temperature was slowly raised to 225° over a 7-hr period and maintained at 225–230° for the next 21 hr. Five fractions[26] were collected which contained 3.2 g of a mixture of fluoro ketone and allylcarbinyl acetate.[25,27] The residue (2.4 g) consisted of approximately 50% of allylcarbinyl acetate, 25% undecomposed ester, and 5% tar; the remainder was two other impurities.

Mass Spectrometric Data.—Measurements were made using a modified CEC 21-103 and an Atlas CH4-B mass spectrometer with an ionization energy of 70 eV. The samples were introduced at 50° into a metal inlet system, and the source temperature was 250°. The $C_3F_4ClO^+$ (*m/e* 163) fragment was used for the isotopic analysis of the fluoro ketone (III), which corresponds to the loss of Cl from the molecular ion. The absence of $C_3F_3{}^{37}Cl^+$ (*m/e* 167) from the untagged fluoro ketone eliminates the possibility of the *m/e* 163 peak being produced by a loss of $^{16}O + {}^{19}F$.

Kinetic and Solvent Studies.—Standard stock solutions approximately 0.1 *M* in Ib were prepared by weighing the appropriate quantity directly into 10-ml volumetric flasks and diluting to mark with solvent. Into a 5-ml ampoule was placed 0.5 ml of the standard solution, and the ampoule was sealed and immersed in a thermostated oil bath. The bath was controlled to ±0.1°. After a specified time period, the ampoules were removed and cooled in an ice bath, and the samples immediately analyzed by gas chromatography.

All vpc measurements were carried out on an F & M Model 700 gas chromatograph with dual thermal conductivity detectors using a 4 ft × 0.125 in. o.d. glass column packed with silicone oil DC-200 on Chromosorb G. Samples of 4 μl were injected with a syringe fitted with a Chaney adapter. Quantitative data were obtained by determining the decrease in peak area of Ib using a Disc integrator. All data represent an average of two or more separate determinations and were reproducible to ±2%.

Registry No.—IVa, 17497-44-8; IVb, 17528-33-5; α-methylbenzyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl propionate, 17497-45-9; 1-phenethoxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl propionate, 17497-57-3; 1-cyclopropylcarbinyloxy-

(26) Good separation of fluoro ketone from lower alkyl acetates is usually achieved with a packed column.

(27) A 6 ft × 0.125 in. o.d. stainless steel column packed with 10% diisodecyl phthalate on Chromosorb G was used isothermally at 110°. An authentic mixture of cyclopropylcarbinyl and allylcarbinyl acetates was conveniently separated with this column.

1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl acetate, 17497-46-0; 1-allylcarbinyloxy-1-(chlorodifluoromethyl)-2-chloro-2,2-difluoroethyl acetate, 17497-47-1.

Acknowledgment.—The authors are grateful to Professor J. Meinwald for many helpful discussions and to A. J. Poje for technical assistance.

Total Synthesis of the Macrocyclic Lactone, Dideoxyzearalane

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Dideoxyzearalane, 2-(10-hydroxyundecyl)benzoic acid lactone (**2**), the simplest macrocyclic lactone having the same skeletal structure as the macrolide zearalenone (**1**) was totally synthesized. Condensation of 10-undecenoic anhydride with phthalic anhydride gave 3-(9-decenylidene)phthalide (**3**). The internal double bond of diene **3** was in effect reduced in alkali with sodium borohydride and the terminal double bond was hydrated with mercuric acetate and sodium borohydride to yield 3-(9-hydroxydecyl)phthalide (**5**). Saponification and catalytic hydrogenolysis of **5** gave 2-(10-hydroxyundecyl)benzoic acid (**7a**). (±)-Dideoxyzearalane (**2**) was obtained by lactonization of **7a** in benzene at high dilution with phosgene as cyclization agent. Optically active (+) **2** was obtained by hydrogenolysis of **10b**, the dibenzoxazolyl ether of zearalane (**10a**), derived from zearalenone (**1**). This (+) **2** and the totally synthesized (±) **2** are spectroscopically and chromatographically identical.

The structure of the macrolide zearalenone (**1**), the anabolic and uterotropic factor isolated from *Gibberella zeae*,[1] was established in these laboratories.[2] Total syntheses of zearalenone (**1**) and several derivatives have been reported.[3] The subject of this report is the total synthesis of dideoxyzearalane, 2-(10-hydroxyundecyl)benzoic acid lactone (**2**), the simplest macrocyclic lactone having the same skeletal structure as zearalenone (**1**).

The condensation of 10-undecenoic anhydride with phthalic anhydride in the presence of sodium acetate or sodium 10-undecenoate according to the procedure of Mowry, *et al.*,[4] gave 3-(9-decenylidene)phthalide (**3**). Saponification of **3** and reduction with sodium borohydride yielded 3-(9-decenyl)phthalide (**4**).

Markovnikov hydration of the terminal double bond of **4** *via* mercuric acetate addition followed by sodium borohydride demercuration by a modification of the procedure of Brown and Geoghegan[5] gave 3-(9-hydroxydecyl)phthalide (**5**). Alternatively, treatment of **3** with mercuric acetate followed by simultaneous demercuration and reduction in alkali with sodium borohydride yielded **5** directly. The crude product, however, was more complex and less readily purified when prepared in this manner. Hydration of **3** *via* formic acid addition[6] gave primarily the desired secondary alcohol resulting from normal Markovnikov hydration, but also appreciable amounts of other secondary alcohols.

Saponification of **5** yielded the salt of the dihydroxy acid **6** which was converted by catalytic hydrogenolysis[7] of the benzylic hydroxyl group into 2-(10-hydroxyundecyl)benzoic acid (**7a**). Methyl ester **7b** was prepared by reaction of **7a** with diazomethane.

In comparison with the relative ease of cyclization of several related hydroxy acids and esters,[3] the cyclization of hydroxy acid **7a** to lactone **2** proved unexpectedly difficult. Trifluoroacetic anhydride, dicyclohexylcarbodiimide, thionyl chloride, and *p*-toluenesulfonyl chloride all proved unsuitable as lactonization agents. Equally unsuccessful were attempted lactonizations of the hydroxy ester **7b** by transesterification employing aluminum isopropoxide, sodium ethoxide with molecular sieves, sodium triphenylmethoxide, sodium hydride, polymeric dibutyltin oxide, or *p*-toluenesulfonic acid as catalysts. Similar difficulties have recently been reported by Baker, Bycroft, and Roberts[8a] and by Musgrave, Templeton, and Munro[8b] in attempts to prepare di-O-methylcurvularin (**8**) by lactonization of hydroxy acid **9**.

Lactonization of hydroxy acid **7a** to (±)-dideoxyzearalane (**2**) was achieved using phosgene with triethylamine in benzene under high dilution conditions.[9] The major by-product appears to be a polymeric, cyclic ester (see below).

The structure of racemic dideoxyzearalane (**2**) was established by elemental analysis and direct comparison (nmr, ir, uv, and tlc) with an authentic sample of (+)-dideoxyzearalane (**2**). (+)-Dideoxyzearalane (**2**) was prepared by replacement of the phenolic groups of zearalane (**10a**) with hydrogen. This deoxygenation was accomplished by catalytic hydrogenolysis of **10b**, the dibenzoxazolyl ether of **10a**, by a modification of the method of Musliner and Gates.[10] Zearalane (**10a**) was obtained from natural zearalenone (**1**) as previously described.[2]

Hydrolysis of (+)-dideoxyzearalane (**2**) with sodium hydroxide in aqueous dimethyl sulfoxide yielded hy-

(1) M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *Nature*, **196**, 1318 (1962).

(2) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966).

(3) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968); N. N. Girotra and N. L. Wendler, *Chem. Ind.* (London), 1493 (1967); W. H. Urry, H. L. Wehrmeister, P. H. Hidy, E. B. Hodge, D. Taub, C. H. Kuo, N. L. Wendler, N. N. Girotra, H. L. Slates, R. D. Hoffsommer, S. Weber, S. N. Dixit, and G. Mullenback, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p Q73; A. D. Cross, J. Fried, I. T. Harrison, and I. Vlattas, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p P7.

(4) D. T. Mowry, E. L. Ringwald, and M. Renoll, *J. Amer. Chem. Soc.* **71**, 120 (1949).

(5) H. C. Brown and P. Geoghegan, Jr., *ibid.*, **89**, 1522 (1967).

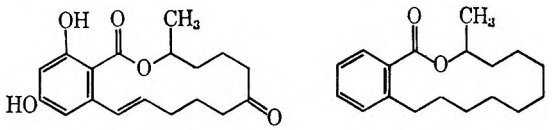
(6) H. B. Knight, R. E. Koos, and D. Swern, *J. Amer. Oil Chem. Soc.*, **31**, 1 (1954).

(7) J. Kollonitsch, H. E. Mertel, and V. F. Verdi, *J. Org. Chem.*, **27**, 3362 (1962).

(8) (a) P. M. Baker, B. W. Bycroft, and J. C. Roberts, *J. Chem. Soc.*, 1913 (1967); (b) O. C. Musgrave, R. Templeton, and H. D. Munro, *ibid.*, 250 (1968).

(9) H. Rinderknecht and V. Ma, *Helv. Chim. Acta*, **47**, 162 (1964); T. B. Windholz, *J. Org. Chem.*, **25**, 1703 (1960). We are indebted to Mr. Windholz for bringing his report, cited above, to our attention.

(10) W. J. Musliner and J. W. Gates, Jr., *J. Amer. Chem. Soc.*, **88**, 4271 (1966).



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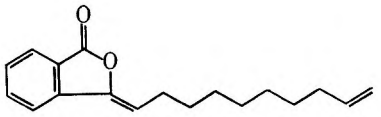

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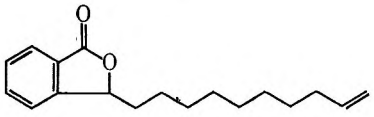

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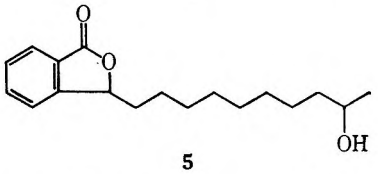

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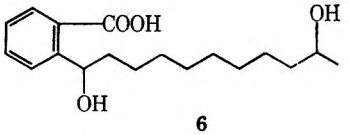

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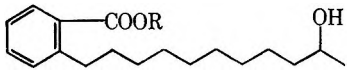
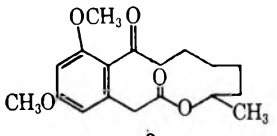


7a, R = H
b, R = CH_3



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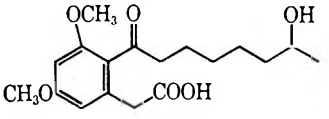

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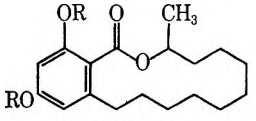
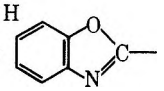


10a, R = H
b, R =



droxy acid (+) **7a** which was converted into methyl ester (+) **7b** with diazomethane. The nmr, ir, and uv spectra and the tlc behavior of these naturally derived products and of the corresponding synthetic compounds were identical.

Lactonization of (+) **7a** with phosgene yielded (+) **2** with complete retention of optical activity through the hydrolysis and relactonization sequence.

The nmr spectrum of dideoxyzearalane (**2**) is characteristically different from the spectra of the open-chain compounds **7a** and **7b**. Replaceable hydrogens are, of course, apparent in the spectra of **7a** and **7b** and absent in the spectrum of **2**. The predictable downfield shift of the multiplet due to the methine hydrogen in **7a** and **7b** (HO—C—H, δ ~3.90 and 3.75 ppm) compared to lactone **2** (RCOO—C—H, δ ~5.35 ppm) is observed. In all cases, the four aromatic hydrogens give a complex pattern of multiplets in the expected 1:3 intensity ratio with the farthest downfield resonance being due to the single hydrogen *ortho* to the carboxyl group. The difference in chemical shift between this *ortho* hydrogen and the chemical shift of the other three hydrogens is considerably less in **2** (ΔHz $\simeq$ 22) than in **7a** (ΔHz $\simeq$ 41) or **7b** (ΔHz $\simeq$ 32). The benzylic hydrogens of the lactone **2** are nonequivalent as clearly shown by their different chemical shifts (δ $\pm$3.3 and 2.7 ppm) and complex splitting patterns. The benzylic hydrogens of the open-chain compounds **7a** and **7b**, however, appear as a crude triplet (δ 3.0 ppm) as expected for nearly equivalent hydrogens on a carbon vicinal to a long methylene group. The nonequivalency of the benzylic hydrogens of dideoxyzearalane (**2**) is probably due to restricted rotation in the sterically crowded lactone.

The nmr spectrum of the major by-product of the lactonization reaction shows no replaceable hydrogens, the methine hydrogen at δ ~5.2 ppm typical of the esters, and patterns for the aromatic and benzylic hydrogens similar to those of the open-chain compounds, suggesting the structure to be a polymeric, cyclic ester or mixture of cyclic esters.

The pharmacological activity of dideoxyzearalane is under study. Application of similar synthetic schemes to the preparation of related products is in progress.

Experimental Section[11]

10-Undecenoic Anhydride.—10-Undecenoic acid (530 g, 2.88 mol) was heated in acetic anhydride (1433 g, 14.0 mol) at reflux for 2.5 hr. Acetic acid and acetic anhydride were removed by distillation at reduced pressure with the pot temperature not exceeding 145°. Molecular distillation of the residue at about 225° (0.05 mm) gave the anhydride (484 g, 96%) as a pale yellow liquid: nmr ($CDCl_3$), δ 5.6 (m, 2, C=C**H**), 4.7 (m, 4, C=CH_2), 2.2 (t, 4, CH_2C=O), 1.9 (m, 4, C=CCH_2), and 1.2 ppm (m, 24, CCH_2C).

Anal. Calcd for $C_{22}H_{38}O_3$: mol wt, 350. Found: equiv wt by titration as an anhydride,[12] 345.

3-(9-Decenylidene)phthalide (3).—The general method of Mowry, *et al.*,[4] for the preparation of alkylidenephthalides was applied to the synthesis of **3**. From 178 g (1.2 mol) of phthalic anhydride and 465 g (1.33 mol) of 10-undecenoic anhydride with 36 g of sodium acetate as catalyst there was obtained 168 g (51%) of **3**: bp 171–183° (0.3 mm); nmr (CCl_4), δ 7.2–8.0 (m, 4, aromatic protons), 5.2–6.2 (m, 2, C=C**H**), 4.6–5.2 (m, 2, C=CH_2), 1.7–2.7 (m, 4, C=CCH_2), and 1.1–1.7 ppm (m, 10, CCH_2C); ir (film), 1770 (C=O), 1680, 1635, 982, and 908 cm^{-1} (olefin); uv max (CH_3OH), 236 mμ (ϵ 17,700), 261 (18,400), 310 (5700).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.9; H, 8.20; sapon equiv, 270; iodine no., 188. Found: C, 79.5; H, 8.15; sapon equiv, 270, 273; iodine no., 182, 183.

3-(9-Decenyl)phthalide (4).—A solution of 3-(9-decenylidene)-phthalide (**3**, 54.0 g, 0.2 mol) and sodium hydroxide (200 g, 5 mol) in 50% aqueous tetrahydrofuran (1 l.) was heated at reflux for 3 hr. Sodium borohydride (37.8 g, 1 mol) was then added

(11) Melting points and boiling points are uncorrected. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del., and in our laboratories. Spectra were recorded on the following instruments: uv, Bausch & Lomb Spectronic 505; ir, Perkin-Elmer 21 spectrometer; nmr, Varian Associates A-60A spectrometer (TMS as internal standard); optical activity, O. C. Rudolph and Sons Model 80 polarimeter.

(12) J. B. Johnson and G. L. Funk, *Anal. Chem.*, **27**, 1464 (1955).

to the solution at room temperature. The solution was stirred for 1 hr at room temperature and 1 hr at reflux and cooled to 10°. The cold mixture was poured rapidly into ice-cold 4 *N* hydrochloric acid (2.2 l.) with the temperature not exceeding 25°. The acidic mixture was stirred for 15 min, saturated with salt, and extracted with four 1-l. portions of ether. The dried ($CaSO_4$) extract was concentrated to 100 ml, filtered to remove a small amount of solid, and further concentrated to yield 54.1 g of yellow liquid. Distillation gave 37.7 g (69%) of **4**: bp 146–149° (0.1 mm); nmr ($CDCl_3$), δ 7.2–8.2 (m, 4, aromatic protons), 5.3–6.6 (m, 2, ArCHOC=O and C=CH), 4.7–5.3 (m, 2, C=CH_2), 1.8–3.0 (m, 4, OCCH_2 and C=CCH_2), and 0.8–1.8 ppm (m, 12.6, CCH_2C); ir (film), 1760 (C=O), 1635, 992, and 910 cm^{-1} (olefin); uv max (CH_3OH), 228 mμ (ε 10,700), 274 (2300), and 282 (2300).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.4; H, 8.85; sapon equiv, 272; iodine no., 93.2. Found: C, 79.7; H, 8.90; sapon equiv, 276; iodine no., 94.8.

A second fraction of product (5.8 g, 11%) was also collected: bp 149–165° (0.1 mm); tlc behavior identical with major fraction; iodine no., 92.8.

3-(9-Hydroxydecyl)phthalide (5). A.—Following, in general, the olefin hydration procedure of Brown and Geoghegan,[6] 3-(9-decenyl)phthalide (**4**, 10.9 g, 0.04 mol) in tetrahydrofuran (10 ml) was added at room temperature to a solution of mercuric acetate (12.8 g, 0.04 mol) in 100 ml of water and 30 ml of tetrahydrofuran. The initial orange color faded to a pale yellow within 12 min. The mixture was stirred for 3.5 hr at room temperature, cooled to 15°, basified with sodium hydroxide (6.0 g, 0.15 mol), and stirred for 15 min more. Ethanol (140 ml) was added and the mixture was cooled to 5°. A solution of sodium borohydride (3.78 g, 0.1 mol) in 3 *N* sodium hydroxide solution (200 ml) was added in 5 min and the alkaline mixture was heated for 1 hr at 70–75°. The mixture was chilled and added in 20 min to ice-cold 4 *N* hydrochloric acid (240 ml). The organic solvents were removed at reduced pressure at 60°. The cooled mixture was saturated with salt and extracted with four 150-ml portions of ether. The dried ($CaSO_4$) extract was evaporated at reduced pressure to give 10.8 g of pale yellow liquid: tlc, two components; terminal double-bond hydration 65–70% (by nmr). The hydration procedure was reapplied to this partially hydrated product to yield 10.5 g of yellow oil: tlc, two major components, one minor component; terminal double-bond hydration 85–95% (by nmr). Purification of this product by column chromatography (silica gel, 2% methanol/benzene) gave 1.13 g of recovered 3-(9-decenyl)phthalide (**4**, 10%) and 8.53 g of 3-(9-hydroxydecyl)phthalide (**5**, 80%): tlc, homogeneous; nmr ($CDCl_3$) δ 7.1–8.1 (m, 4, aromatic protons), 5.2–5.8 (m, 1, ArCHOC=O), 3.4–4.2 (m, 1, OCH), and 0.7–3.4 ppm (m, 20 with 1 removable by deuteration, OH, CCH_2C, and $OCCH_3$, the CH_3 doublet is visible, centered at 1.2 ppm, J = 6 Hz); ir (film), 3400 (OH), 1750 (C=O), and 1108 cm^{-1} (CO, secondary alcohol); uv max (CH_3OH), 228 mμ (ε 10,500), 273 (2100), and 280 (1700).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.4; H, 9.03. Found: C, 74.4; H, 9.00.

B.—Hydration of 3-(9-decenylidene)phthalide (**3**, 81 g, 0.3 mol) by the above procedure with rehydration of the initial product gave 67.5 g of a five-component (tlc) product mixture. Distillation [bp 213–220° (0.08 mm)] and column chromatography (Florisil, benzene gradually enriched with methanol used as solvent) gave purified **5** (40%): tlc, homogeneous; nmr ($CDCl_3$), δ 6.9–8.1 (m, 4, aromatic protons), 5.1–5.9 (m, 1, ArCHOC=O), 3.3–4.1 (m, 1, OCH), and 0.6–2.7 ppm (m, 19.3 with 0.9 removable by deuteration, OH, CCH_2C, and $OCCH_3$, the CH_3 doublet is visible, centered at 1.2 ppm, J = 6 Hz).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.4; H, 9.03; O, 16.5. Found: C, 74.1; H, 9.09; O, 16.9.

2-(10-Hydroxyundecyl)benzoic Acid (7a).—3-(9-Hydroxydecyl)phthalide (**5**, 2.0 g, 0.0069 mol) in tetrahydrofuran (15 ml) and 20% aqueous sodium hydroxide (15 ml) was heated at reflux for 2 hr. The tetrahydrofuran was removed by distillation and the residue was diluted to 100 ml with water and adjusted to a pH of 10.2 with hydrochloric acid. Palladium (0.5 g, 5% Pd/C) was added and the mixture was hydrogenated in a Parr hydrogenator for 12 hr at 75–80° at 50-psi hydrogen pressure.[7] The filtered mixture was extracted with ether. The aqueous solution was acidified with hydrochloric acid, saturated with salt, and extracted with four 100-ml portions of ether. Removal of the ether by evaporation gave 1.74 g (86%) of 2-(10-hydroxyundecyl)benzoic acid (**7a**) as an oil: nmr ($CDCl_3$), δ 7.7–8.2 (m, 1, aromatic proton), 6.9–7.7 (m, 5 with 2 removable by deuteration, aromatic protons, OH, and COOH), 3.5–4.2 (m, 1, OCH), 2.6–3.5 (crude t, 2, $ArCH_2$), and 0.9–2.6 ppm (m, 19, CCH_2C and $OCCH_3$, the CH_3 doublet is visible, centered at 1.2 ppm, J = 6 Hz); ir (film), 3300 (OH) and 1690 cm^{-1} (COOH); uv max (CH_3OH), 230 mμ (ε 6570) and 280 (850).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 74.0; H, 9.65; neut equiv, 292. Found: C, 74.5; H, 9.65; neut equiv, 291.

Methyl 2-(10-hydroxyundecyl)benzoate (7b) was obtained from **7a** (diazomethane) as a neutral oil: tlc, homogeneous; nmr ($CDCl_3$), δ 7.5–8.0 (m, 1, aromatic proton), 6.8–7.5 (m, 3, aromatic protons), 3.2–4.0 (m, 4, OCH and $COOCH_3$), 2.2–3.2 (crude t, 2, $ArCH_2$), 1.7–2.2 (m, 1 removable by deuteration, OH), and 0.60–1.7 ppm (m, 19, CCH_2C and $OCCH_3$, the CH_3 doublet is visible, centered at 1.2 ppm, J = 6 Hz); ir (film), 3350 (OH) and 1715 cm^{-1} (C=O); uv max (CH_3OH) 239 mμ (ε 7440) and 289 (1220).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.5; H, 9.87. Found: C, 74.2; H, 9.81.

O,O-Di-(2-benzoxazolyl)zearalane (10b).—A stirred mixture of zearalane (**10a**,[2] 30.6 g, 0.1 mol), 2-chlorobenzoxazole (34.8 g, 0.23 mol), and potassium carbonate (35.4 g, 0.26 mol) in acetone (400 ml) was heated at reflux for 24 hr. The warm mixture was filtered and the filter cake was washed with acetone. Concentration and cooling of the filtrate gave 45.7 g (85%) of **10b**: mp 120.5–122.5°; nmr ($CDCl_3$), δ 7.0–7.8 (m, 10, aromatic protons), 4.9–5.7 (m, 1, ArCOOCH), 2.2–3.5 (m, 2, $ArCH_2$), and 0.9–2.0 ppm (m, 19.7, CCH_2C and $OCCH_3$).

Anal. Calcd for $C_{32}H_{32}N_2O_5$: C, 71.1; H, 5.97; N, 5.18. Found: C, 71.8; H, 5.76; N, 5.23.

(+)-Dideoxyzearalane (2).—A solution of **10b** (46.1 g, 0.085 mol) in ethanol (450 ml) was reduced in three portions each in the presence of 5 g of 5% Pd/C catalyst. The reductions were carried out in a Parr hydrogenator at 70° at a hydrogen pressure of 50 psi.[13] The filtered reduction mixtures were evaporated (rotary evaporator) to yield 43.5 g of an oil–solid residue. This residue was twice heated with 300 ml *n*-hexane giving 21 g of benzoxazolidone, mp 136–138°. Evaporation of the hexane solution gave 22.5 g of oil. This oil was redissolved in hexane and the hexane solution was washed with 5% sodium hydroxide solution, 3 *N* hydrochloric acid, and water. The solution was then char treated (Darco G-60), filtered, and evaporated to yield 20.8 g (89%) of (+)-dideoxyzearalane (**2**) as a water-white oil: tlc, homogenous; $[\alpha]_{546}^{25}$ +92° (c 1, CH_3OH); nmr ($CDCl_3$), δ 7.6–7.8 (m, 1, aromatic proton), 7.0–7.5 (m, 3, aromatic protons), 5.0–5.7 (m, 1, ArCOOCH), 3.0–3.7 (m, 1, ArCH), 2.4–3.0 (m, 1, ArCH), and 0.8–2.1 ppm (m, 19, CCH_2C and $OCCH_3$, the CH_3 doublet is visible, centered at 1.2 ppm, J = 6 Hz); ir (film), 1710 cm^{-1} (C=O); uv max (CH_3OH) 228 mμ (ε 6500) and (960).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.55. Found: C, 78.6; H, 9.94.

(+)-2-(10-Hydroxyundecyl)benzoic Acid (7a).—A solution of (+)-dideoxyzearalane (16.2 g, 0.059 mol) in dimethyl sulfoxide (200 ml) and 20% aqueous sodium hydroxide (120 ml) was heated at reflux for 24 hr. Water (200 ml) was added to the cooled mixture. The alkaline solution was extracted with three 200-ml portions of chloroform and acidified with concentrated hydrochloric acid (60 ml). The acidic mixture was extracted with three 200-ml portions of chloroform, and the chloroform extract was washed with water (100 ml). Further purification was achieved by extraction of the hydroxy acid into aqueous sodium bicarbonate solution, reacidification, and reextraction into chloroform. Removal of the solvent gave 15.6 g (90%) of (+) **7a** as a yellow oil: $[\alpha]_{546}^{25}$ +5° (*c* 1, CH_3OH); nmr ($CDCl_3$), δ 8.0–8.2 (m, 1, aromatic proton), 7.0–7.7 (m, 3, aromatic protons), 6.8–7.0 (m, 2, COOH) and COH), 3.5–4.2 (m, 1, OCH), 2.8–3.3 (crude t, 2, $ArCH_2$), and 1.1–2.0 ppm (m, 19, CCH_2C and $OCCH_3$, the CH_3 doublet is visible, centered at 1.2 ppm, J = 6 Hz); ir (film), 3325 (OH) and 1690 cm^{-1} (C=O); uv max (CH_3OH), 230 mμ (ε 7100) and (1400).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 74.0; H, 9.65. Found: C, 73.8; H, 9.66.

Methyl (+)-2-(10-hydroxyundecyl)benzoate (7b) was obtained from (+) **7a** (diazomethane) as a neutral oil: tlc, homogeneous;

(13) This procedure is patterned after that of Musliner and Gates[10] except that ethanol is used as a solvent at a higher temperature than that recommended.

$[\alpha]_{546}^{25}$ +6° (*c* 1, CH_3OH); nmr ($CDCl_3$), δ 7.6–8.0 (m, 1, aromatic proton), 7.0–7.6 (m, 3, aromatic protons), 3.5–4.2 (m, 4, OCH and $COOCH_3$), 2.5–3.5 (crude t, 2, $ArCH_2$), and 0.9–2.5 ppm (m, 20, 1 removable by deuteration, OH, CCH_2C, and $OCCH_3$, the CH_3 doublet is visible, centered at 1.2 ppm, J = 6 Hz); ir (film), 3325 (OH) and 1715 cm^{-1} (C=O); uv max (CH_3OH) 230 mμ (ε 7300) and 1270).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.5; H, 9.87. Found: C, 74.6; H, 9.95.

(+)-Dideoxyzearalane (2) by Cyclization of (+) 7a.—To a cold (8°), stirred solution of (+) **7a** (2.10 g, 0.0072 mol) and triethylamine (1.68 g, 0.017 mol) in benzene (2050 ml) was added 8 ml of phosgene solution (12.5% in benzene). The mixture was stirred at 8° for 2 hr, at room temperature for several days, and at reflux for 43 hr. The reaction mixture was then washed with water and 3 *N* hydrochloric acid, dried (Na_2SO_4), and evaporated finally at high vacuum to yield 2.08 g of an oil. This oil was separated into fractions by column and preparative plate chromatography to yield 0.47 g (24%) of (+)-dideoxyzearalane: $[\alpha]_{546}^{25}$ +90° (*c* 1, CH_3OH); tlc, homogeneous (four solvent systems) and identical with the behavior of the (+)-dideoxyzearalane obtained by hydrogenolysis of **10b**. The nmr, ir, and uv spectra were also all identical with the corresponding spectra of (+)-dideoxyzearalane obtained by hydrogenolysis of **10b**.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.55. Found: C, 78.8; H, 9.93.

The other major, partially purified, product (0.5 g) had a low R_f on tlc plates and an nmr spectrum resembling that of dideoxyzearalane except in the aromatic and benzylic hydrogen regions as described in the discussion section.

(±)-Dideoxyzearalane (2).—A solution of (±) **7a** (0.9 g, 0.0031 mol), triethylamine (0.72 g, 0.007 mol), and 3.5 ml of phosgene solution (12.5% in benzene), prepared at 8°, was stirred at 8° for 2 hr, at room temperature overnight, and at reflux for 79 hr. The product, isolated as described for recyclized (+)-dideoxyzearalane, was obtained as an oil (0.21 g, 25%) identical in tlc behavior with that of (+)-dideoxyzearalane. The nmr, ir, and uv spectra were also all identical with the corresponding spectra of (+)-dideoxyzearalane.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.55. Found: C, 78.5; H, 10.0.

Registry No.—2 (+), 17397-59-0; 2 (±), 17397-60-3; **3**, 17393-24-7; **4**, 17393-25-8; **5**, 17414-48-1; **7a**, 17393-26-9; **7a** (+), 17397-61-4; **7b**, 17393-27-0; **7b** (+), 17397-22-7; **10b**, 17393-28-1; 10-undecenoic anhydride, 17393-29-2.

The Synthesis of DL-Zearalenone[1]

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DL-Zearalenone (1) has been synthesized by a Wittig reaction between (deca-5,9-dion-1-yl)triphenylphosphonium bromide, diethylene ketal (**17**), and ethyl 4,6-dihydroxy-2-formylbenzoate dimethyl ether (**5**), followed by base-catalyzed lactonization of the derived hydroxy ester **21**, and cleavage of protecting groups.

Zearalenone[3,4] (**1**), a metabolite of pathogenic fungi, has been isolated[5,6] from infected corn by groups at Purdue and at the University of Minnesota. Other structurally related resorcylic acid lactones[7-9] are notable for their antifungal and antibiotic activity. Potent steroidlike anabolic and uterotrophic activity ascribed[5] to zearalenone was therefore of particular interest and prompted the synthesis described here. Syntheses of zearalenone and a related substance, curvularin, have also been completed by other groups.[10-12]

Of the three principal approaches to macrolides which have been described, Baeyer–Villiger oxidation[13] of macrocyclic ketones, per acid oxidation[14] of bicyclic enol ethers, and the direct cyclization of hydroxy acids and esters,[15-17] the last is synthetically most direct and was selected in the present case. The synthesis was further divided into the construction of aromatic (**5**) and aliphatic (**17**) portions, to be linked by a Wittig reaction.

The aromatic portion was readily constructed from ethyl *o*-orsellinate diacetate[18] (**2**) by oxidation with chromium trioxide in acetic acid–acetic anhydride to the aldehyde tetraacetate **3**, followed by hydrolysis to the phenolic aldehyde **4**, and methylation to the required ethyl 4,6-dihydroxy-2-formylbenzoate dimethyl ether (**5**) (Scheme I).

The aliphatic part was constructed as follows. Carbethoxylation[19] of 1-hexen-5-one (**6**) with diethyl carbonate and sodium hydride gave the β-keto ester **7**. Michael addition to methyl vinyl ketone then extended the carbon chain to the required length forming the diketo ester **8**. Hydrolysis and decarboxylation of this substance led, not unexpectedly, to a cyclic product **9** rather than the required *n*-decyl derivative **12**. However, basic hydrolysis of the keto ester **8** was achieved by way of the intermediate ketal **10** in which the reactive functions are protected. Decarboxylation and ketal cleavage under acidic conditions then gen-

(1) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967, Publication No. 338 from the Syntex Institute of Steroid Chemistry, p 7P. For Publication No. 337, see F. Alvarez, E. Denot, E. Necoechea, J. Calva, P. Crabbé, and A. Bowers, submitted for publication.

(2) Postdoctoral Fellow, 1965–1966.

(3) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966).

(4) C. H. Kuo, D. Taub, R. D. Hoffsommer, and N. L. Wendler, *Chem. Commun.*, 761 (1967).

(5) M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *Nature*, **196**, 1318 (1962).

(6) C. J. Mirocha, C. M. Christensen, and G. H. Nelson, *Appl. Microbiol.*, **15**, 497 (1967).

(7) A. J. Birch, O. C. Musgrave, R. W. Richards, and H. Smith, *J. Chem. Soc.*, 3146 (1959).

(8) R. N. Mirrington, E. Ritchie, C. W. Shoppee, S. Sternhell, and W. C. Taylor, *Aust. J. Chem.*, **19**, 1265 (1966).

(9) F. McCapra and A. I. Scott, *Tetrahedron Lett.*, 869 (1964).

(10) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Chem. Commun.*, 225 (1967); *Tetrahedron*, **24**, 2443 (1968).

(11) N. N. Girotra and N. L. Wendler, *Chem. Ind.* (London), 1493 (1967).

(12) P. M. Baker, B. W. Bycroft, and J. C. Roberts, *J. Chem. Soc.*, 1913 (1967).

(13) C. H. Hassall, *Org. Reactions*, **9** (1957).

(14) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966).

(15) M. Stoll and P. Bolle, *Helv. Chim. Acta*, **31**, 98 (1948).

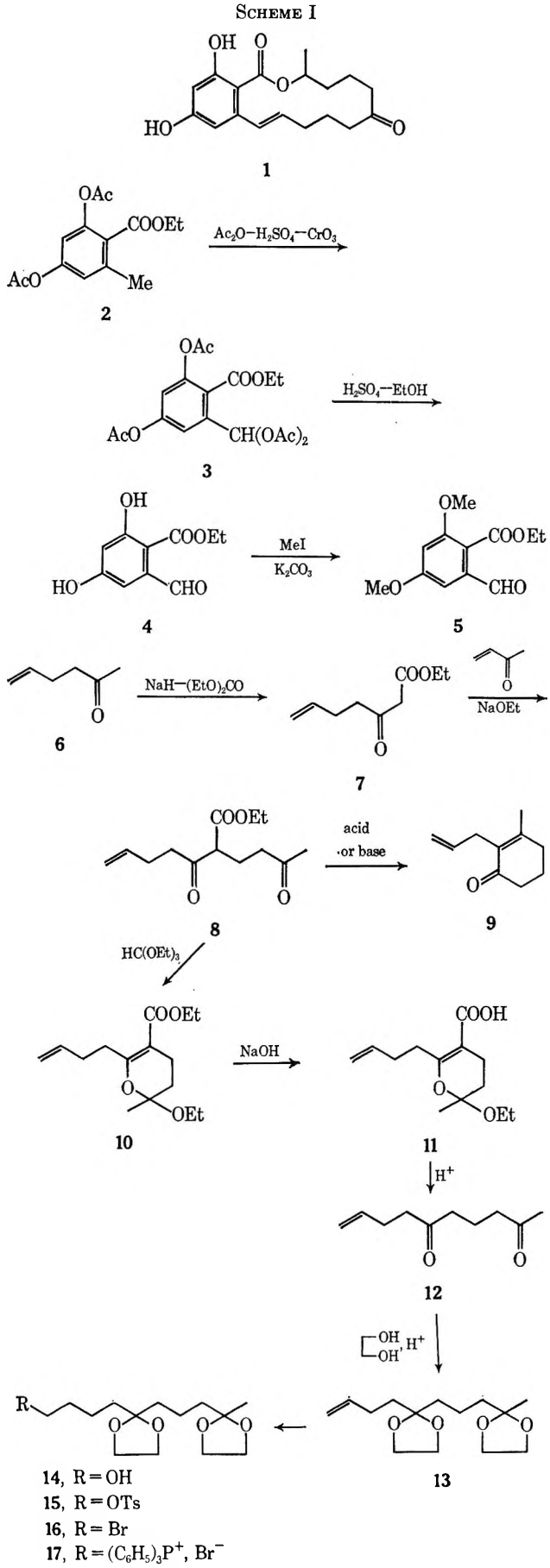
(16) J. W. Hill and W. H. Carothers, *J. Amer. Chem. Soc.*, **55**, 5031 (1933).

(17) M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **17**, 1283 (1934).

(18) A. Sonn, *Ber.*, **61**, 926 (1928).

(19) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, *J. Amer. Chem. Soc.*, **63**, 2252 (1941).

SCHEME I

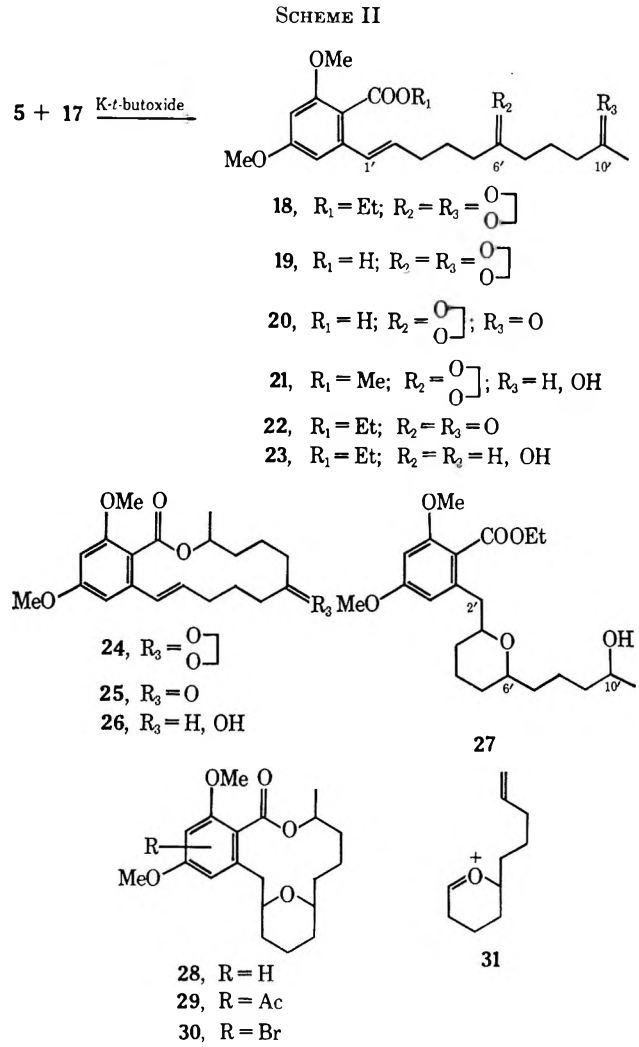


erated 1-decene-5,9-dione (**12**) containing the carbon skeleton and correctly positioned oxygen atoms of the aliphatic portion.

Ethylene ketal formation and hydroboration[20] of the olefinic bond gave the alcohol **14** which was further converted into the amorphous phosphonium salt **17** *via* the *p*-toluenesulfonate ester **15** and the bromide **16** intermediates.

Coupling of the aldehyde **5** and phosphonium salt **17** by a Wittig reaction in dimethyl sulfoxide proceeded normally leading to the ester **18**, containing the carbon skeleton of zearalenone and the 1′ double bond but lacking differentiation between functional groups at positions 6′ and 10′. The configuration of the double bond was not determined at this stage; however, completion of the synthesis gave DL-zearalenone of known *trans* stereochemistry. (See Scheme II.)

SCHEME II



The mass spectrum of the ester **18** showed a molecular ion (*m/e* 478), and also peaks at *m/e* 87, 201, and 349 corresponding to the predicted fission α to the ketal groups.[21] Specific cleavage of the ketal at C-10 of the side chain of the acid **19** in aqueous acetone containing *p*-toluenesulfonic acid proceeded in 85% yield forming the monoketal **20**. By contrast, the corresponding ester **18** was cleaved to a mixture of monoketals and the diketone **22**. It has been shown[22] that a neighboring

(20) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(21) G. Von Mutzenbecher, Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *Steroids*, **2**, 475 (1963).

(22) T. C. Bruice and D. Piszkiewicz, *J. Amer. Chem. Soc.*, **89**, 3568 (1967).

carboxyl group does not catalyze the acidic hydrolysis of a ketal. In our case, there appears to be an inhibition of cleavage of the C-6 ketal by a somewhat distant carboxyl group but not by the corresponding ester.

The keto acid **20** was esterified with diazomethane, and then the ketone at C-10 was reduced by sodium borohydride yielding **21**. The lactone ring was formed in 8% yield by base-catalyzed intramolecular ester exchange of the hydroxy ester **21** in the presence of *t*-amyl alcohol as a proton source, the methanol formed being fractionally distilled out of the mixture to displace the ester–lactone equilibrium in favor of the lactone **24**. Cleavage of the remaining ketal group gave 4,6-dihydroxy-2-(10′-hydroxy-1-undecen-6′-on-1′-yl)-benzoic acid lactone dimethyl ether (**25**), DL-zearalenone dimethyl ether, which exhibited an infrared (ir) spectrum indistinguishable from that of a specimen prepared from natural zearalenone.[23] Although the yield at the lactonization stage was low (8%), it was quite sufficient to allow completion of the synthesis. Similar yields have been reported in the direct lactonization of simple α,ω-hydroxy acids.[24]

Several reagents were considered for the final stage, removal of the ether-protecting groups. Reaction of the dimethyl ether **25** with boron trifluoride etherate or with sodium diphenylphosphide[25] led only to monoethers while boron tribromide[26] in dichloromethane gave complete cleavage in 34% yield to DL-zearalenone (**1**).

Differentiation of the two ketonic functions of the diketo ester **22** and lactonization was also achieved in another way. Reduction with sodium borohydride gave the diol **23**. Base-catalyzed addition of the 6′-hydroxyl group to the aromatic ester activated double bond then led to ethyl 4,6-dihydroxy-2-(10′-hydroxy-2′,6′-oxyundec-1′-yl)benzoate dimethyl ether (**27**). This in turn was converted by sodium hydride into the lactone **28** in 15% yield. The mass spectrum showed the molecular ion and a fragment *m/e* 153 which is probably due to the ion **31**. Cleavage of the pyran ring by acidic reagents to the alcohol **26**, or other derivatives, which would be convertible into zearalenone (**1**) was not achieved. For example, treatment with acetic anhydride and *p*-toluenesulfonic acid resulted in acylation of the aromatic system forming **29**. Neither was it possible to introduce bromine selectively at the benzylic carbon atom of **28** for subsequent generation of the double bond by reductive methods.

Experimental Section[27]

Ethyl 4,6-Dihydroxy-2-dihydroxymethylbenzoate Tetraacetate (3).—A solution of 3 g of the ester **2**[18] in 25 ml of acetic acid, 17 ml of acetic anhydride, and 3 ml of sulfuric acid was cooled to 0°, and 3 g of chromium trioxide was added in small portions during 2 hr. After another 3 hr the reaction mixture was poured onto ice; excess sodium metabisulfite solution was added; and the products were extracted with ether. Chromatography on silica gel and crystallization from ether gave 900 mg of the tetraacetate, mp 97–98°.

Anal. Calcd for $C_{18}H_{20}O_{10}$: C, 54.54; H, 5.09; O, 40.37. Found: C, 54.61; H, 5.36; O, 39.81.

Ethyl 4,6-Dihydroxy-2-formylbenzoate (4).—A solution of 850 mg of the tetraacetate **3** in 20 ml of ethanol, 5 ml of water, and 0.5 ml of sulfuric acid was heated under reflux for 2 hr. Excess sodium bicarbonate solution was added, and the mixture was evaporated *in vacuo*. Trituration of the residue with ether, filtration, and evaporation of solvent from the filtrate gave the phenol **4** in crude form.

Ethyl 4,6-Dihydroxy-2-formylbenzoate Dimethyl Ether (5).—A mixture of 900 mg of the crude phenol **4** and 14 g of potassium carbonate in 84 ml of acetone and 24 ml of methyl iodide was heated under reflux for 4 hr. The mixture was filtered to remove inorganic salts and evaporated to drynesss, and the residue was dissolved in ether which was then washed with water. Evaporation of the solvent and crystallization of the residue from acetone–hexane gave 650 mg of the dimethyl ether: mp 110–111°; ir (Nujol) 1605, 1625, and 1770 cm^{-1}.

Anal. Calcd for $C_{21}H_{14}O_6$: C, 60.50; H, 5.92; O, 33.58. Found: C, 60.18; H, 5.81; O, 33.47.

Ethyl 1-Hepten-5-on-7-oate (7).—A solution of 81 g of 1-hexen-5-one (**6**) in 100 ml of ether was added during 2 hr to a boiling mixture of 179 g of diethyl carbonate and 37 g of sodium hydride (50% dispersion in oil) in 300 ml of ether. After the solution was heated under reflux for 2 hr more, ethanol was added to destroy the excess hydride, and the mixture was poured onto ice and acidified with acetic acid. Extraction with ether and distillation gave 124 g of ester, bp 85–95° (0.5 mm).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29; O, 28.20. Found: C, 63.32; H, 8.45; O, 28.27.

6-Carbethoxy-1-decene-5,9-dione (8).—A solution of 88 g of the keto ester **7** in 1 l. of absolute ethanol was cooled to −10°, and sodium ethoxide (from 0.5 g of sodium) was added. To this solution was added 37 g of methyl vinyl ketone during 1 hr, and the mixture was kept at −10° for another 2 hr. Excess acetic acid was then added to neutralize the base, and the solvents were evaporated *in vacuo*. The residue was extracted with ether which was then washed with sodium bicarbonate solution and with water. Evaporation of the solvent and distillation gave 71 g of the diketo ester **8**: bp 140–150° (0.6 mm); *m/e* 195 ($M^+ - OEt$).

9-Ethoxy-5,9-oxy-1,5-decadiene-6-carboxylic Acid (11).—Treatment of the diketo ester **8** with 5% ethanolic sodium hydroxide or with sulfuric acid in acetic acid led to an oily product, **9**: nmr 1.90 (s, 3, CH_3), 2.97, 3.07 (d, 2, CH_2), and 4.6–5.3 ppm (m, 3, $CH{=}CH_2$).

A solution of 13 g of the diketo ester **8** in 120 ml of dioxane and 13 ml of triethyl orthoformate containing 3 g of *p*-toluenesulfonic acid was kept at 20° for 3 hr. Pyridine was added to neutralize the acid; the solution was diluted with water; and the product was extracted with ether. The ether solution was dried over magnesium sulfate, and the solvent was removed *in vacuo*. Chromatography on silica gel gave 8 g of the ester **10** which was not further purified. Basic hydrolysis of the ester **8** gave the enone **9**: nmr 1.90 (s, 3, CH_3), 2.97, 3.07 (d, 2, CH_2), 4.6–5.3 (m, 2, $=CH_2$), and 5.3–6.1 ppm (m, 1, =CH).

A solution of 8.3 g of the ester **10** in 13 ml of water and 9 ml of ethanol containing 9 g of potassium hydroxide was heated under reflux for 48 hr. The cooled solution was extracted with ether to remove neutral substances and acidified with dilute hydrochloric acid. Extraction with ether gave, after drying with magnesium sulfate, evaporation of the solvent, and crystallization from hexane, 5.6 g of acid **11**: mp 110–111°; uv max (methanol) 242 mμ (ε 11,990); nmr 1.13 (t, J = 7 cps, CH_2CH_3) and 1.45 ppm (s, CH_3).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39; O, 26.63. Found: C, 64.77; H, 8.63; O, 26.6.

1-Decene-5,9-dione (12) and 1-Decene-5,9-dione Diethylene Ketal (13).—A solution of 8.1 g of the acid **11** in 45 ml of dioxane and 15 ml of water containing 1.3 g of *p*-toluenesulfonic acid was allowed to stand at 20° for 15 hr. Ether was added; the mixture was washed with sodium bicarbonate solution and with water and dried over magnesium sulfate; and the solvent was removed *in vacuo*. Chromatography on silica gel gave 4.0 g of the dione **12**: bp 80° (0.03 mm); nmr 2.12 (s, $COCH_3$) and 4.8–6.2 ppm (m, $CH{=}CH_2$).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.20; H, 9.94; O, 18.87.

(23) Supplied by Professor C. J. Mirocha to whom we are indebted.

(24) M. Kerschbaum, *Ber.*, **60B**, 902 (1927).

(25) F. G. Mann and M. J. Pragnell, *J. Chem. Soc.*, 4120 (1965).

(26) J. W. F. McComie and M. L. Watts, *Chem. Ind.* (London) 1658 (1963).

(27) Uv spectra were measured in methanol and nmr spectra in deuteriochloroform. Nmr spectra are reported in δ values relative to tetramethylsilane. Mass spectra were taken with an Atlas CH-4 spectrometer at 70 eV. We wish to thank Dr. L. Throop and his associates for the physical measurements herein reported.

A solution of 55 g of the diketone 12 in 500 ml of benzene and 81 g of ethylene glycol containing 6 g of *p*-toluenesulfonic acid was heated under reflux for 6 hr with separation of the water formed (Dean–Stark separator). Pyridine was added to the cooled solution which was then washed with water and dried over magnesium sulfate. Evaporation of the solvent and distillation of the residue gave 33 g of the diketal **13**: bp 145–150° (0.4 mm); nmr 1.28 (s, CH_3) and 3.91 ppm (OCH_2CH_2O).

1-Hydroxydeca-5,9-dione Diethylene Ketal (14).—A solution of 33 g of the olefin **13** in 100 ml of diglyme was treated with 3.5 g of sodium borohydride followed by 25 ml of boron trifluoride etherate in 20 ml of diglyme. The mixture was cooled, and 30 ml of 3 *N* sodium hydroxide and 30 ml of 30% hydrogen peroxide simultaneously added with care. The mixture was diluted with water and extracted with ether. The ether solution was dried over magnesium sulfate, and the solvent was removed *in vacuo* to give 28 g of the alcohol **14**, nmr 3.61 ppm ($-CH_2O$). For analytical purposes a sample was hydrolyzed with aqueous acetone containing *p*-toluenesulfonic acid to 1-hydroxydeca-5,9-dione, mp 51–53° from hexane–benzene.

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.92; H, 9.55.

1-Bromodeca-5,9-dione Diethylene Ketal (16).—A solution of 2 g of the alcohol **14** in 5 ml of pyridine was treated with 3 g of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at 20° for 2 hr and then cooled in ice–water, and 1 ml of water was added. After the mixture stood for 1 hr at 20°, to allow hydrolysis of the unreacted reagent, hexane was added, the mixture was filtered, and the filtrate was washed ten times with water. Evaporation of the solvent gave the tosylate ester **15**, which was used in the next reaction without further purification.

The crude tosylate ester **15** was dissolved in 30 ml of acetone containing 10 g of lithium bromide, and the mixture was stirred for 6 hr. The acetone was removed *in vacuo*, and the residue was treated with water and extracted with ether. The extract was dried over magnesium sulfate, and the solvent was removed *in vacuo*. Chromatography on silica gel gave 1.6 g of the oily bromide **16**: nmr 3.41 (t, J = 7 cps, CH_2Br) and 3.91 ppm (OCH_2CH_2O); *m/e* 321 ($M^+ - CH_3$).

(Deca-5,9-dion-1-yl)triphenylphosphonium Bromide Diethylene Ketal (17).—A solution of 1.7 g of the bromide **16** and 2 g of triphenylphosphine in 7 ml of benzene was heated under reflux for 48 hr. The solvent was evaporated *in vacuo*, and the residue washed five times with ether. Removal of ether *in vacuo* gave 2.3 g of the phosphonium salt **17** as a hygroscopic gum: nmr (d_6-dimethyl sulfoxide), 1.22 (s, CH_3), 3.83 (s, OCH_2CH_2O), and 7.81–7.91 ppm (aromatic H).

Ethyl 4,6-Dihydroxy-2-(1′-undecen-6′,10′-dion-1′-yl)benzoate Diethylene Ketal Dimethyl Ether (18).—A solution of 0.30 g of the aldehyde **5** and 1.1 g of the phosphonium salt **17** in 11 ml of dimethyl sulfoxide was dried over molecular sieves and then transferred to another flask, and a solution of 0.30 g of potassium *t*-butoxide in 1 ml of dimethyl sulfoxide added under nitrogen. After heating at 47° for 5 hr, the mixture was poured into water and extracted with ether. Evaporation of the solvent and chromatography on silica gel gave 0.35 g of the ester **18**: bp 180–185° (7×10^{-3} mm); nmr 1.28 (s, CH_3), 3.88 (s, OCH_2CH_2O), and 6.0–6.6 ppm (m, 4, Ar–H and =CH); *m/e* 478 (M^+), 433 ($M^+ - OEt$), 349, 201, 129, and 87 (α-ketal cleavage).

Methyl 4,6-Dihydroxy-2-(10′-hydroxy-1′-undecen-6′-on-1′-yl)benzoate Dimethyl Ether 6′-Ethylene Ketal (21).—A solution of 13 mg of the ester **18** and 0.5 g of potassium hydroxide in 5 ml of dimethyl sulfoxide was heated at 75° under nitrogen for 4 hr. The solution was acidified with dilute hydrochloric acid, diluted with water, and extracted with dichloromethane. Evaporation of the solvent gave the acid **19** which was further treated with 1 ml of acetone containing 0.1 ml of water and 1 ml of *p*-toluenesulfonic acid for 8 hr. Addition of water, extraction with benzene, and evaporation of the solvent gave the acid **20**: nmr 2.14 (s, $COCH_3$) and 3.90 ppm (s, OCH_2CH_2O).

Addition of diazomethane in ether to the acid **20** gave the methyl ester which was further treated with 20 mg of sodium borohydride in 1 ml of ethanol for 10 min followed by the addition of 0.2 ml of acetone. The solution was evaporated to dryness, and the residue was extracted with benzene. Concentration of the extracts gave the ester **21** in 85% over-all yield from **18**. Acid-catalyzed ketal cleavage gave methyl 4,6-dihydroxy-2(10′-hydroxyundec-1′-en-6′-on-1′-yl)benzoate dimethyl ether: *m/e* 360 ($M^+ - H_2O$), 329 ($M^+ - OMe$), and 248.

4,6-Dihydroxy-2-(10′-hydroxy-1′-undecen-6′-on-1′-yl)benzoic Acid Lactone 4,6-Dimethyl Ether (24).—To 5 ml of *t*-amyl alcohol was added 30 mg of sodium, and the mixture was heated until dissolution was complete. A solution of 10 mg of the hydroxy ester **21** in 100 ml of dry toluene was added, and the solution was distilled through a Dufton column during a period of 6 hr, a total of 20 ml of distillate being collected. Excess acetic acid was added, and the solvents was removed *in vacuo*. Extraction of the residue with dichloromethane and evaporation of the solvent gave the lactone **24**. This product was treated with 5 mg of *p*-toluenesufonic acid in 0.5 ml of acetone, followed by addition of excess triethylamine and evaporation to dryness. Extraction of the residue with dichloromethane and preparative tlc of the product on silica gel gave 0.8 mg of the lactone **25**: mp 128–129° from hexane (lit.[10] mp 124–126°); ir (supercooled film) 1720 cm^{-1} (lactone) (the spectrum was identical with that of an authentic specimen of zearalenone dimethyl ether); *m/e* 346 (M^+).

4,6-Dihydroxy-2-(10′-hydroxy-1′-undecen-6′-on-1′-yl)benzoic Acid Lactone, DL-Zearalenone (1).—A solution of 0.4 mg of the lactone **25** in 0.1 ml of dry methylene dichloride was treated with 0.01 ml of boron tribromide. After 1 hr at 20°, the mixture was added to sodium bicarbonate solution at 0°, and the product was extracted with ether. Tlc and distillation gave 0.2 mg of DL-zearalenone (**1**): bp 115–120° (7×10^{-3} mm) (natural zearalenone had bp 115–120° at 8×10^{-3} mm); R_f on silica gel chromatoplate 0.41 (hexane–acetone 7:3), identical with that of the natural product;[23] the synthetic and natural compounds had the same retention time on gas chromatography (SE-30 on Diatoport S at 220°); *m/e* 318 (M^+), 300, 284, 256, 189, and 188. These peaks occur in the mass spectrum of natural zearalenone.

Ethyl 4,6-Dihydroxy-2-(10′-hydroxy-2′,6′-oxyundec-1′-yl)benzoate Dimethyl Ether (27) and 4,6-Dihydroxy-2-(10′-hydroxy-2′,6′-oxyundec-1′-yl)benzoic Acid Lactone Dimethyl Ether (28).—A solution of 30 mg of the diketone **22** in 2 ml of methanol was treated with 50 mg of sodium borohydride. After 30 min the excess borohydride was destroyed with acetone, and the solvent was evaporated *in vacuo*. Water was added to the residue, and the product was extracted with ether. Chromatography on silica gel gave 22 mg of the diol **23**.

A solution of 22 mg of the diol **23** in 150 ml of dry benzene containing 2 mg of sodium hydride (50% dispersion in oil) was slowly distilled during 2 hr (50 ml of distillate collected). Addition of water, separation of the benzene layer, and evaporation gave the pyran **27**: nmr 1.13 (d, J = 6 cps, $OCHCH_3$), 1.34 (t, J = 6 cps, OCH_2CH_3), 2.50–3.00 (m, $ArCH_2$ and CH–O), and 4.32 ppm (q, J = 6 cps, OCH_2CH_3).

A solution of 107 mg of the diol **23** in 400 ml of dry toluene containing 11 mg of sodium hydride (50% dispersion in oil) was distilled during 26 hr with collection of 100 ml of distillate. Excess acetic acid was added to the cooled solution, followed by distilled during 26 hr with collection of 100 ml of distillate. Excess acetic acid was added to the cooled solution, followed by evaporation *in vacuo*. The benzene-soluble part of the residue was purified by preparative tlc yielding 16 mg of the lactone **28**: nmr 1.34 (d, J = 6.5 cps, $OCHCH_3$), 2.31 (q, J_{gem} = 16, J_{vic} = 2.5 cps, $ArCH_2CH$–O), 3.24–3.70 (m, CH–O), 3.75, 3.76 (OCH_3), and 6.18–6.40 ppm (m, Ar–H); *m/e* 348 (M^+), 196, 178, and 153.

Reactions of 4,6-Dihydroxy-2-(10′-hydroxy-2′,6′-oxyundec-1′-yl)benzoic Acid Lactone Dimethyl Ether (28). A.—A solution of 20 mg of the pyran **28** in 1 ml of acetic anhydride containing 30 mg of *p*-toluenesulfonic acid was heated at 60° for 60 hr. The solution was poured into water, and the products were extracted by benzene. Evaporation of the solvent and chromatography of the residue gave 10 mg of **29**: nmr 2.40 (s, CH_3CO) and 6.35 ppm (s, 1, Ar–H); *m/e* 390 (M^+).

B.—A mixture of 5.0 mg of the pyran **28** and 2.6 mg of N-bromosuccinimide in 0.3 ml of carbon tetrachloride was refluxed for 45 min while irradiating with uv light. The solution was evaporated, 1 ml of ethanol containing 1% of acetic acid and 100 mg of zinc dust were added. After stirring for 15 hr, the mixture was filtered, and the solvent was removed *in vacuo*. Chromatography on silica gel gave a mixture of **30** and starting material: nmr 6.42 (s, 1, Ar–H); *m/e* 426 (M^+).

Registry No.—**1**, 14328-07-5; **3**, 17605-04-8; **5**, 17605-05-9; **7**, 17605-06-0; **8**, 17605-07-1; **9**, 17605-08-2; **11**, 17605-09-3; **12**, 17605-10-6; **13**, 17605-11-7; **14**, 17605-12-8; **16**, 17605-13-9; **17**, 17605-14-0; **18**, 17605-15-1; **21**, 17605-16-2; **27**, 17605-17-3; **28**, 17605-18-4.

Aza Steroids. V.[1] Introduction of 11-Hydroxy and 11-Amino Groups

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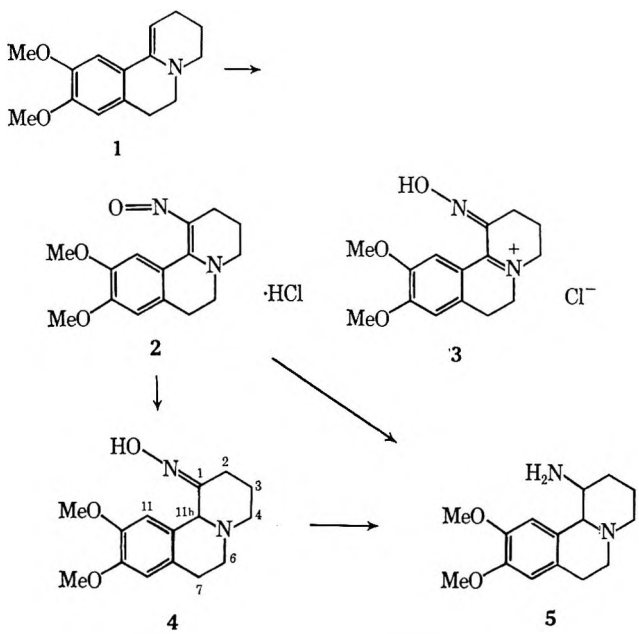
Introduction of hydroxyl and amino groups at position 11 of the 8-aza steroid nucleus has been accomplished. The configurations of the products were deduced by spectral methods.

As part of a continuing program[1] in this laboratory on the synthesis of 8-aza steroids, a convenient method for introduction of the 11β-hydroxyl group characteristic of corticosteroids was needed. The present report describes this work and a concurrently discovered route to 11-amino-8-aza steroids.

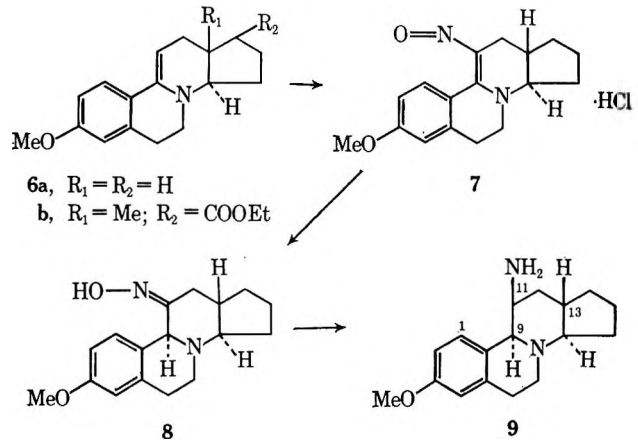
Initial studies were carried out in the related tricyclic benzo[*a*]quinolizine series in order to bypass possible stereochemical complications due to the C–D ring fusion of the aza steroid nucleus. The known[2] cyclic enamine **1** was treated with nitrosyl chloride[3] at low temperature to give a bright yellow 1:1 adduct **2** in high yield. This product was assigned the nitroso structure rather than that of the tautomeric quaternary oxime **3** on the basis of spectral data. Thus the infrared spectrum showed no oxime hydroxyl absorption nor any bands in the 1620–1640-cm^{-1} region characteristic of quaternary salts such as **3**. In addition, the presence of an N–H salt band at 2650 cm^{-1} gave further indication of the nitroso form **2**.



Reduction of **2**, either catalytically or with borohydride, gave a single oxime, **4**. In this product, the B–C ring junction appears to be in the *cis* conformation, as evidenced by the lack of Bohlmann bands[4] in the ir spectrum and the low-field position[5] (4.55 ppm) of the nmr singlet[6] of the angular proton at C-11b. Further, examination of Dreiding models shows that the B–C *trans* oxime is destabilized relative to both *cis* conformations by severe crowding between the oxime nitrogen and the aromatic C-11 proton.

Catalytic reduction of either **2** or **4** furnished a single aminoquinolizidine, **5**. For this product, a *trans*-quinolizidine conformation is indicated by the presence of Bohlmann bands[4] and an upfield[5] (3.23 ppm) signal for the angular hydrogen. This signal appeared as a broad singlet, $W_{1/2}$ = 5 cps, indicative of coupling between the axial C-11b proton (required for *trans* ring fusion) with an equatorial hydrogen at position 1. Thus the amine group in **5** must be axial;[7] this configuration minimizes interaction of the functional group with the nearby aromatic proton.[8]

In the tetracyclic series, an analogous series of reactions was carried out to furnish, starting with enamine **6a**, nitroso adduct **7**, oxime **8**, and amine **9**. As



observed in the tricyclic series, spectral data for these products showed a *cis*-quinolizidine conformation for **8** but a *trans*-quinolizidine conformation and axial amino group for **9**. The relationship of the hydrogens at C-9 and C-13 in **9** must be *anti*[9] [as shown in con-

(1) Part IV: R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Med. Chem.*, **10**, 451 (1967).

(2) (a) R. Child and F. L. Pyman, *J. Chem. Soc.*, 36 (1931); (b) Y. Ban and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **8**, 653 (1960).

(3) H. Metzger, *Tetrahedron Lett.*, 203 (1964).

(4) (a) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); (b) F. Bohlmann, *Ber.*, 91, 2157 (1958); (c) W. E. Rosen, *Tetrahedron Lett.*, 481 (1961).

(5) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).

(6) The fact that this signal is unsplit is clear evidence that the original nitrosation had indeed taken place at C-1.

(7) Drieding models of the two *cis* conformations of **4** reveal no reason to expect significant stability differences between the two, with the likelihood that both conformers are present in equilibrium. For either one, reduction from the side of the oxime farthest removed from the aromatic ring can be predicted from the models; for both conformers, this would introduce the hydrogen at C-1 *cis* to the angular hydrogen at C-11b. One conformer would give initially a *cis*-quinolizidine with an equatorial amine; the other, a *cis* quinolizidine and an axial amine. Both of these intermediates would undergo inversion at the ring nitrogen to give the more stable *trans*-quinolizidine with an axial amine.

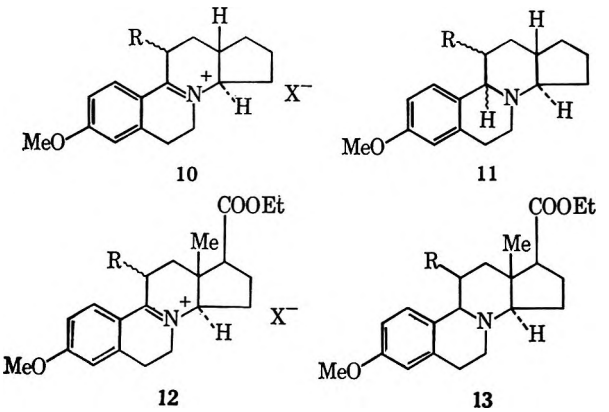
(8) The aromatic signals for products **4** and **5** and the N acetate of **5** appeared in the range of 6.5–6.7 ppm, as reported[5] for a number of *cis*-and *trans*-dimethoxybenzoquinolizines unsubstituted at position 1. Thus it appears that no significant interaction occurs between an axial C-1 substituent and the aromatic proton at C-11. This is in contrast to the observation made for products, **11c** isomers A and C, containing an equatorial C-1 substituent.

(9) In this series of papers, the terms *syn* and *anti* refer to the relationship of the hydrogen at C-9 and the substituent at C-13.

formational diagram **11c**, isomer B (NH_2 in place of OH)] since the axial C-9 hydrogen in **9** and the *trans* C–D ring junction allow only one configuration and conformation, that containing the normal steroid backbone.

Although the oximes described above afforded a good route to aminoaza steroids, they failed in their primary purpose of providing a route for hydroxylation of position 11. When products **2**, **4**, **7**, and **8** were treated with 10% H_2SO_4 and 6 *N* HCl, both with and without added formalin, with levulinic acid in HCl, or with sodium nitrite in both acetic acid and HCl, ketonic material was formed (as evidenced by ir analysis), but in no case could a pure ketone be obtained. Further work on hydrolysis was abandoned when the procedure described below was developed.

Low temperature bromination[10] of enamine **6a** gave an immediate crystalline yellow precipitate of the 11-bromo quaternary bromide, **10a** (X = Br), as an epimeric mixture (*ca.* 3:1 ratio by tlc). Borohydride reduction of this mixture gave a single bromo base, **11a**, which slowly lost HBr on standing. The same sequence on the more highly substituted enamine, **6b**, gave different results. The mixture of salts, **12a**, (X = Br; 1:1 ratio by tlc), gave on reduction no product corresponding to **13a**, but instead a single isomer of the product of reductive debromination, **13e**. A similar reduction may have been responsible for loss of the second isomer of **10a**.



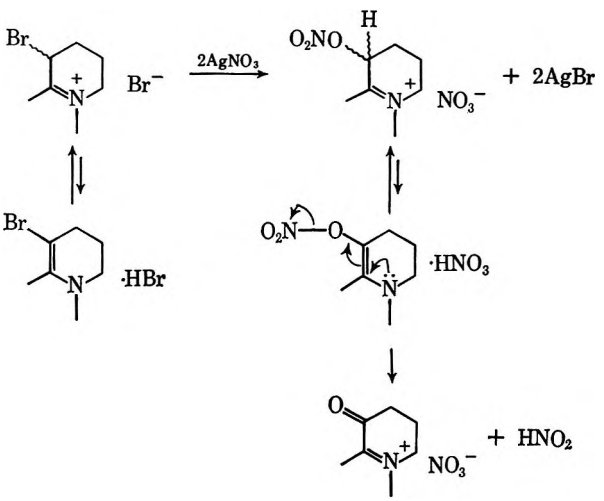
a, R = Br
b, R = OAc
c, R = OH
d, R = O
e, R = H

Product **11a** was found to resist displacement reactions with nucleophilic agents, all reactions leading to recovered **11a** or to enamine **6a** *via* elimination. However, treatment of the 11-bromo quaternary bromides **10a** and **12a** (X = Br) with potassium acetate in acetic acid gave, from **10a**, a 30% yield of a mixture of the corresponding acetoxy salts, **10b**, and from **12a**, a 10% yield of a single isomer of **12b**, both conveniently isolated as their perchlorates (X = ClO_4).

The mixture of acetoxy salts **10b** could not be separated and was therefore reduced and hydrolyzed to afford a mixture of three (isomers A, B, and C) of the four possible isomers of **11c** about the two new assymmetric centers. This mixture was easily separated by chromatography on alumina. In contrast, the single isomer of **12b** was reduced and hydrolyzed to give one isomer of **13c**.

A better yield in the displacement step was accomplished by modification of a procedure developed by Emmons.[11] Treatment of mixtures **10a** and **12a** (X = Br) with silver nitrate in acetonitrile afforded the corresponding ketones **10d** and **12d** (X = ClO_4), respectively, in up to 70% yields. This is in contrast to the reported[11] course of this reaction, in which a base such as piperidine was required to cleave the initially formed nitrate ester, the reaction being an example of a concerted α elimination initiated by base-catalyzed abstraction of an α-hydrogen atom. In the case at hand, the addition of base is not required owing to the enamine–immonium ion tautomeric equilibrium known[2b] to exist in such systems. Thus, the schematic representation shown in Scheme I can be written for the process.

SCHEME I



Reduction of the two keto salts **10d** and **12d** with potassium borohydride in ethanol proceeded in high yield to give, in the case of **10d**, two (isomers A and B) of the three isomers of **11c** described above and, in the case of **12d**, the same single base **13c**.

The configurations of alcohols **11c**, isomers A, B, and C, and alcohol **13c** were deduced by spectral methods, and the assigned structures are given in the conformational diagrams shown in Chart I.

For **13c**, the presence of Bohlmann bands[4] and an upfield[5] signal for the C-9 hydrogen established the *trans*-quinolizidine conformation and thus the *anti-trans* steroidal backbone. The hydroxyl group in **13c** is assigned the axial or β orientation on the basis of the data summarized in Table I.

TABLE I

	C-13 methyl δ ($CHCl_3$)	C-13 methyl δ (pyr)	C-13 methyl δ (D_2O) on ·HCl	Carbinol H δ	Carbinol H $W_{1/2}$, cps	C-1 H, δ
13c	1.00	1.33	1.20	4.4	8	7.32
13e[a]	0.82	0.93	0.95			7.32

[a] Reference 1.

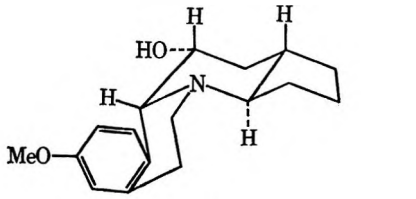
The downfield shift of a steroidal angular methyl signal due to the presence of a 1,3 diaxially disposed

(10) R. L. Pederson, J. L. Johnson, R. P. Holysz, and A. C. Ott, *J. Amer. Chem. Soc.*, **79**, 1115 (1957).

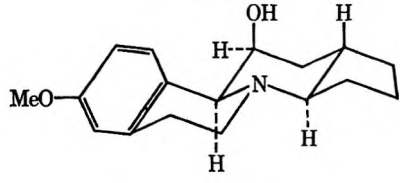
(11) W. D. Emmons and J. P. Freeman, *ibid.*, **77**, 4415 (1955).

hydroxyl group is well known.[12] It is seen that the methyl signal of the unsubstituted base **13e** is shifted downfield by the hydroxyl group of **13c** by 0.18 and 0.40 ppm, respectively, in $CDCl_3$ and pyridine, and by 0.25 ppm when comparisons are made of the hydrochloride salts in D_2O. Furthermore, the half band width of a carbinol proton signal (5–10 cps for equatorial and 15–30 cps for axial) has been used for direct configurational assignment of a hydroxyl group.[13] For **13c**, this value is 8 cps (after D_2O exchange to remove coupling with the hydroxyl proton), and this is in good agreement with the reported value for an equatorial carbinol proton.

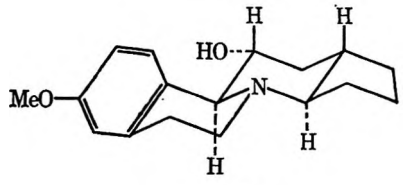
CHART I



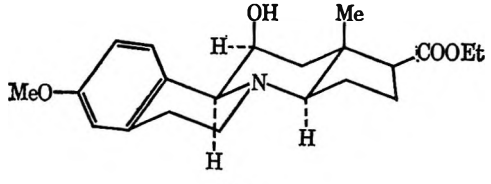
11c, A



11c, B



11c, C



13c

The aromatic region of the nmr spectrum of **13c** is identical with that of **13e** (unsubstituted position 11) and with that of ethynylestradiol (Varian Spectra Catalogue #343). Since molecular models reveal severe crowding between an 11α (equatorial) substituent and the aromatic proton at C-1, the unperturbed aromatic signal for **13c** provides further evidence for an axial substituent.[14]

The spectral data obtained for the three isomers of **11c** are given in Table II.

TABLE II

Isomer	1 H, δ	9 H, δ	11 H, δ	11 H, $W_{1/2}$ (cps)	Bohlmann bands
A	8.16 d	4.15–4.6	4.15–4.6	*ca.* 24	–
B	7.32 d	3.2 or less	4.4	6	+
C	7.88 d	3.2 or less	3.5–4.0	*ca.* 24	+

Isomers B and C both show strong Bohlmann bands[4] and no downfield signal[5] for the angular (C-9) proton. These two products thus have the same *anti–trans*[9] steroidal backbone as **13c**. Isomer B has the configuration corresponding to **13c** in that it has an axial hydroxyl group, as evidenced from the downfield chemical shift (4.4 ppm) and half band width (6 cps) of the equatorial carbinol proton. Also like **13c**, isomer B shows an unperturbed signal for the aromatic C-1 proton.

Isomer C is the 11 epimer of isomer B. The equatorial nature of the hydroxyl group is shown by the downfield displacement of the aromatic C-1 signal[14] and by the broad upfield[15] signal of the axial carbinol proton.

Isomer A is the C-9 epimer of isomer C. Its *cis*-quinolizidine conformation is indicated by lack of Bohlmann bands.[4] A broad three-proton signal centered at 4.35 ppm was shown by D_2O exchange to include the hydroxyl proton as well as the C-9 and C-11 protons. Thus the C-9 proton is found well downfield from its axial counterpart in isomers B and C, as expected, owing to its equatorial nature.[5] The hydroxyl group in isomer A is shown to be α or equatorial by the large downfield displacement of the aromatic C-1 proton and the broad half band width (24 cps after D_2O exchange) due to the axial carbinol proton.[16]

Products **13c** and isomers A, B, and C of **11c** show interesting differences in the hydroxyl regions of the ir spectrum. Aaron and coworkers[17] have shown that simple 1-, 2-, and 3-hydroxyquinolizidines exist in the *trans* conformation, and that those products in which the hydroxyl and electron pair are 1,3 diaxially disposed exhibit strong intramolecular hydrogen bonding. Of the three available isomers of **11c**, only B showed a hydrogen bond which dilution studies indicated to be intramolecular. This observation supports the configurational assignment. The conformationally analogous **13c** shows no intramolecular hydrogen bond, which is, however, not surprising when it is considered that, in the OH···N bonded conformation of this compound, the hydroxyl hydrogen would be subject to steric compression by the *syn* axial methyl group.

Product **13c** thus contains five assymetric centers, all of which are in the same configuration as found in carbocyclic steroids. Use of this product for further elaboration of 8-aza steroids will be described in subsequent publications.

(12) K. Tori and E. Kondo, *Steroids*, **4**, 713 (1964). These authors reported an average downfield displacement of the 18-methyl signal by an 11β-hydroxyl group of 0.24 ppm in $CDCl_3$ and 0.51 ppm in pyridine. In contrast an 11α (equatorial) hydroxyl group displaced the methyl signal upfield by 0.03 and 0.08 ppm, respectively.

(13) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

(14) The spectra of the dicentrine bases (Varian Spectra Catalogue #342 and #349) provide examples of the displacement of an aromatic proton by a similarly positioned substituent. Compare also isomers A and C of **11c**.

(15) Axial carbinol protons are generally found *ca.* 0.5 ppm upfield from their equatorial epimers: E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Strothers, *Tetrahedron Lett.*, 741 (1962).

(16) The large downfield shift of the axial carbinol proton in isomer A compared to that of isomer C, while surprising at first sight, finds an explanation when it is taken into account that A has an axial substituent (C-9) in the position adjacent to the carbinol whereas C has an equatorial substituent in this position. Analogous cases in simple alkyl-substituted cyclohexanols have been described in the literature.[15]

(17) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

Experimental Section[18]

Nitroso Hydrochloride 2.—Enamine **1** was liberated from 25.0 g (0.0767 mol) of its quaternary iodide by treatment of an aqueous solution of the salt with excess 10 *M* potassium hydroxide, and the base was extracted into toluene (*ca.* 500 ml). The toluene solution was dried (potassium carbonate) and filtered, then chilled in an acetone–Dry Ice bath to −80°. A solution of 5.5 g (0.084 mol) of nitrosyl chloride in 150 ml of toluene was then added, with stirring, during 90 min, maintaining the reaction mixture at −80°. After stirring for a further 90 min, the solution was allowed to warm to *ca.* 0° and filtered. The crude solid was recrystallized directly from 1:1 methanol–ether, furnishing 19.4 g (81%) of the nitrosated product as bright yellow crystals, mp 198–200° dec. Further recrystallization from methanol–ether gave an analytical sample of mp 198–200°; ν_{max}^{Nujol} 2700, 1680 (weak, broad) cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2O_3 \cdot HCl$: C, 57.97; H, 6.16; N, 9.01; Cl, 11.41. Found: C, 58.26; H, 6.26; N, 9.01; Cl, 11.29.

Oxime 4 Method A. Borohydride Reduction.—To a stirred solution of 9.5 g (0.0306 mol) of **2** in 100 ml of water and 25 ml of ethanol was added a solution of 2 g (0.037 mol) of potassium borohydride in 25 ml of water; the yellow color of **2** slowly disappeared during this addition. The mixture was stirred for 2 hr, 200 ml of water added, and the resulting mixture chilled and filtered, giving 7.65 g (90%) of off-white solid, mp 193–196° dec. A colorless analytical sample was obtained by two recrystallizations from acetonitrile, and had mp 191–195°; $\nu_{max}^{CHCl_3}$ 3600, 3270, 1660 (weak C=N) cm^{-1}; γ_{max}^{Nujol} 3200, 2700 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.49; H, 7.35; N, 10.38.

The hydrobromide salt was prepared by passing excess hydrogen bromide into a slurry of 6 g of the crude oxime in 50 ml of absolute ethanol. The resulting mixture was heated and diluted with more absolute ethanol to effect solution. Addition of ether to the warm solution gave 7.2 g of the salt, mp 185–189°. Two recrystallizations from methanol–ether gave 5.1 g of colorless, analytically pure material: mp 190–192°; ν_{max}^{Nujol} 3200, 2550, 2650, 2700 (NH^+) cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2O_3 \cdot HBr$: C, 50.43; H, 5.92; N, 7.84; Br, 22.37. Found: C, 50.19; H, 6.02; N, 8.13; Br, 22.59, 22.36.

Method B. Catalytic Reduction.—A solution of 5 g (0.016 mol) of **2** in 300 ml of acetic acid was hydrogenated at room temperature in the presence of 0.15 g of platinum oxide catalyst at an initial pressure of 3 atm of hydrogen. After 90 min the uptake of hydrogen had stopped. The reaction mixture was filtered and evaporated. The residue was dissolved in *ca.* 100 ml of water and made basic (pH 8) with alkali. On cooling and filtering 4.0 g of crude product separated, mp 186–193°. Recrystallization from acetonitrile then furnished 2.9 g (66%) of the pure oxime **4**, mp 192–194°, identical with the material prepared by method A.

Diamine 5. By Reduction of 2.—To a solution of 12.5 g (0.0403 mol) of **2** in 300 ml of acetic acid was added 0.5 g of platinum oxide, and the resulting mixture was hydrogenated for 4 hr at 3.35 atm. A second portion of 0.2 g of platinum oxide was added and the hydrogenation continued for an additional 2 hr. The reaction mixture was filtered, the catalyst thoroughly washed with warm water, and the combined solvents were treated with 10 ml of 6 *N* hydrochloric acid and evaporated. The residue was triturated with ethyl acetate and filtered, giving 15.5 g of the crude salt of **5**. A colorless analytical sample (4.75 g) was obtained by recrystallization from aqueous isopropyl alcohol. This had mp 283–284° and retained the mole of water of crystallization after drying at 80° under high vacuum: ν_{max}^{Nujol} 3500, 3200, 2850, 2800, and 2750 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 51.29; H, 7.46; N, 7.98; Cl, 20.19. Found: C, 51.21; H, 7.49; N, 8.15; Cl, 20.01, 19.91.

The free base was obtained as a solid with mp 113–119° by treatment of an aqueous solution of the dihydrochloride with excess 10 *M* potassium hydroxide and filtration. Two recrystallizations from Skellysolve B furnished an analytial sample, mp 121–123°. This material became tan on standing for several days: $\nu_{max}^{CHCl_3}$ 2730, 2800 (Bohlmann), 3200, 1590 cm^{-1}.

The N-acetyl derivative of the 1-amino compound, prepared by treatment of the free base with acetic anhydride in pyridine and recrystallized from Skelly B, had mp 119–120°; ν_{max}^{Nujol} 3380, 1640 cm^{-1}.

Diamine 5. By Reduction of 4.—The reduction of **4** was carried out in the same way as described for reduction of **2**. The product, obtained in 58% yield, was identical with that described above.

Nitroso Adduct 7.—Enamine **6a** (37.2 g, 0.146 mol) was liberated from its quaternary bromide by treatment of an aqueous solution of 49.0 g of the salt with excess 5% sodium hydroxide solution. The precipitated base was extracted into 1 l. of ether. The solution was dried over potassium carbonate and cooled to −80°. A solution of 10.5 g (0.16 mol) of nitrosyl chloride in 200 ml of toluene was added dropwise over a 1-hr period. After stirring for a further 1 hr, the mixture was allowed to warm up to room temperature, and the yellow solid was filtered to give 45.3 g (96%) of material, mp 206–208°. A sample was recrystallized from ethanol: mp 208–210°; ν_{max}^{Nujol} 1610, 2550 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}N_2O_2 \cdot HCl$: C, 63.65; H, 6.60; N, 8.73. Found: C, 63.45; H, 6.59; N, 8.78.

Oxime 8.—The reduction of **7** was carried out with potassium borohydride as described for preparation of **4**. The yield of base once recrystallized from acetonitrile, mp 192–194°, was 85%. A sample was recrystallized again for analysis: mp 197–198°; $\nu_{max}^{CHCl_3}$ 1620, 1650 (weak, broad).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.46; H, 7.79; N, 10.10.

Diamine 9.—**9** was prepared from **7** or **8** by catalytic reduction (platinum oxide in acetic acid) as described for **5**. The dihydrobromide was obtained as a white powder, mp 279–281° after two recrystallizations from methanol: ν_{max}^{Nujol} 2550, 2675, 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}N_2O \cdot 2HBr$: C, 47.02; H, 6.04; Br, 36.80. Found: C, 47.15; H, 6.08; Br, 36.94.

The free base was obtained as white crystals which darkened on standing, mp 90–91° after recrystallization from Skellysolve B: ν_{max}^{Nujol} 3300, 1610 cm^{-1}; $\nu_{max}^{CHCl_3}$ 2780, 2710 (Bohlmann), 3250 cm^{-1}; δ (C-9) 3.5 ppm; $W^1/_2$ = 6 cps.

Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 74.94; H, 8.83; N, 10.42.

Bromo Salt 10a (X = Br).—Enamine **6a** (27.2 g, 0.094 mol) was liberated from its quaternary bromide (35.8 g) and extracted into 840 ml of ether as described for the preparation of **7**. The dried (potassium carbonate) ether solution was cooled to −80° and 14.4 g (0.09 mol) of bromine in 100 ml of methylene chloride was added dropwise over a 1-hr period. The yellow slurry was stirred at −80° for an additional 1/2 hr, then allowed to warm to room temperature. The yellow salt was filtered and dried to give 32.5 g, 82%, mp 170–172°. A sample was recrystallized from ethanol for analysis: mp 172–173°; ν_{max}^{Nujol} 1605, 1615, 1560 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}Br_2NO$: C, 49.18; H, 5.10; Br, 38.49. Found: C, 48.98; H, 5.00; Br, 38.67.

On tlc (1-butanol–acetic acid–water, 5:2:3), the analytical material showed two spots, R_f 0.2 and 0.3, in a ratio of *ca.* 3:1.

Bromo Base 11a.—A solution of 1.0 g of salt **10a** (X = Br) in 20 ml of methanol was treated with cooling with 1.0 g of sodium borohydride in portions over 0.5 hr. The solution was diluted with 100 ml of water and the solid filtered. Two recrystallizations from acetone–water gave white needles: mp 215–216°; the material darkened on standing; $\nu_{max}^{CHCl_3}$ 2720, 2780 cm^{-1} (Bohlmann).

Anal. Calcd for $C_{17}H_{22}BrNO$: C, 60.72; H, 6.59; N, 4.17. Found: C, 60.66; H, 6.63; N, 4.42.

Acetoxy Salt 10b (X = ClO_4).—A suspension of 20.0 g (0.048 mol) of **10a** (X = Br) in 300 ml of acetic acid containing 11 g (0.112 mol) of fused potassium acetate was stirred at room temperature. The solution slowly turned orange as the salt dissolved and potassium bromide separated. After 48 hr, the solid was filtered, washed with acetic acid, and dried to afford 9.1 g (73%) of the theoretical potassium bromide. The filtrate was evaporated to dryness; the residue was dissolved in 100 ml of water and treated with excess 10% perchloric acid. After

(18) Melting points were taken on a Fisher-Johns block and are uncorrected. Ultraviolet, ir, and nmr spectra were determined on Beckman DK-1, Baird Model 455, and Varian A-60 instruments, respectively. Tlc was done on Brinkman silica gel F_{254} plates, and the spots were visualized with an iodine chamber. All samples for which analytical data are reported showed a single spot. The nmr spectra were run in $CDCl_3$ unless otherwise specified.

cooling, the water was decanted from the gum, which crystallized on scratching with ethanol to give 6.0 g (30%) of yellow solid, mp 156–160°. Two recrystallizations from ethanol gave the analytical sample: mp 160–163°; ν_{max}^{Nujol} 1605, 1745 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}ClNO_7$: C, 55.14; H, 5.85; Cl, 8.56. Found: C, 55.35; H, 5.84; Cl, 8.59.

Although subsequent work showed **10b** to be a mixture, no tlc solvent system was found which resolved the material into two spots.

Keto Salt 10d (X = ClO_4).—A solution of 8.3 g (0.02 mol) of bromo salt **10a** (X = Br) in 500 ml of acetonitrile was treated with a solution of 6.9 g (0.046 mol) of silver nitrate in 300 ml of acetonitrile. An immediate precipitate of silver bromide formed. The slurry was stirred in the dark at room temperature for three days. The silver bromide was filtered (7.52 g, 94%), and the filtrate concentrated to a dark oil. This was taken up in 100 ml of water, and a little dilute hydrochloric acid added to precipitate any remaining silver. After filtration, the clear filtrate was treated with 25 ml of 10% perchloric acid. The oily precipitate crystallized on scratching to give 5.0 g (68%) of yellow solid, mp 175–180°. A sample was recrystallized twice from methanol: mp 182–184°; ν_{max}^{Nujol} 1590, 1610, 1730 cm^{-1}.

Anal. Calcd for $C_{17}H_{20}ClNO_6$: C, 55.21; H, 5.45; N, 3.79; Cl, 9.59. Found: C, 55.21; H, 5.35; N, 3.64; Cl, 9.74.

Bromo Salt 12a (X = Br).—**12a** was prepared in the way described for bromo salt **10a** (X = Br) in 95% yield. The product was recrystallized from ethanol–ether for analysis: ν_{max}^{Nujol} 1620, 1740 cm^{-1}.

Anal. Calcd for $C_{21}H_{27}Br_2NO_3$: C, 50.32; H, 5.43; Br, 31.98. Found: C, 50.06; H, 5.53; Br, 31.94.

On tlc (1-butanol–acetic acid–water, 5:2:3), the analytical material showed two spots, R_f 0.1 and 0.2, in a ratio of *ca.*1:1.

Acetoxy Salt 12b (X = ClO_4).—**12b** was prepared as described for **10b** (X = ClO_4) in 10% yield. The crude product was recrystallized twice from ethanol: mp 173–175°; ν_{max}^{Nujol} 1550, 1600, 1735 cm^{-1}.

Anal. Calcd for $C_{23}H_{30}ClNO_9$: C, 55.26; H, 6.05; Cl, 7.09. Found: C, 55.20; H, 6.01; Cl, 7.19.

Keto Salt 12d (X = ClO_4).—**12d** was prepared in 54% yield in the way described for **10d**. The product was recrystallized from methanol for analysis: mp 160–162°; ν_{max}^{Nujol} 1605, 1730 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}ClNO_8$: C, 55.33; H, 5.75; N, 3.07; Cl, 7.78. Found: C, 55.15; H, 5.62; N, 3.36; Cl, 7.92.

Hydroxy Bases 11c, Isomers A, B, C. By Reduction and Hydrolysis of 10b.—A solution of 11.0 g (0.0265 mol) of 11-bromo salt **10a** in 250 ml of acetic acid was mixed with a solution of 5.5 g (0.056 mol) of fused potassium acetate in 50 ml of acetic acid. The mixture was stirred for 2 days at room temperature. The mixture was evaporated to dryness, and the residue taken up in 200 ml of water and 300 ml of ethanol. Potassium borohydride (10 g) was added in portions over 1 hr at 5°. The mixture was stirred for 1 hr, then diluted with 50 ml of 20% sodium hydroxide solution, and refluxed for 1 hr. The ethanol was removed by distillation, and the oil was extracted with methylene chloride. The organic phase was washed with water, dried, and concentrated to 7.8 g of an orange semisolid residue. This was slurried in acetonitrile and filtered to give 1.6 g of off-white solid, mp 176–180°. This is almost pure isomer B.

The mother liquor was concentrated to an oil and chromatographed on 500 g of neutral alumina. The column was washed with benzene and eluted with 1 l. of anhydrous ether to give 1.8 g of yellow oil. This material showed no hydroxyl in the ir spectrum and was not investigated further. Elution with 1.5 l. of 1% ethanol in ether afforded 0.7 g of yellow oil which solidified to give isomer C mixed with a trace of isomer B. Further elution with 3% ethanol in ether gave 0.2 g of mixed isomers B and C. Elution with 8% ethanol in ether then gave 0.6 g of pure isomer A.

The solid eluted with 1% ethanol in ether was recrystallized from ethyl acetate to give pure isomer C: mp 171°; $\nu_{max}^{CH_2Cl_2}$ 2760, 2820 (Bohlmann), 2840, 3620 cm^{-1} (free OH, concentration independent).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.41; H, 8.33; N, 4.95.

Isomer B, obtained by direct crystallization, was recrystallized for analysis from benzene: mp 189–190°; $\nu_{max}^{CH_2Cl_2}$ 2730, 2740, 2780 (Bohlmann), 3280–3480 cm^{-1} (bonded OH, concentration independent).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.56; H, 8.52; N, 4.99.

Isomer A, obtained from the column by elution with 8% ethanol in ether, was recrystallized from benzene–Skellysolve C for analysis: mp 176–177°; $\nu_{max}^{CH_2Cl_2}$ 3623, 3130–3450 cm^{-1} (free and bonded OH, concentration dependent).

Anal. Calcd for $C_{17}H_{23}NO_2$: C 74.69; H, 8.48; N, 5.12. Found: C, 74.47; H, 8.45; N, 5.34.

On tlc (50:50 ethyl acetate–acetone), isomers A, B, and C migrated as sharp, round spots of R_f 0.1, 0.5, and 0.6, respectively.

Hydroxy Bases 11c Isomers A and B. By Reduction of 10d.—A solution of 0.5 g of **10d** (X = ClO_4) in 25 ml of methanol was treated with 0.5 g of potassium borohydride in portions over a 1-hr period. The solution was left for 1 hr, then poured into water. The product was filtered to give 0.3 g of white solid, mp 135–145°. By tlc (see previous experiment), this material was shown to be a mixture of isomers A and B.

Hydroxy Base 13c. By Reduction of 12d.—A solution of 17.1 g of **12d** (X = ClO_4) in 1 l. of methanol was reduced as described in the previous experiment with 10 g of potassium borohydride. The methanol was evaporated, and residue was partitioned between water and ether. The ether was washed, dried, and concentrated to 12.7 g (94% yield) of off-white solid, mp 137–142°.

Recrystallization from acetonitrile furnished the analytical sample: mp 149–150°; $\nu_{max}^{CCl_4}$ 2740, 2830 (Bohlmann), 2840, 3622 cm^{-1} (free OH, concentration independent).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.16; H, 8.22; N, 4.13.

Registry No.—**2**, 17413-16-0; **4**, 17413-33-1; **4** HBr, 17413-17-1; **5**, 17413-18-2; **5** 2HCl, 17413-19-3; **7**, 17413-34-2; **8**, 17413-20-6; **9**, 17413-21-7; **9** 2HBr, 17413-22-8; **10a** (X = Br), 17413-23-9; **10b** (X = ClO_4), 14713-24-0; **10d** (X = ClO_4), 17413-35-3; **11a**, 17413-25-1; **11c** (isomer A), 17413-26-2; **11c** (isomer B), 17413-27-3; **11c** (isomer C), 17413-28-4; **12a** (X = Br), 17413-29-5; **12b** (X = ClO_4), 17448-00-9; **12d** (X = ClO_4), 17413-30-8; **13c**, 17413-31-9; **13e**, 17413-32-0.

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Calophyllum Products. III. The Structure of Blancoic Acids[1a-c]

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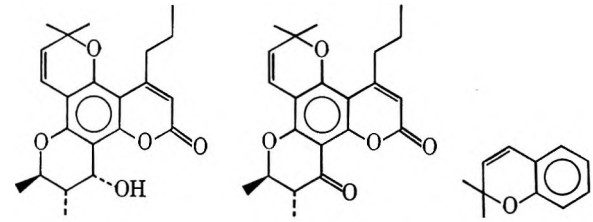
Blancoic acid, the major constituent of the bark resin of *Calophyllum blancoi* Pl. and Tr., is shown to have the structure **24**. The synthesis of the derivative methyl O-methyldihydroblancoate (**13**) is described, and the stereochemistry of blancoic acid is discussed in part. This compound represents a new extension of the complex coumarin derivatives found generally in *Calophyllum* resins.

As part of our study of the products of the botanical family Guttiferae, we have recently examined the bark resins of a number of species from the genus *Calophyllum*, a widely distributed group of tropical trees. One of these is *Calophyllum blancoi* Pl. and Tr., a member of the genus native to the Philippine Islands, where it is used as a source of dye and in the treatment of wounds. Extraction of the powdered bark yields *ca.* 5% of a yellow resin. Thin layer chromatography (tlc) of this resin showed it to consist largely (>75%) of one compound. We have isolated this material in chromatographically and spectrally homogeneous, though noncrystalline, form and have named it blancoic acid.[2]

Structure.—Blancoic acid, on the basis of combustion, titrimetric, and mass spectral analyses, is a monocarboxylic acid with the molecular formula $C_{24}H_{32}O_6$. The uv spectrum is complex, but is not suggestive of a coumarin, despite the frequent occurrence of this system in *Calophyllum*[3-5] and related genera.[6-8]

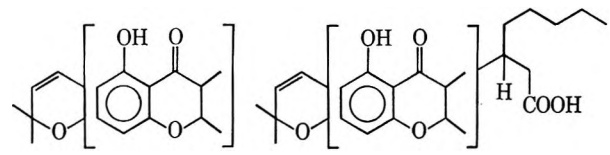
Upon catalytic hydrogenation over Adams catalyst in ethanol, blancoic acid absorbs 1 mol of hydrogen, leading to dihydroblancoic acid $C_{24}H_{34}O_6$. This reduction is attended by a marked simplification of the uv spectrum, which now resembles that of an oxygenated acetophenone.

The nmr spectrum of blancoic acid (Figure 1) is highly informative, especially when compared with those of costatolide (**1**), from *Calophyllum costatum* F. M. Bailey, and its derivative oxodihydrocostatolide (**2**).[4] Among the peaks found are those at τ 3.45 (d, J = 10 Hz), 4.65 (d, J = 10 Hz), and 8.56 (s), characteristic of the 2,2-dimethylchromene ring (**3**), a common element in *Calophyllum* products.[3-5] Chemical confirmation of the presence of this system was obtained from its characteristic degradation in hot aqueous base to yield acetone and acetaldehyde.[3,4] As would be expected, the low-field doublets vanish from the spectrum of dihydroblancoic acid to be replaced by triplets at τ 8.27 and *ca.* 7.4, indicating that it is the double bond of this ring that is reduced.



1 2 3

Also visible in the spectrum of blancoic acid are a six-line multiplet (1 H) at τ 5.96 and two doublets (each 3 H) at 8.52 and 8.82. The first doublet is partially obscured by the signal at τ 8.56 from the methyl groups of the 2,2-dimethylchromene ring but is revealed when this shifts to 8.67 in dihydroblancoic acid. These peaks correspond in detail with those recorded for the 2,3-dimethylchromanone ring of **2**[4] and suggest the presence of the same system in blancoic acid. In agreement and extension, both the ir (6.14 μ) and nmr (τ −2.28) spectra indicate a conjugated carbonyl group with an adjacent chelated hydroxyl function. Thus the partial structure may be elaborated as **4**.



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The nmr spectrum of blancoic acid shows no signals resulting from aromatic protons; so a group $C_8H_{15}O_2$ containing the carboxyl function must be attached at the sixth position on the benzene ring. Signals which can be attributed to this fragment are found at τ 6.43 (1 H), 7.36 (2 H), and 9.15 (3 H). The last is a highly skewed triplet, of the sort arising from the terminal methyl group of a long *n*-alkyl chain.[9] The common occurrence of 4-alkylcoumarins in the subfamily Calophylloideae[4-7] suggests that we may be dealing with an acid related to a hydrolyzed dihydrocoumarin and leads to the extended structure **5**. In this case the benzylic methine would give rise to the signal at τ 6.43 and the methylene adjacent to the carboxyl to that at

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S078. Taken in part from the Ph.D. Thesis of K. D. Sears, University of Washington, 1968. (b) For previous papers in this series, see part II, G. H. Stout, M. M. Krahn, and G. D. Breck, *Tetrahedron Lett.*, 3285 (1968); part I, G. H. Stout and K. L. Stevens, *J. Org. Chem.*, **29**, 3604 (1964). (c) Supported in part by Public Health Service Grant GM-12095 from the National Institute of General Medical Sciences. (d) Institute of Forest Products Research Fellow, University of Washington, 1964–1966.

(2) It should be noted that, with the exception of dihydroblancolide (**10**), all derivatives of blancoic acid are similarly noncrystalline. Thus all comparisons between compounds and all tests for homogeneity rest on chromatographic and spectral properties.

(3) J. Polonsky, *Bull. Soc. Chim. Fr.*, 1079 (1957); J. Polonsky and Z. Baskevitch, *ibid.*, 929 (1957).

(4) G. H. Stout and K. L. Stevens, *J. Org. Chem.*, **29**, 3604 (1964).

(5) S. K. Nigam, C. R. Mitra, G. Kuensch, B. C. Das, and J. Polonsky, *Tetrahedron Lett.*, 2633 (1967).

(6) C. Djerassi, E. J. Eisenbraun, R. A. Finnegan, and B. Gilbert, *J. Org. Chem.*, **25**, 2164 (1960); R. A. Finnegan, M. P. Morris, and C. Djerassi, *ibid.*, **26**, 1180 (1961); R. A. Finnegan and W. H. Mueller, *ibid.*, **30**, 2342 (1965).

(7) L. Crombie, D. E. Gaines, and A. McCormick, *Tetrahedron Lett.*, 145, 151 (1966).

(8) T. R. Govindachari, B. R. Pai, P. S. Subramaniam, U. R. Rao, and N. Muthukumaraswamy, *Tetrahedron*, **23**, 4161 (1967).

(9) *Cf.* spectra 216 and 282: W. S. Bhacca, D. P. Hodis, L. F. Johnson, E. A. Pier, and J. N. Shoolery, "NMR Spectra Catalog," Vol. I, Varian Associates, Palo Alto, Calif., 1962.

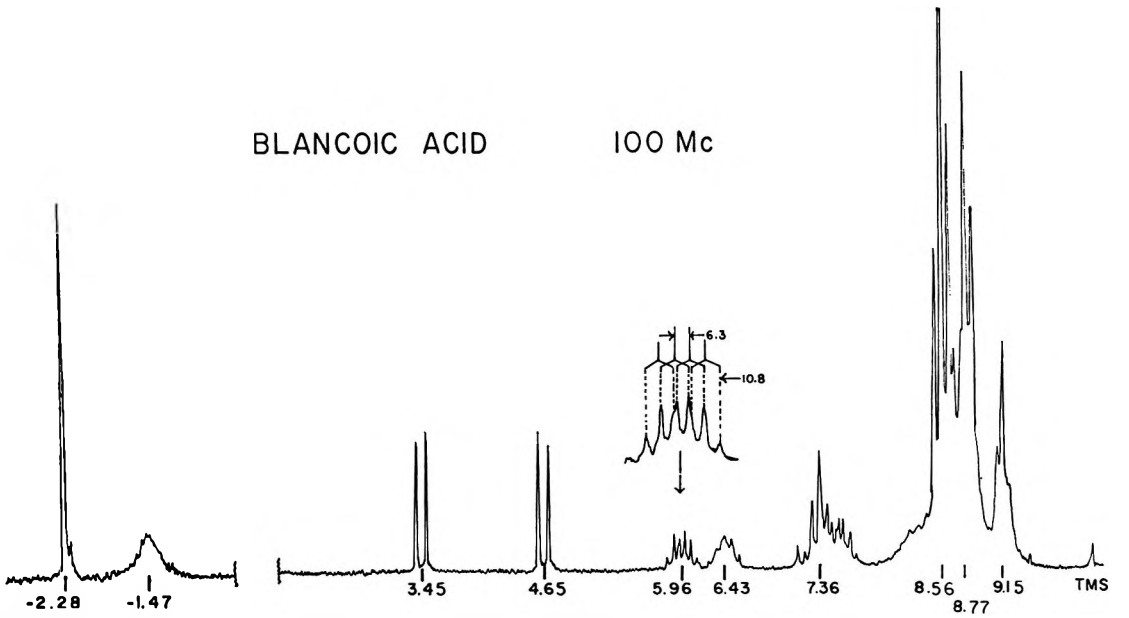


Figure 1.—The 100-MHz nmr spectrum of blancoic acid in CCl_4. The region below the break has twice the amplitude of the rest of the spectrum.

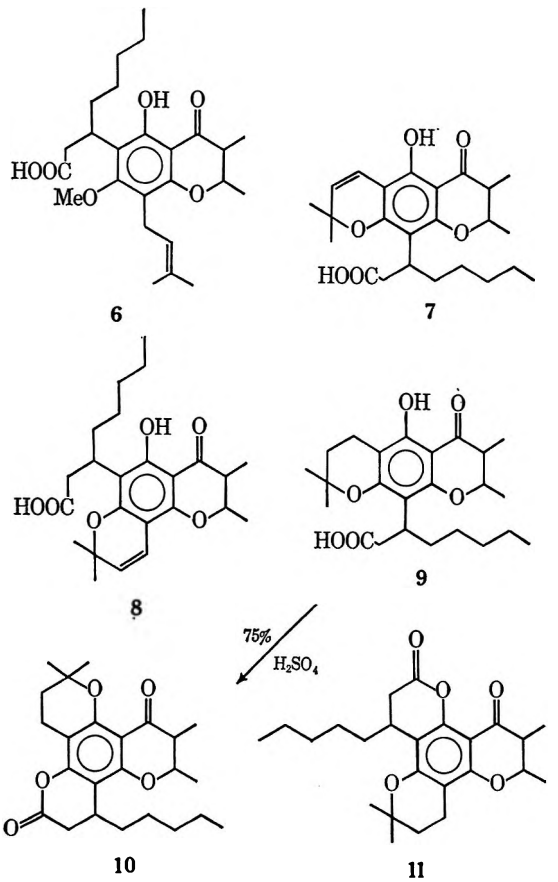
7.36. Oxidation of blancoic acid with dilute nitric acid confirmed the proposed structure by yielding *n*-pentylsuccinic acid, identified by comparison with an authentic sample.

Once the various aromatic substituents have been identified, the remaining problem is to orient them properly about the central ring. The coumarins and related products from the Guttiferae have uniformly been based on a phloroglucinol oxygenation.[3-8] Biosynthetic analogy suggests strongly that the pattern will hold as well for blancoic acid. Furthermore the excellent agreement between the uv spectra of dihydroblancoic acid and similar derivatives of papuanic acid (**6**),[1a,10] for which independent evidence exists showing the disposition of the oxygens, requires that they possess the same substitution. If the remaining oxygen is placed to conform to these arguments, two structures, **7** and **8**, are possible for blancoic acid.

Of these possibilities, **8** has been rejected because of the failure of blancoic acid and its derivatives to lactonize under the influence of either acetic anhydride or dicyclohexylcarbodiimide, reagents which readily induce lactonization in **6**.[10] Thus we propose **7** as the structure of blancoic acid.

Early in the study of these compounds, however, a lactonic product was obtained by the prolonged stirring of dihydroblancoic acid (**9**) in 75% sulfuric acid. Clearly this material, dihydroblancolide, cannot be a simple lactone derived from **7**. Instead, we propose that it has the structure **10**, arising by acid-catalyzed rearrangement of the dimethylchroman ring followed by lactonization onto the now available hydroxyl. Such rearrangements have been observed previously in similar systems.[11]

Evidence for the proposed structure derives from several sources. First, the material having the structure **11**, *i.e.*, the dihydrolactone related to **8**, has been prepared from papuanic acid and is clearly different



from dihydroblancolide.[10] Second, comparison of the uv spectra of dihydroblancolide and **11**, which may be viewed as dioxyacetophenones since one oxygen atom has been effectively "removed" by esterification, shows that the former exhibits the marked bathochromic shift of its long-wavelength band characteristic of 2,6-dihydroxyacetophenone, while the latter resembles 2,4-dihydroxyacetophenone instead (Table I). Finally, the possibility of an alternative rearrangement of the chromanone ring, rather than the chroman, can be

(10) G. H. Stout, G. L. Hickernell, and K. D. Sears, *J. Org. Chem.*, **33**, 1491 (1968).

(11) G. A. Howard, J. R. A. Pollock, and A. R. Tatchell, *J. Chem. Soc.*, 174 (1955).

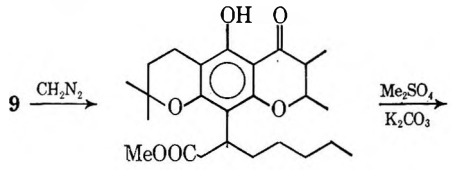
TABLE I

UV SPECTRA OF DIHYDROBLANCOLIDE AND RELATED COMPOUNDS

	λ_{max}, mμ	ε	λ_{max}, mμ	ε
Dihydroblancolide (10)	281	17,000	336	5200
2,6-Dihydroxyacetophenone	269	12,900	341	3500
2,4-Dihydroxyacetophenone	278	15,100	315	7100
Cyclodemethylpapuanolide (11)	284	13,700	314	3600

ruled out since this would again lead to a product having the gross structure and uv spectrum of **11**.

Synthesis.—To confirm the arguments leading to the proposed structure, we undertook to synthesize a derivative of dihydroblancoic acid. Methyl O-methyldihydroblancoate (**13**), prepared by methylation of dihydroblancoic acid first with diazomethane and then with dimethyl sulfate and potassium carbonate, was elected as a suitable meeting point of the natural and synthetic routes.



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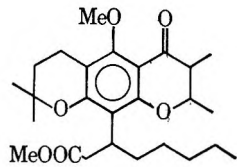

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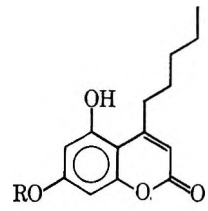
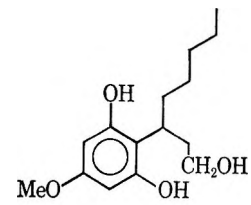
The two major problems encountered in the synthesis were the preparation of the dihydrocoumarin system and the necessity for devising routes that led unambiguously to the orientation of the various rings. The first was ultimately solved by the method described below and the second by the combination of a blocking group and a symmetrical intermediate.

The synthetic sequence began with treatment of phloroglucinol with ethyl 3-ketooctanoate under the classical von Pechmann conditions.[12] A good yield of 4-*n*-pentyl-5,7-dihydroxycoumarin (**14**) was obtained. Partial methylation with dimethyl sulfate and aqueous sodium carbonate gave a mixture of monomethylated products, from which the desired 7-methyl ether (**15**) could be isolated by taking advantage of its failure to extract into dilute carbonate solutions.

Reduction of coumarin with lithium aluminum hydride has been shown to give reasonable yields of 3-(2-hydroxyphenyl)propanol.[13] Treatment of **15** with this reagent in refluxing tetrahydrofuran, however, led to a product whose nmr spectrum was entirely inconsistent with its formulation as the phenylpropanol **16**. Analytical results, although allowing the expected $C_{15}H_{24}O_4$, favored $C_{15}H_{22}O_4$. The uv and ir spectra indicated that both the ester and the double bond had been reduced, but a diffuse triplet at τ 4.62 (1 H) had appeared instead of the signal expected for a methylene bearing a hydroxyl. Treatment with acetic anhydride and pyridine, even under forcing conditions, led to only a diacetate in which the diffuse triplet had



14, R = H
15, R = Me



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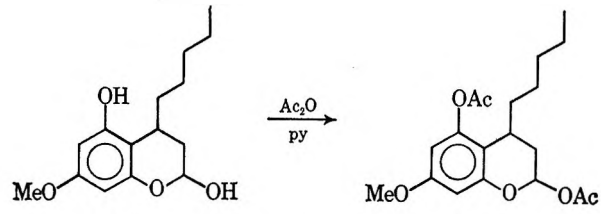
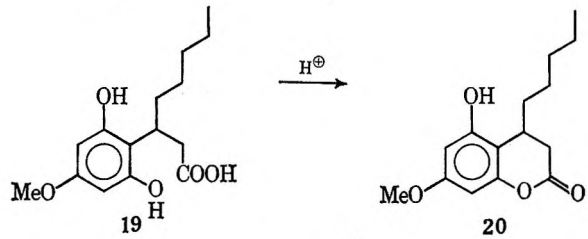
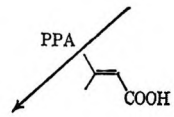
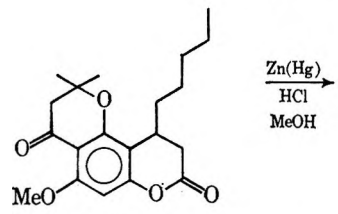


17 **18**



19 **20**





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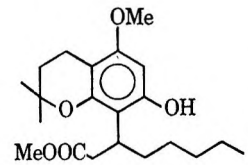

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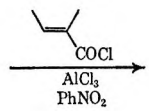


13

shifted to τ 3.7. In view of these data, a positive Tollens test, and the ready oxidation to an acid or lactone (see below), the reduction product is formulated as the cyclic hemiacetal **17**.

Although lithium aluminum hydride has occasionally been used to form hemiacetals from lactones, these reactions have usually involved carefully controlled conditions.[14] Thus the isolation of such a product from a reaction conducted at elevated temperatures with a large excess of reductant is unexpected.[15]

(12) See S. Wawzonek in "Heterocyclic Compounds," Vol. II, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1951, pp 181–187.

(13) F. A. Hochstein, *J. Amer. Chem. Soc.*, **71**, 305 (1945).

(14) G. E. Arth, *ibid.*, **75**, 2413 (1953); M. Hinder and M. Stoll, *Helv. Chim. Acta*, **37**, 1866 (1954).

(15) See also K. Heusler and A. Wettstein, *ibid.*, **45**, 347 (1962), and references cited there.

Oxidation of **17** with alkaline silver oxide led to the acid **19**, which closed readily in the presence of mineral acids to the lactone **20**. Better yields of **20** were later obtained by direct oxidation of **17** with Jones reagent.[16]

Acylation of **20** with senecioic acid in polyphosphoric acid (PPA) gave the desired chromanone **21**. Because of the symmetry of the molecule resulting from the opening of the lactone ring in **20**, possible intramolecular ester interchange represented no threat at this time.

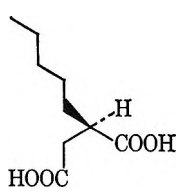
Clemmensen reduction of **21**, carried out with methanol as a cosolvent, produced simultaneous reduction of the chromanone carbonyl and the conversion of the lactone to the corresponding methyl ester (**22**).

Various methods, including the use of PPA, were studied for the introduction of tiglic acid to form the 2,3-dimethylchromanone ring, but the most successful was the use of tigloyl chloride, aluminum chloride, and nitrobenzene to effect a one-step acylation and ring closure onto **22**. Under these conditions **13** was obtained in fair yield as a mixture of stereoisomers, which could be separated by preparative tlc into two fractions. One of these, although presumably still a mixture of diastereomers (see below), was identical chromatographically and in its uv, ir, and nmr spectra with methyl O-methyldihydroblancoate prepared from dihydroblancoic acid.

The spectral identity of the natural and synthetic materials thus justifies the arguments made during the analysis of blancoic acid and confirms particularly the presence of the phloroglucinol oxygenation pattern and the location of the acid side chain as in **7**.

Stereochemistry.—Blancoic acid is optically active and contains three asymmetric centers, two in the chromanone ring and one in the acidic chain. The nmr signal at τ 5.96 results from the proton at C-2 in the chromanone ring and has a coupling constant of 11 Hz with the adjacent C-3 proton. As discussed previously in the case of costatolide,[4] this value is consistent only with *trans* diaxial protons or (2e,3e) methyl substitution.

The stereochemistry of the acid chain is given absolutely by the isolation of optically active (*R*)(+)-pentylsuccinic acid (**23**)[17] from the oxidative degradation of blancoic acid. Thus a partial representation of the stereochemistry of the system is **24**. The relationship between the two asymmetric regions is under study in connection with the stereochemistry of papuanic acid and the other members of this group of compounds, but a detailed discussion is reserved for a later paper.[18]



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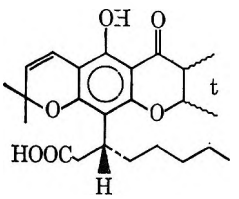

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The synthetic **13** was resolved by tlc into two fractions, although four *dl* pairs are expected. The more mobile fraction, which corresponded to the natural material, has the nmr spectrum of a *trans*-dimethylchromanone and presumably includes both epimers at the position bearing the *n*-pentyl chain. The other fraction, which has the same uv spectrum but is formed in smaller amounts, is assumed to be the corresponding mixture of *cis* products, since we have found that these are uniformly more polar than their *trans* isomers. Studies on derivatives of papuanic acid have indicated that isomers differing only in the configuration of the asymmetric center in the acid chain can be separated chromatographically only when the free rotation of this chain is prevented by lactonization.

Discussion

Blancoic acid was the first dihydrocoumarinic acid isolated from the resins of a *Calophyllum* species. Since it was first discovered, others have been found. Papuanic and isopapuanic acids have been obtained from *C. papuanum*,[1a,10] and apetalic acid, from *C. apetalum*.[19] All four compounds are very similar, apetalic acid differing from blancoic acid only in having a *cis*-dimethylchromanone ring and the more common *n*-propyl chain in place of *n*-pentyl.

These compounds, like their coumarin analogs,[4,5] show the tendency of this genus to elaborate derivatives containing an even number of carbon atoms linearly disposed in an acidic side chain. Such a chain may be reasonably supposed to be derived from acetate, the connection to the aromatic ring then arising in formal analogy to the von Pechmann reaction. Support of this view is provided by the recent evidence of Kunesch and Polonsky that the acid chain in the related 4-phenylcoumarins of *C. inophyllum* is derived from phenylalanine without any rearrangement.[20]

Since the completion of our studies on blancoic acid, we have encountered it again as the principal component of the resin extracted from *Calophyllum saigonensis* Pierre. This species, obtained from Thailand, gave extracts whose appearance on tlc plates resembled greatly that of similar extracts from *C. blancoi*. Although the major constituents were the same, the minor components were not however; so the two samples were not identical.

Experimental Section

All melting points were taken on a Kofler hot stage and are corrected. The infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer. The letter in parentheses signifies a strong, medium, or weak absorption. Most of the nmr spectra were obtained on a Varian A-60 spectrometer; a few were taken by Mr. B. J. Nist on a Varian HR-60. The letter in parentheses refers to the multiplicity and the number following the letter, when given, is the estimated intensity. All column chromatography used 922 silica gel, <200 mesh, supplied by Grace–Davidson Chemical Co., with mixtures of hexane and ethyl acetate as elutants. Tlc plates were prepared with silica gel G from Brinkman Instruments. Solutions were dried with anhydrous magnesium sulfate unless otherwise stated. Combustion analyses were performed by Dr. A. Bernhardt of Mülheim (Ruhr), West Germany. Uv spectra were taken in 95% EtOH.

(16) A. Bowers, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2548 (1953).

(17) A. Fredga, *Tetrahedron*, **8**, 126 (1960); A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjöberg, and S. Sjöberg, *J. Chem. Soc.*, 3928 (1965).

(18) G. H. Stout and G. L. Hickernell, to be published.

(19) T. R. Govindachari, D. Prakash, and N. Visiwanathan, *Tetrahedron Lett.*, 4177 (1967).

(20) G. Kunesch and J. Polonsky, *Chem. Commun.*, 317 (1967).

Isolation of Blancoic Acid (7).—The ground bark (35 g) of *Calophyllum blancoi* Pl. and Tr. (Guttiferae) was extracted in a Soxhlet extractor with pentane for 5 hr. The yellow solution was extracted twice with 5% Na_2CO_3, and the pentane layer was discarded. The aqueous extract was acidified with HCl and extracted with ether, which was dried and evaporated to give 1.62 g of a viscous yellow liquid (4.6%). Tlc of this material showed that it was predominantly blancoic acid. Column chromatography (1:20 EtOAc–hexane) gave 0.78 g (2.2%) of purified blancoic acid. Analytically pure material was obtained by sublimation (120°, 10^{-5} Torr) of a sample pure by tlc. A yellow glass was obtained (blancoic acid is soluble in all common organic solvents and all attempts at crystallization failed): ir (CCl_4) 5.85 (s), 6.08 (s), 6.15 (s), 6.37 μ (m); uv max (95% EtOH), 255 sh, 267 mμ (ϵ 39,900), 275 (42,200), 300 (11,300), 312 (11,800), 365 (2160); nmr (CCl_4) τ 9.15 (t), 8.82 (d), 8.62, 8.56 (s), 8.47, 7.16–7.83 (m, 3), 5.73–6.60 (m, 2), 4.65 (d, 1), 3.45 (d, 1), −1.60 (broad, 1), −2.28 (s, 1) [the nmr spectrum at 100 MHz resolved the multiplet between τ 5.73 and 6.60 into discrete multiplets: 5.96 (m, J = 6.3, 10.8 H_2, 1) and 6.43 (m, 1) (Figure 1)]; $[\alpha]^{25}D$ −66.7° (*c* 0.0712, $CHCl_3$).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; mol wt, 416. Found: C, 69.10; H, 7.66; mol wt (titration), 409.

Dihydroblancoic Acid (9).—Blancoic acid (100 mg, 0.24 mmol) was added to 15 mg of prereduced platinum oxide in ethanol. Hydrogen uptake was rapid and was complete after 1 hr (0.22 mmol). The platinum was filtered off, and the ethanol was evaporated to yield a viscous light yellow liquid. Tlc showed that no blancoic acid remained and that the product was essentially pure **9**. An analytical sample was prepared by column chromatography and sublimation (120°, 10^{-5} Torr) to give a light yellow glass: ir (CCl_4) 5.83 (s), 6.12 (s), 6.26 μ (m); uv max (95% EtOH) 298 mμ (ϵ 15,300), 342 (2200); nmr (CCl_4) τ 9.15 (t), 8.82 (d), 8.67 (s), 8.52 (d), 8.27 (t, 2), 7.16–7.83 (m, 5), 5.73–6.60 (m, 2), −1.18 (broad, 1), −2.28 (s, 1).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.86; H, 8.21.

Dihydroblancolide (10).—Dihydroblancoic acid (0.94 g, 2.2 mmol) was added to 15 ml of 75% aqueous sulfuric acid, and the solution was stirred for 3 days at room temperature. When it was poured into ice–water, a gummy mass formed. Tlc showed the presence of a trace of starting material in addition to two major fluorescent spots behind the starting material, the one with higher R_f being much larger. This material was separated by preparative tlc to give 210 mg (24%) primarily of the compound constituting the front fluorescent spot and 70 mg (8%) of material from the back spot. The major product, dihydroblancolide, was rechromatographed by preparative tlc and crystallized several times to yield **10** as a white solid from hexane: mp 153.5–154.5°; ir (CCl_4) 5.62 (s), 5.92 (s), 6.28 μ (s); uv max 281 mμ (ϵ 17,000), 336 (5180); nmr (CCl_4) τ 9.15 (t), 8.92 (d), 8.65 (s), 8.28 (t, 2), 7.15–8.00 (m, 5), 6.82 (m, 1), 5.96 (m, 1).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.93; H, 8.14.

The material constituting the back spot gave uv max 281 and 336 mμ; ir (CCl_4) 5.62 (s), 5.92 (s), 6.28 μ (s).

Methyl Dihydroblancoate (12).—Dihydroblancoic acid (131 mg, 0.31 mmol) in methanol was treated at 4° with excess freshly distilled ethereal diazomethane. After 10 min the solvent and excess diazomethane were evaporated to give a yellow oil. An analytical sample was obtained by preparative tlc and sublimation (100°, 10^{-5} Torr): uv max 298 mμ (ϵ 15,300), 340 (2280); nmr (CCl_4) τ 9.14 (t), 8.82 (d), 8.65 (s), 8.50 (d), 8.26 (t, 2), 6.50 (s, 3), −2.28 (s, 1).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.61; H, 8.56.

Methyl O-Methyldihydroblancoate (13).—Methyl dihydroblancoate (100 mg, 0.23 mmol) dissolved in acetone was refluxed 2 days with dimethyl sulfate (0.1 ml) and excess anhydrous K_2CO_3. The solution was filtered, poured into a 5% Na_2CO_3 solution, and extracted twice with ether; the ethereal extract was dried and evaporated to give a yellow oil. This was purified by preparative tlc to obtain 54 mg (53%) of a slightly viscous light yellow oil that was purified again by preparative tlc and sublimed (100°, 10^{-5} Torr) before analysis: ir (CCl_4) 5.74 (s), 5.89 (s), 6.28 (s), 6.85 μ (s); uv max 290 mμ (ϵ 15,700), 335 sh; nmr (CCl_4) τ 9.15 (t), 8.88 (d), 8.67 (s), 8.53 (d), 8.28 (t, 2), 7.40 (d), 6.54 (s, 3), 6.28 (s, 3).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.08; H, 8.79.

Base Degradation of Blancoic Acid.—A small pear-shaped flask fitted with a condenser and a nitrogen tube was charged with blancoic acid (200 mg) and 10 ml of 5% NaOH. A tube led from the top of the condenser into a solution of 2,4-dinitrophenylhydrazine reagent. After the reaction mixture had refluxed for 3 hr, an orange precipitate had formed in the 2,4-dinitrophenylhydrazine solution. The precipitate was chromatographed on Whatman No. 1 paper using the organic phase of cyclohexane (60), methanol (12), acetic acid (1), and water (2) as the solvent.[4] The sample separated into two spots that had the same R_f's as samples of acetone and acetaldehyde DNP's run simultaneously.

(*R*)-(+)-*n*-Pentylsuccinic Acid from Dihydroblancoic Acid.—Dihydroblancoic acid (207 mg) was treated with 25 ml of 50% nitric acid in a 50-ml boiling flask fitted with a reflux condenser. The mixture was kept at room temperature for 1 day and then heated gently on a steam bath for 2 days. It was allowed to cool, and the excess nitric acid was reduced with sodium bisulfite before the aqueous solution was extracted exhaustively with ether. The ethereal extracts were dried, filtered, and evaporated to give a light yellow oil (12.8 mg). The oil was dissolved in 2 ml of 5:1 hexane–benzene and refrigerated for several weeks. The white crystals of pentylsuccinic acid were filtered, washed with hexane, and air dried (3.2 mg, 3.4%): mp 79–82°; mmp 79–83°; ir ($CHCl_3$) 3.43 (m), 3.50 (w), 5.84 (s), 6.26 (w), 7.75 μ (w); ORD (95% EtOH) (c 0.054), $[\phi]_{500}$ +32°, $[\phi]_{450}$ +63°, $[\phi]_{400}$ +115°, $[\phi]_{350}$ +197°, $[\phi]_{300}$ +350°, $[\phi]_{250}$ +770°, $[\phi]_{225}$ +2070° (peak), $[\phi]_{206}$ 0°.

Ethyl 3-Ketocaprylate.—A suspension of sodium hydride in mineral oil containing *ca.* 48 g (2 mol) of NaH was filtered with a coarse sintered-glass filter and the residue was washed three times with petroleum ether (bp 30–60°). The hydride was transferred to a nitrogen-swept three-necked 2-l. flask fitted with a condenser, stirrer, and a 500-ml dropping funnel. The hydride was covered with 250 ml of anhydrous ether, and ethyl carbonate (236 g, 2 mol) was added. 2-Heptanone (114 g, 1 mol), dissolved in 250 ml of anhydrous ether, was added dropwise over 5 hr with stirring and refluxing. After 12 hr the solution was cooled to room temperature, and the stirring was stopped. The following day the sodium salt was decomposed by the gradual addition of 125 ml of glacial acetic acid. Upon the addition of water the precipitated sodium acetate dissolved, and two phases separated. The aqueous phase was extracted twice with ether. The ethereal extracts were combined, washed twice with 5% $NaHCO_3$, and dried. The solvent was removed on the steam bath and the residue distilled. The fraction with bp 102–108° (10 mm) [lit.[21] bp 108–110° (11 mm)] was collected to give 114 g (61%) of ethyl 3-ketocaprylate.

4-*n*-Pentyl-5,7-dihydroxycoumarin (14).—To an ice-cold mixture of phloroglucinol (50 g, 0.397 mol) and ethyl 3-ketocaprylate (77.5 g, 0.417 mol) was added 450 ml of 75% H_2SO_4 over 2 hr. After the addition the reaction was stirred at room temperature for 4 hr. The yellow precipitate that formed was poured into 2000 ml of ice–water, filtered, and washed with water. The material was recrystallized twice from 50% EtOH–H_2O and dried to yield 59 g (60%) of light cream-colored crystals, mp 230–250°. Tlc showed the product to give predominantly one fluorescent spot. An analytical sample was prepared by column chromatography. White crystals, mp 235–237°, were obtained after recrystallization from ethyl acetate–hexane: uv max 252 mμ (ϵ 1180), 260 (6830), 328 (13,500).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.43; H, 6.50. Found: C, 67.62; H, 6.58.

4-*n*-Pentyl-5-hydroxy-7-methoxycoumarin (15).—To a 1-l. round-bottomed flask containing 600 ml of methanol and 50 ml of water were added **14** (20 g, 0.081 mol) and dimethyl sulfate (16 ml, 21.3 g, 0.17 mol). The mixture was stirred while a solution of Na_2CO_3 (25 g, 0.236 mol) in 125 ml of water was added dropwise over 7 hr. After 15 hr the solution, in which some precipitate had formed, was poured into 800 ml of water, acidified with HCl, and extracted with three portions of ether. The combined extracts (1200 ml) were extracted with three 300-ml portions of 10% Na_2CO_3, followed by two 200-ml portions of 5% NaOH. The ether layer was washed with water, dried, and evaporated to give 1.74 g of the dimethylated coumarin. The carbonate extracts were acidified with HCl and extracted twice with ether. The extract was dried and evaporated to yield 11.73

(21) S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, **69**, 2677 (1947).

g of starting material, which also contained some of the undesired monomethylated product. This material may be recycled to prepare more of the desired product. The hydroxide extracts were acidified with HCl and extracted with ether. As the dried ethereal solution was concentrated on the steam bath, the product began to crystallize from the solution. When approximately 75 ml remained, evaporation was stopped and after 2 hr 4.56 g (*ca.* 52%, based on unrecovered starting material) of white crystals, mp 156–160°, were filtered off. Tlc showed one major fluorescent spot of **15** ahead of a trace of starting material. An analytical sample was obtained by column chromatography followed by crystallization from ethyl acetate–hexane: mp 160–162°; uv max 250 mμ (ε 6090), 258 (7200), 321 (14,700); nmr (CF_3COOH) τ 9.05 (t, 3), 8.50 (m, 6), 6.92 (m, 2) 6.12 (s, 3), 3.78 (s, 1), 3.52 (s, 2).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.65; H, 6.77.

2,5-Dihydroxy-4-*n*-pentyl-7-methoxychroman (17).—Dry tetrahydrofuran (100 ml) and $LiAlH_4$ (3 g) were placed in a 1-l. three-necked flask equipped with a condenser, N_2 inlet tube, and dropping funnel. After the solution was brought to reflux, **15** (8 g, 0.031 mol) in 300 ml of dry THF was added dropwise over 7 hr. After 13 hr the reaction vessel was cooled and ice–water was added slowly. When the excess $LiAlH_4$ had reacted the solution was swamped with water, acidified with HCl, and extracted three times with ether. Drying of the ethereal extract and evaporation gave 8.5 g of a red viscous liquid. Tlc showed several products; the major one had the spot with the highest R_f. Column chromatography gave 3.45 g (43%) of white crystals: mp 102–103° after recrystallization from CH_2Cl_2–hexane; ir (CH_2Cl_2) 2.80 (m), 3.05 (w), 6.15 (s), 6.27 μ (s); uv max 270 mμ (ε 700), 278 sh; nmr ($CDCl_3$) τ 9.10 (t, 3), 7.02 (m, 1), 6.32 (s, 3), 4.62 (t, 1), 4.02 (q, 2).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.58; H, 8.59.

2,5-Diacetoxy-4-*n*-pentyl-7-methoxychroman (18).—The chroman **17** (52 mg) was treated with pyridine (2 ml) and acetic anhydride (1 ml). After 24 hr the solution was poured into ice–water and extracted twice with ether; the ether was washed with 2 *N* HCl and water, dried, and evaporated to yield 47 mg of an oil. Preparative tlc gave 38 mg (55%) of liquid product with an R_f greater than that of the starting material. The same product was obtained when the reaction was carried out on the steam bath for 2 hr: ir (CCl_4) 5.75 (s), 6.13 (s), 6.30 μ (m); nmr ($CDCl_3$) τ 9.10 (t, 3), 7.90 (s, 3), 7.67 (s, 3), 7.12 (m, 1), 6.30 (s, 3), 3.71 (m, 3).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.88; H, 7.83.

4-*n*-Pentyl-5-hydroxy-7-methoxydihydrocoumarin (20).—A solution of **17** (3.70 g) in 15 ml of reagent grade acetone was cooled to 4°. Chromic acid reagent[16] was slowly added until the solution had a faint red-orange tinge. A green precipitate formed during the reaction. After 10 min the solution was poured into a large excess of water and extracted three times with ether. The ethereal extract was washed twice with water, dried, and evaporated to give 3.32 g of a viscous orange liquid. Column chromatography gave 1.61 g (44%) of white crystals: mp 99–100° after recrystallization from hexane–CH_2Cl_2; ir (CH_2Cl_2) 2.74 (m), 2.90 (w), 5.65 (s), 6.12 (s), 6.24 (s), 6.60 μ (s); uv max 297 mμ sh, 293 (ε 1870); nmr ($CDCl_3$) τ 9.13 (t, 3), 8.21 (m, 2), 6.65 (m, 1), 6.28 (s, 3), 3.75 (q, 2).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.33; H, 7.76.

3,4,9,10-Tetrahydro-2,2-dimethyl-5-methoxy-10-*n*-pentyl-4,8-dioxo-2H,8H-[1,2-*b*:3,4-*b*′]benzodipyran (21).—Senecioic acid (3-methylcrotonic acid, 200 mg, 2.00 mmol) was mixed thoroughly with **20** (400 mg, 1.51 mmol) to form a finely powdered mixture. This was placed in a small weighing bottle (12 ml), and approximately 11 g of polyphosphoric acid was added. The mixture was stirred on a Thermix hot plate maintained at 120°. After 0.5 hr the hot dark red solution was dumped into ice–water. After dissolution of the red gummy mass which formed, the solution was extracted three times with ether. The combined ether layers were washed twice with 5% $NaHCO_3$, dried, and evaporated to give 448 mg of a dark cream-colored solid. Recrystallization from hexane–CH_2Cl_2 gave 350 mg (67%) of white product, mp 150–152°. A sample suitable for analysis was prepared by preparative tlc: mp 151.5–152.5°; ir (CH_2Cl_2) 5.63 (s), 5.90 (s), 6.26 μ (s); uv max 276 mμ (ε 15,700), 322 (4080); nmr ($CDCl_3$) τ 9.10 (t, 3), 8.53 (s, 6), 7.26 (m, 4), 6.71 (m, 1), 6.12 (s, 3), 3.78 (s, 1).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.53; H, 7.63.

Methyl 3-[8-(2,2-Dimethyl-5-methoxy-7-hydroxy)chromanyl]-octanoate (22).—Into a 50-ml pear-shaped flask containing a magnetic stirring bar were placed 20 ml of methanol, 4 ml of water, 8 ml of glacial acetic acid, 16 g of freshly prepared zinc amalgam, and the chromanone **21** (284 mg). Concentrated HCl (6 ml) was added and stirring was begun. After 3 hr the solution was decanted into a large excess of water, the zinc amalgam was rinsed several times with ether–water; and the washings were added to the water. This was extracted three times with ether, and the ether was washed with 5% $NaHCO_3$, dried, and evaporated to give 264 mg of crude product. Tlc showed two major spots, both having R_f's higher than starting material, and the ir spectra indicated the presence of some of the chroman lactone. The crude product was dissolved in 17 ml of methanol; 3 drops of concentrated H_2SO_4 were added; and the solution was refluxed for 0.25 hr. The reaction was poured into a large excess of water and extracted three times with ether. The extracts were washed with water, dried, and evaporated to give 245 mg of product. Column chromatography gave 155 mg (52%) of desired methyl ester **22** as white crystals: mp 93–95° after recrystallization from hexane; ir (CCl_4) 2.98 (w), 5.84 (s), 6.19 (s), 6.27 μ (s); uv max 272 mμ (ε 770), 280 sh; nmr (CCl_4) τ 9.25 (t), 8.70 (s), 8.28 (t, 3), 6.39 (s, 3), 6.28 (s, 3), 4.08 (s, 1).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.08; H, 8.95.

A 44-mg (16%) sample of the chroman lactone was also obtained, mp 89–91° after recrystallization from methanol.

Synthetic Methyl O-Methyldihydroblancoate (13).—The chroman ester **22** (106 mg) in 6 ml of nitrobenzene was placed in a small pear-shaped flask. Tigloyl chloride[4] (144 mg) and a large excess of anhydrous $AlCl_3$ were added. The flask was stoppered and stirred magnetically for 2 days. The reaction mixture was poured into ice–water and dilute HCl. The solution was heated on the steam bath for 0.25 hr, cooled, and extracted twice with ether. The ethereal extract was washed once with 5% $NaHCO_3$ and twice with water and then steam distilled to remove the ether and nitrobenzene. The cooled residual solution was extracted twice with CH_2Cl_2, and the extracts were dried and evaporated to give a yellow oil. Tlc showed two spots which were identically fluorescent; the upper spot had the same R_f and fluorescence as natural methyl O-methyldihydroblancoate. Preparative tlc gave 20 mg of a slightly viscous light yellow oil corresponding to the upper spot. The sample was purified for analysis by tlc and sublimation (100°, 10^{-5} Torr): ir (CCl_4) 5.74 (s), 5.89 (s), 6.28 (s), 6.85 μ (s); uv max 290 mμ (ε 14,700), 335 sh; nmr (CCl_4) τ 9.15 (t), 8.88 (d), 8.67 (s), 8.53 (d), 8.28 (t, 2), 7.40 (d), 6.54 (s, 3), 6.28 (s, 3).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.13; H, 8.74.

The lower spot gave 9 mg (7%) of a light yellow oil with uv max 290 and 335 sh mμ.

Registry No.—**9,** 17244-43-8; **10,** 17244-44-9; **11,** 17244-45-0; **12,** 17243-88-8; **13,** 17243-89-9; **14,** 17243-90-2; **15,** 17243-91-3; **17,** 17243-92-4; **18,** 17243-93-5; **20,** 17243-94-6; **21,** 17243-95-7; **22,** 17243-96-8; **23,** 3975-91-5; **24,** 17243-98-0; 2,6-dihydroxyacetophenone, 699-83-2; 2,4-dihydroxyacetophenone, 89-84-9.

Acknowledgments.—We wish to thank Mr. Gary Hickernell for carrying out the oxidation of dihydroblancoic acid and the isolation of pentylsuccinic acid. The 100-MHz nmr spectrum of blancoic acid was obtained through the kindness of Dr. K. L. Stevens, U. S. Department of Agriculture, Albany, Calif. The plant materials on which this study was based were generously provided by the Department of Forestry, Republic of the Philippines, and the Forest Herbarium, Thailand.

Calophyllum Products. IV. Papuanic and Isopapuanic Acids[1a-c]

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Papuanic acid from the bark resin of *Calophyllum papuanum* Lauterb. is shown to have the structure and absolute stereochemistry **29a** by a combination of degradative, synthetic, and X-ray crystallographic methods. Isopapuanic acid, also present in the resin, is the C-2 epimer **30a**. The stereochemistry and conformations of these compounds and their epimerization and bromination products are discussed. The synthesis of a derivative of papuanic acid is described.

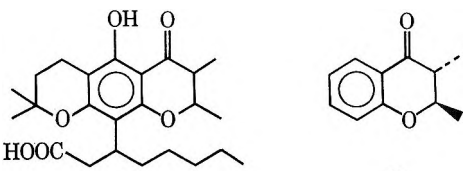
Pentane extraction of the ground bark of *Calophyllum papuanum* Lauterb., a New Guinea species of the family Guttiferae, yields a surprising 13% of yellow-green resin. Thin layer chromatography (tlc) showed this to consist of *ca.* 95% of two similar compounds, with only a small amount of impurities. The major components can be extracted from the pentane solution with aqueous carbonate, and careful chromatography on silica gel then yields pure papuanic and isopapuanic acids.[2] Both compounds are monocarboxylic acids of the formula $C_{25}H_{36}O_6$, as shown by combustion analyses, titration, and high resolution mass spectrometry. Although papuanic acid, the major product, may be obtained as a solid following prolonged cooling of the pure material, neither compound can be crystallized from solvents. Consequently they and most of their derivatives have been handled only as glasses.

Structure.—Catalytic hydrogenation of papuanic acid led to the rapid uptake of 1 mol of hydrogen and the formation of dihydropapuanic acid, $C_{25}H_{38}O_6$. The uv spectra of the starting material and product are nearly identical. These spectra are very similar to that of dihydroblancoic acid (**1**)[1b] and clearly represent the same oxygenated acylphenone system.

The nmr spectrum of papuanic acid (Figure 1) is very clear and allows the identification of nearly every proton in the molecule. It shows no aromatic protons, requiring that the benzene ring indicated by the uv spectrum be fully substituted as in **1** and other *Calophyllum* products.[3-6] Among the substituents are clearly a methoxyl group (τ 6.28, 3 H) and a chelated hydroxyl (−2.34, 1 H).

A group of signals at τ 5.88 (m, 1 H), 8.51 (d, 3 H), and 8.84 (d, 3 H) represents the now familiar *trans*-2,3-dimethylchromanone **2**, which has appeared so repeatedly in *Calophyllum*.[1b,3,5,7] The carbonyl group gives rise as expected to a band at 6.11 μ in the ir spectrum and must be adjacent to the hydroxyl mentioned above.

Another group of signals at τ 4.90 (t, 1 H), 6.81 (d, 2 H), 8.28 (s, 3 H), and 8.34 (s, 3 H) is readily assigned to an isopentenyl chain, a common substituent throughout the Guttiferae.[8] In dihydropapuanic acid the vinyl signal at 4.90 vanishes, and the benzylic–allylic doublet at 6.81 becomes a broad triplet at 7.45. These changes confirm that it is the double bond of this chain that is reduced.



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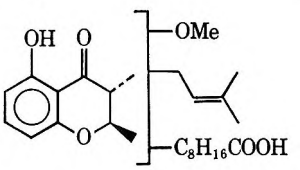


3

These fragments and the remainder of the molecule can be combined as in **3**. The side chain bearing the carboxyl group produces clear signals in the nmr spectrum of papuanic acid only at τ 7.18 (d, 2 H), the methylene adjacent to the carboxyl, and 9.16 (t, 3 H), the terminal methyl of a *n*-alkyl chain. The shift of the isopentenyl benzylic methylene in dihydropapuanic acid reveals an additional multiplet at 6.55 (1 H), which represents a benzylic methine. Comparison of these signals with those of blancoic acid[1b] suggests that papuanic acid contains the same 3-aryloctanoic acid system (**4**). The isolation of *n*-pentylsuccinic acid after vigorous oxidation of papuanic acid substantiates this proposal.

Treatment of papuanic acid under mild conditions with either acetic anhydride–pyridine or dicyclohexylcarbodiimide (DCC) led to the formation of papuanolide, $C_{25}H_{34}O_5$. This product is characterized by the absence from its nmr spectrum of the signals corresponding to both the chelated hydroxyl and the carboxylic proton (τ −1.76). In addition the ir band of the acid function shifts from 5.84 to 5.60 μ expected for a phenolic ester, while the chromanone carbonyl absorption moves from 6.11 to 5.89. These results show that lactonization must have occurred onto the

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S078. Taken in part from the Ph.D. Theses of G. L. Hickernell and K. D. Sears, University of Washington, 1968. (b) For the previous paper in this series, see G. H. Stout and K. D. Sears, *J. Org. Chem.*, **33**, 4185 (1968). (c) Supported in part by Public Health Service Grant GM-12095 from the National Institute of General Medical Sciences. (d) National Science Foundation Cooperative Fellow, 1964–1966. National Science Foundation Fellow, 1966–1968. (e) University of Washington Institute of Forest Products Research Fellow 1964–1966.

(2) Although papuanic acid may be isolated chromatographically without prior carbonate extraction, the isopapuanic acid so obtained is contaminated with a neutral oil.

(3) J. Polonsky, *Bull. Soc. Chim. Fr.*, 1079 (1957).

(4) G. H. Stout and K. L. Stevens, *J. Org. Chem.*, **29**, 3604 (1964).

(5) S. K. Nigam, C. R. Mitra, G. Kuensch, B. C. Das, and J. Polonsky, *Tetrahedron Lett.*, 2633 (1967).

(6) T. R. Govindachari, D. Prakash, and N. Viswanathan, *ibid.*, 4177 (1967).

(7) G. H. Stout, M. M. Krahn, and G. D. Breck, *ibid.*, 3285 (1968).

(8) *Inter alia:* B. F. Burrows, W. D. Ollis, and L. M. Jackman, *Proc. Chem. Soc.*, 177 (1960); G. H. Stout, V. F. Stout, and M. J. Welsh, *Tetrahedron*, **19**, 667 (1963); B. Jackson, H. D. Locksley, and F. Scheinmann, *J. Chem. Soc., C*, 178 (1966).

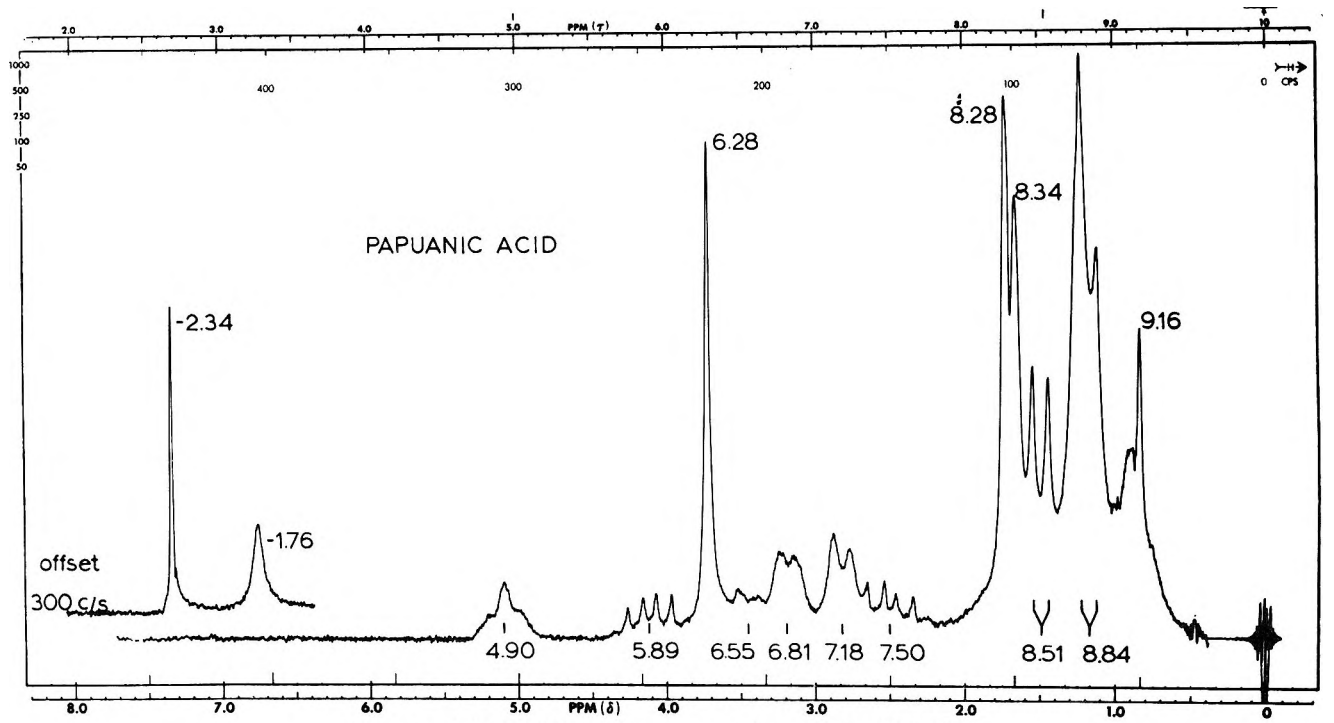
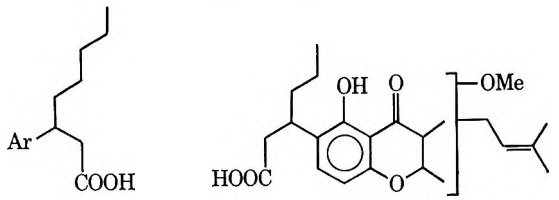


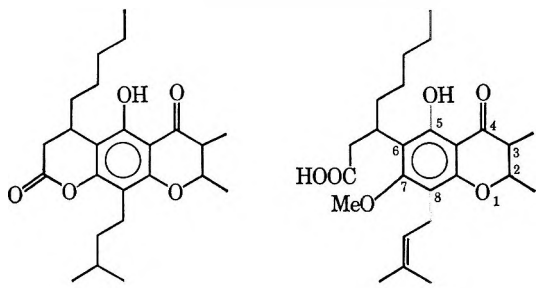
Figure 1.—The 60-MHz nmr spectrum of papuanic acid in CCl_4.

chelated hydroxyl, and thus that the carboxylic chain must occupy the adjacent position (**5**).

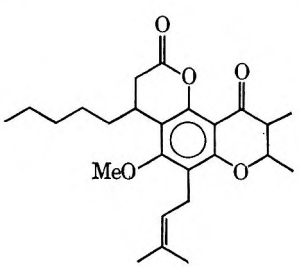


4 **5**

Although it may be assumed by analogy with blancoic acid and other products of *Calophyllum* species that oxygenation of papuanic acid is based on a phloroglucinol pattern, independent evidence is available to prove the point. Demethylation of dihydropapuanic acid by brief treatment with hydriodic acid in acetic anhydride gave demethyldihydropseudopapuanolide, $C_{24}H_{34}O_5$, a lactone similar in its properties to papuanolide. The new product, however, shows a nmr signal at τ −2.10 (1 H) and an ir band at 6.12 μ, indicating that the chelated hydroxyl is still present. Lactone formation must therefore involve a newly formed hydroxyl at the remaining position *ortho* to the carboxylic chain, and consequently demethyldihydropseudopapuanolide has the structure **6**. The corresponding structure for papuanic acid is thus **7**, and papuanolide is **8**.



6 **7**



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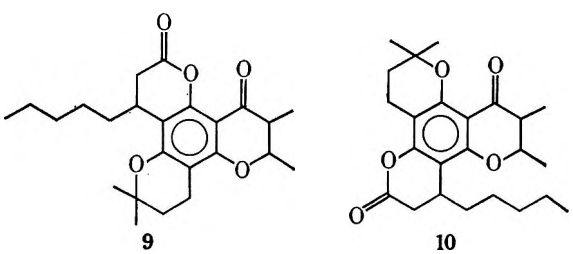
Demethylation of papuanic acid under the same conditions, followed by treatment with DCC, led to yet another lactone, cyclodemethylpapuanolide (**9**). The absence of the nmr and ir signals associated with the chelated hydroxyl shows the direction of lactonization, while the nmr spectrum now shows the peaks [τ 7.40 (t, 2 H), 8.32 (t, 2 H), 8.67 (s, 2 H)] expected for a 2,2-dimethylchroman ring rather than those of an isopentenyl chain. The product **9** was particularly important because it differs from dihydroblancolide (**10**) only in an interchange of the lactone and chroman rings, and a comparison of the two compounds illuminated the rearrangement leading to **10**.[1b]



9 **10**

Isopapuanic acid shows the same chemical and physical behavior as papuanic acid, and the close similarity is maintained throughout the parallel series of derivatives. In particular, isopapuanic acid also yields pentylsuccinic acid on oxidation and also lactonizes onto the chelated hydroxyl group. A significant

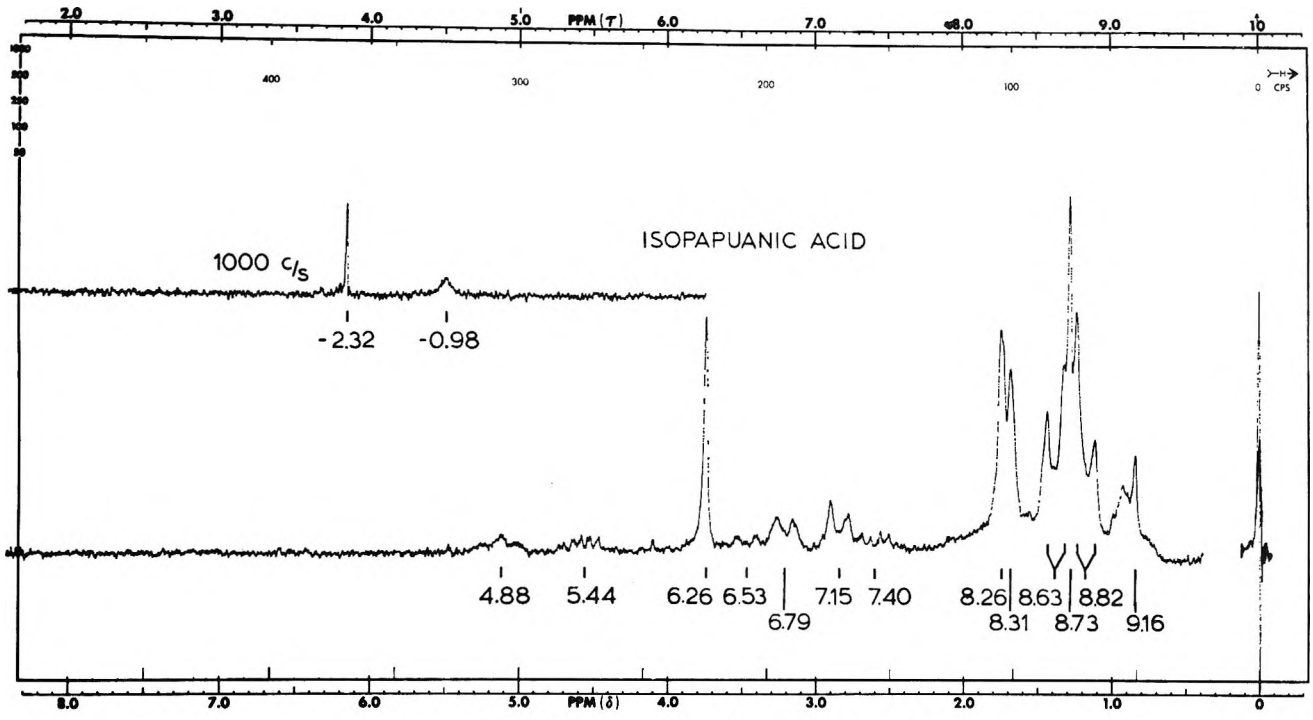
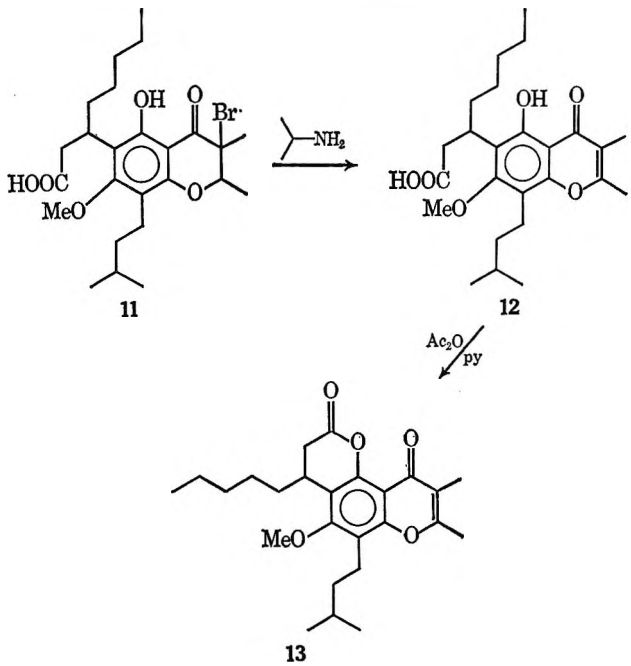


Figure 2.—The 60-MHz nmr spectrum of isopapuanic acid in CCl_4.

difference between the two molecules does appear, however, in the nmr spectra (Figure 2). Isopapuanic acid shows the signals resulting from the 2,3-dimethylchromanone ring at τ 5.44 (m, 1 H), 8.63 (d, 3 H), and 8.82 (d, 3 H). Besides the shift in position, the low-field multiplet also shows J = 3, 6 Hz instead of J = 10, 6 Hz as found in papuanic acid. As has been discussed in analogous cases,[4,6,7] these changes are indicative of *cis*-2,3-dimethyl substitution in isopapuanic acid, in contrast to the *trans* arrangement in papuanic.

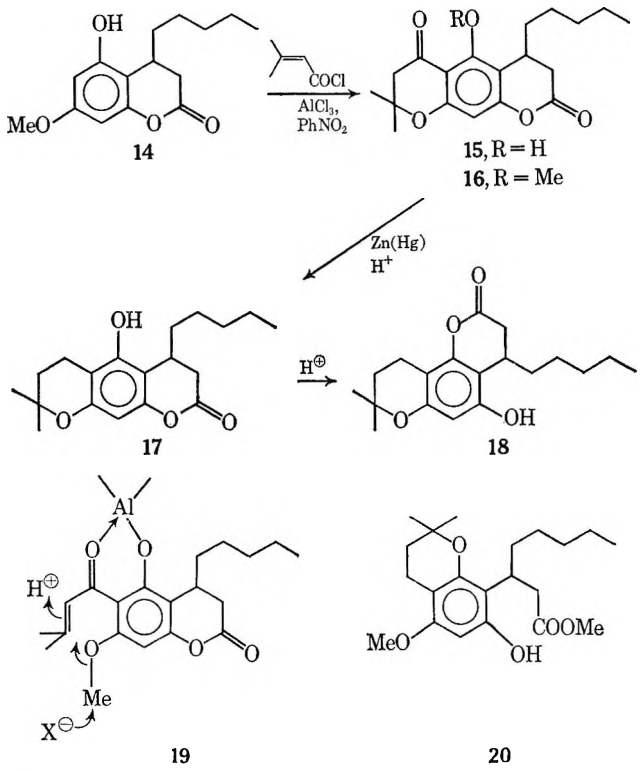
To confirm that both papuanic and isopapuanic acids have the structure **7**, differing only in stereochemistry, both compounds were converted into the same chromone (**13**). Bromination of either dihydropapuanic or dihydroisopapuanic acid with bromine in glacial acetic acid led to mixtures of *cis*- and *trans*-3-bromo derivatives (**11**). Dehydrohalogenation of the *trans* isomers gave the acid **12**, neopapuanic acid, which was lactonized in the usual way to **13**, neopapuanolide. Products obtained from both starting materials were identical chromatographically and in all spectral details.



Synthesis.—The structure deduced for papuanic acid was confirmed by the synthesis of a derivative, methyl cyclodemethylpapuanate (**26**). The key intermediate in this synthesis proved to be the hydroxychromanone lactone **22**, whose methyl ether **21** had previously been prepared in the synthesis of methyl O-methyldihydroblancoate.[1b]

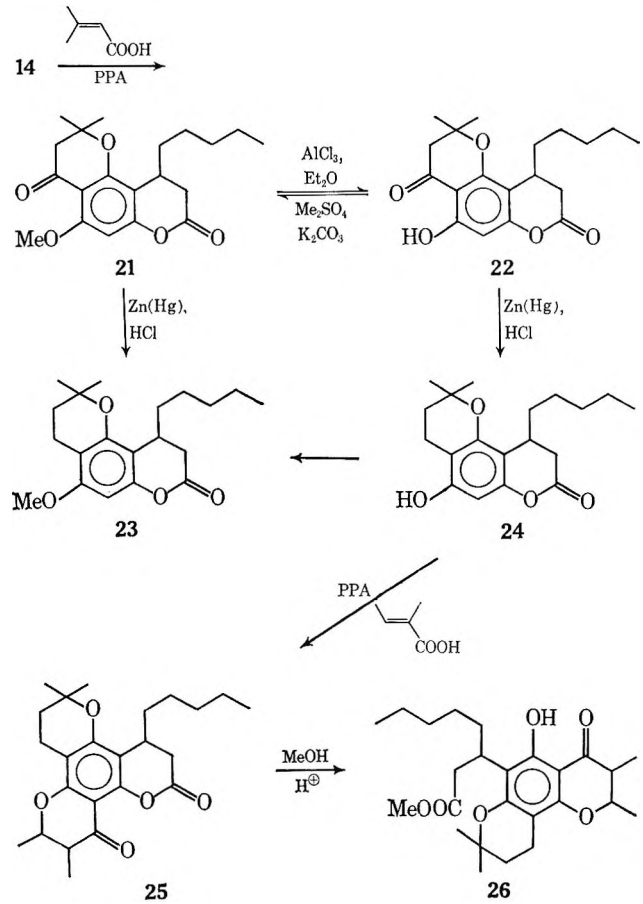
During early attempts to synthesize **21**, it was observed that treatment of the dihydrocoumarin **14** with senecioyl chloride and aluminum chloride in nitrobenzene led to a lactonic product containing a chelated hydroxyl but no methoxyl group. This was assumed to be **22**, arising by simple demethylation, although such a reaction is surprising since the conditions used generally do not cause ether cleavage. Clemmensen reduction of this material, however, led to *two* chroman products, one of which was formed at the expense of the other upon prolonged reaction. Since the conditions were too mild to produce rearrangement of the chroman ring, a lactone interchange, although incompatible with structure **22**, appeared to be involved. Evidence that the starting chromanone was in fact **15**, the only alternative structure consistent with the spectra, was obtained by its methylation to a methyl ether (**16**) different from **21**. On this basis the two reduction products are assigned the structures **17** and **18**.

To account for this unexpected result, we suggest that the demethylation observed is a consequence of the particular unsaturated acid used in the acylation. If the aromatic substitution occurs in a complex in which coordination of the carbonyl and hydroxyl groups with aluminum holds the side chain in a favorable orientation, electrophilic attack on the double bond can transmit electron demand to the ether oxygen as shown in



19 and increase the ease of demethylation. It is possible that this reaction depends on the ability of senecioic acid to generate a tertiary carbonium ion upon protonation of its double bond, since the reaction of **20** with tigloyl chloride under very similar conditions did not lead to demethylation.[1b]

The desired product, **22**, was ultimately obtained by the demethylation of **21** using aluminum chloride in ether.[9] Methylation returned **21**, showing the absence of rearrangement. Clemmensen reduction of **22** gave a single product, **24**, whose structure was confirmed by methylation to **23**, previously prepared by reduction of **21**.[1b]



The insertion of the 2,3-dimethylchromanone system into **24** was accomplished with tiglic acid and polyphosphoric acid, tigloyl chloride and aluminum chloride, the reagents of choice in the blancoic acid series, proving inferior here. The product **25**, a mixture of stereoisomers (see below), proved difficult to extract from silica gel plates and was converted with acidic methanol into the corresponding methyl esters (**26**). These could be separated into two fractions, of which the more mobile showed the nmr characteristics of a *trans* chromanone and the less mobile those of the *cis* compounds. These products were identical in their chromatographic behavior and their uv, ir, nmr, and mass spectra with corresponding fractions obtained by esterification of the cyclodemethyl acids prepared by hydriodic acid demethylation of the natural mixture of papuanic and isopapuanic acids.

Stereochemistry.—Papuanic acid possesses three asymmetric centers, two in the chromanone ring and one in the octanoic acid chain. As has already been discussed, it differs from isopapuanic acid in having *trans* rather than *cis* substitution in the chromanone, *i.e.*, in *one* of these centers. The stereochemical identity of the acidic chains of the two molecules was shown by the correspondence of the ORD curves of samples of neopapuanolide (**13**) prepared from each acid. Further confirmation and evidence of the absolute configuration at this center was obtained by the isolation of (+)-(*R*)-*n*-pentylsuccinic acid (**27**)[10] from the oxidative degradations of both papuanic and isopapuanic acids.

Treatment of papuanic acid with dilute base gave a mixture of starting material and an isomeric product, epipapuanic acid. The nmr spectrum of epipapuanic acid is clearly that of a *cis*-2,3-dimethylchromanone and is essentially indistinguishable from that of isopapuanic acid. The two compounds are clearly different, however, since they show opposite signs of rotation. Since the third asymmetric center must be the same in both, epipapuanic and isopapuanic acids are not enantiomers, but they must have opposite configurations at both C-2 and C-3. Since epimerization of papuanic acid at C-3 leads to epipapuanic acid, a single inversion at C-2 must therefore be required to produce isopapuanic acid, and the two molecules differ only with respect to the stereochemistry at that center.

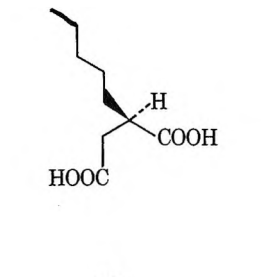
In confirmation, base-catalyzed epimerization of isopapuanic acid gave epiisopapuanic acid, similar in nmr absorption to papuanic acid but again differing in sign of rotation. Similarly, reactions involving strong acid treatment (*e.g.*, HI demethylation) lead to pairs of products epimeric at C-3 and different in the papuanic and isopapuanic acid series.

Corresponding to the epimerization experiments, bromination of dihydropapuanic and dihydroisopapuanic acids also produces mixtures of different *cis*- and *trans*-3-bromo derivatives.

(9) W. Baker, *J. Chem. Soc.*, 662 (1941).

(10) A. Fredga, *Tetrahedron*, **8**, 126 (1960); A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjöberg, and S. Sjöberg, *J. Chem. Soc.*, 3928 (1965).

Extensive degradative attempts to obtain one or the other of the asymmetric centers of the chromanone ring in a form proving the absolute configuration were unsuccessful. Ultimately a crystalline bromo compound (**28**) was obtained from dihydrodemethylpseudopapuanolide (**6**) and was shown by X-ray crystallographic techniques to have the structure and absolute configuration indicated.[11] Since the preparation of this compound leaves the configuration at C-2 unchanged, papuanic acid is therefore **29a**, and isopapuanic is acid **30a**. Epipapuanic and epiisopapuanic acids are **29b** and **30b**, respectively.



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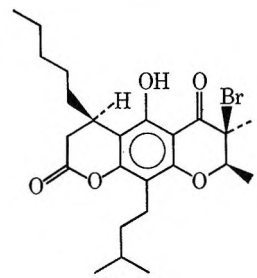
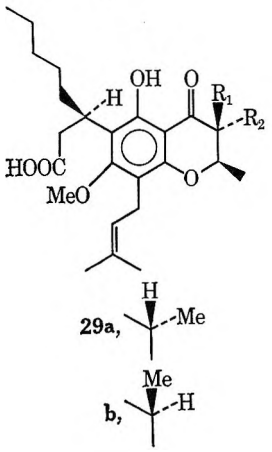
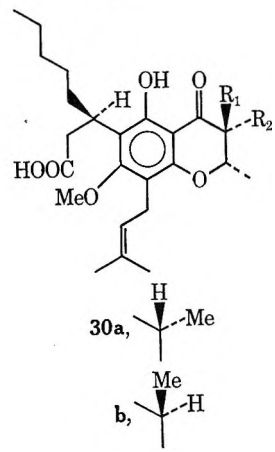


28





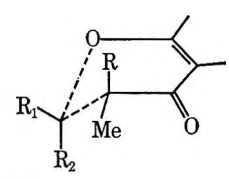
The availability of a complete set of stereoisomers in this series of compounds permits us to consider the conformational differences which exist among them. As has previously been discussed,[4] the change in $J_{2,3}$ between the *trans* and *cis* compounds reflects a change from a (2e,3e) methyl arrangement to (2e,3a) or (2a,3e). A decision in favor of the latter orientation can be made on the basis of the chemical shifts of the various signals associated with the chromanone ring (Table I).

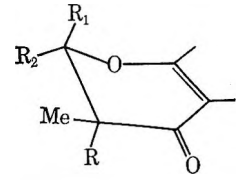
TABLE I
CHROMANONE NMR SIGNALS OF VARIOUS PAPUANIC ACID STEREOISOMERS

	C-2H, τ	C-2Me, τ	C-3H, τ	C-3Me, τ
Papuanic acid (**29a**)	5.89	8.51	7.50	8.84
Isopapuanic acid (**30a**)	5.44	8.63	7.40	8.82
Epipapuanic acid (**29b**)	5.50	8.62	7.55	8.77
Epiisopapuanic acid (**30b**)	5.88	8.50	7.50	8.81

It is clear from Table I that the C-2 proton signal shifts downfield and the methyl signal upfield on passing from the *trans* to the *cis* compounds. The C-3 signals, however, are only slightly affected. Since axial substituents are more shielded than their equatorial counterparts,[12] these changes indicate that it is the C-2 methyl group that becomes axial in the *cis* isomers.[13] This occurs regardless of whether actual inversion occurs at C-2, as in isopapuanic acid, or at C-3, as in epipapuanic acid. To achieve this result, however, the basic epimerization of papuanic acid must be accompanied as shown by a conformational flip of the chromanone ring.[14]

The structural assignment and conformational analysis of the 3-bromo derivatives is complicated by the absence of $J_{2,3}$. Nevertheless the desired results can be obtained by a more roundabout argument. Comparison of the ir and uv spectra of dihydropapuanic and isopapuanic acids with those of their *cis*- and *trans*-3-bromo derivatives (Table II) shows that in all cases bromination is accompanied by marked shifts of the uv maxima to longer wavelengths and by no significant changes in the ir carbonyl absorption.





29a, R = H; R_1 = Me; R_2 = H
30a, R = H; R_1 = H; R_2 = Me
31a, R = Br; R_1 = Me; R_2 = H
32a, R = Br; R_1 = H; R_2 = Me

29b, R = H; R_1 = Me; R_2 = H
30b, R = H; R_1 = H; R_2 = Me
31b, R = Br; R_1 = Me; R_2 = H
32b, R = Br; R_1 = H; R_2 = Me

TABLE II
SPECTRAL PROPERTIES OF BROMINATED DIHYDROPAPUANIC ACIDS

	Ir, μ	Uv, mμ
Dihydropapuanic acid	6.11	285, 356
trans-3-Bromo (**31a**)	6.12	292, 367
cis-3-Bromo (**31b**)	6.11	296, 373
Dihydroisopapuanic acid	6.12	287, 358
cis-3-Bromo (**32a**)	6.13	294, 369
trans-3-Bromo (**32b**)	6.15	296, 369

These results are consistent only with an axial orientation of the bromine atom, since an equatorial bromine causes a hypsochromic shift in the carbonyl-stretching band[15] and has relatively little effect on the uv spectrum.[16] Such a result is expected in view of the unfavorable dipole–dipole interactions in equatorial α-bromo ketones and the small difference in energy between the *cis*- and *trans*-methyl arrangements in this series.

Given the axial orientation of the bromine atoms, the conformation at C-2 follows from the observation

(11) I. Singh and G. H. Stout, in preparation.

(12) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp 115–119.

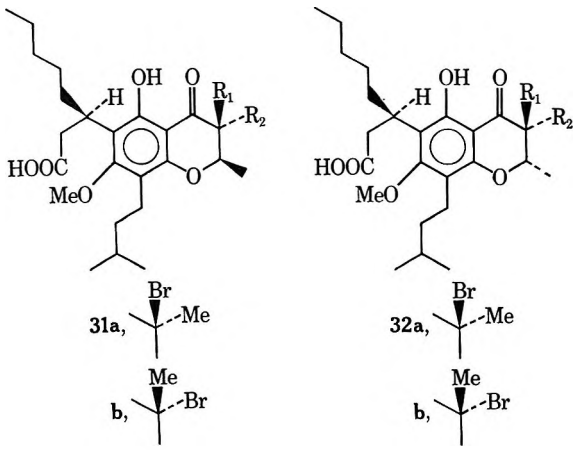
(13) This is presumably a consequence of the "3-alkyl ketone effect." See N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **84**, 2201 (1962).

(14) The structures are represented in the "sofa" form [E. M. Philipin and T. S. Wheeler, *Proc. Chem. Soc.*, 167 (1958)] rather than the more familiar half-chair conformation because the former is in much better accord with the X-ray results on **28**.

(15) R. N. Jones, D. A. Ramsey, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 2828 (1952); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 460–469.

(16) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

that the nmr signal from the C-2 proton appears in one isomer of each pair at τ 5.3 and in the other at *ca.* 6.2.[17] The former is clearly the product with the equatorial proton and *cis* methyls, *i.e.*, **31b** and **32a**, while the latter is the *trans* compound with the axial proton, **31a** and **32b**.



In confirmation of these arguments, only those isomers assigned the *trans* configuration, 3-bromodihydropapuanic acid (**31a**) and 3-bromodihydroepiisopapuanic acid (**32b**), are dehydrobrominated when treated with isopropylamine. The *cis* isomers are unaffected. This result is entirely in agreement with the proposed configurations, since only the *trans* isomers have the large dihedral angle between the proton and bromine needed for easy elimination.

Final support of these views was obtained from the crystallographic structure analysis of **28**, which was selected as a *trans* isomer on the basis of its nmr spectrum and so proved to be. In addition the axial orientation of the bromine was also confirmed, at least in the solid state.[11]

The epimerization experiments on both papuanic and isopapuanic acids led to equilibrium mixtures in which the ratio of *trans/cis* isomers was *ca.* 2:1. These findings indicate a relatively small energy difference between the two configurations, as might be expected from the reduced number of axial–axial interactions possible in this system. Bromination of the two dihydro acids, on the other hand, leads to 2:1 *cis/trans* product ratios. This result is reasonable, however, if the reaction is assumed to proceed through the chromanone enol, in which favored bromine approach is from the side away from the C-2 methyl group.

Discussion

Papuanic and isopapuanic acids represent the first pair of stereoisomeric products isolated from a species of *Calophyllum*. The results outlined above, together with those obtained for other related dihydrocoumarinic acids from this genus,[1b,7] suggest a common stereochemistry (*R*) for the asymmetric center of the acid side chain but greater variation in the chromanone ring. Since the difference between papuanic and isopapuanic acids occurs at the very stable C-2 and not, as might have been expected, at the readily epimerizable C-3, it must reflect a true lack of specificity in the biosynthesis.

The determination of the absolute stereochemistry of papuanic acid and its isomers now provides a basis for the extension of studies into the stereochemistry of the related members of this series by ORD and CD methods. These compounds also provide relatively rigid models for investigations more generally into the interaction of molecular asymmetry and the acylphenone chromophore. Studies in both of these areas are currently in progress and will be described in subsequent papers.[18]

Since lactonization is possible in papuanic acid, it may be regarded formally as a hydrolyzed dihydrocoumarin, unlike the previously reported blancoic[1b] and apetalic[6] acids, which are incapable of lactone formation without rearrangement. As a result it can no longer be suggested that the formation of these acids occurs only in those cases in which the normal biosynthetic paths leading to coumarins are blocked. It would clearly be of interest, therefore, to know at what stage in the biosynthesis the reduction occurs which produces papuanic acid rather than its coumarin analog. Comparison with the other *Calophyllum* products suggests that some precursor other than the coumarin itself is involved, but a clear decision will have to await further studies.

Experimental Section

All melting points were taken on a Kofler hot stage and are corrected. Combustion analyses were performed by Dr. A. Bernhardt of Mülheim (Ruhr), West Germany. Silica gel 922 (200–325 mesh) from Grace–Davisson Chemical Co. was used in all column chromatography with various concentrations of hexane and ethyl acetate as elutants. For tlc Merck silica gel G was used, again with mixtures of hexane and ethyl acetate. Unless otherwise stated, anhydrous $MgSO_4$ was used to dry solutions. Uv spectra were taken on a Cary Model 14 spectrophotometer in 95% EtOH. Ir spectra were taken on a Perkin-Elmer Model 21 with a NaCl prism. The letter in parentheses signifies a strong (s), medium (m), or weak (w) absorption band. Most nmr spectra were obtained on a Varian A-60 spectrometer, but some were taken by Mr. B. J. Nist on a Varian HR-60. The letter in parentheses refers to the multiplicity of the peak. The number following the letter, when given, is the estimated integrated intensity of the peak. In some instances the area could be measured and this is indicated. Mass spectra were determined on an AEI Model MS 9 with the aid of Mrs. M. M. Krahn.

Isolation of Papuanic and Isopapuanic Acids.—The ground bark (418 g) from *Calophyllum papuanum* Lauterb. (Guttiferae), collected near Lae, New Guinea, was extracted with pentane in a Soxhlet extractor for 2 hr. Most of the yellow material was extracted at the end of $^1/_2$ hr. Upon evaporation of the pentane 52 g (12%) of a viscous yellow-green resin was obtained.

The crude resin (1.99 g) in 50 ml of hexane was extracted with Na_2CO_3 (0.57 g) in 50 ml of water. The hexane layer was extracted a second time with Na_2CO_3 (0.10 g) in 25 ml of water. Each of the two base fractions was acidified carefully with 5% HCl to pH 7 and extracted once with 25 ml of ether. The bright yellow ether solutions were dried and filtered. After evaporation of the ether extract i contained a bright yellow oil (1.55 g) and extract ii a yellow-brown oil (0.28 g). The carbonate-insoluble substances remaining in the hexane were isolated as a yellow-green oil (0.09 g).

Column chromatography of 9.50 g of the yellow–green crude resin on 450 g of silica gel gave eight major fractions, of which three were homogeneous by tlc. The elutant (7:1 hexane–ethyl acetate) was not changed during the course of the separation. Data from the chromatogram are shown in Table III.

(17) This region is obscured by other signals, and it is not possible to locate the peak exactly.

(18) G. H. Stout and G. L. Hickernell, unpublished results.

TABLE III
CHROMATOGRAPHY OF *C. papuanum* RESIN

Fraction	Composition[a]	Vol., ml	Wt, g	Resin, %
1	X	75	0.175	2
2	X	375	0.145	2
3	P	225	3.266	34
4	P > I	60	0.587	6
5	P = I	75	0.591	6
6	I > P	360	1.657	17
7	I	630	1.286	14
8	I, X	300	0.222	2

[a] P = papuanic acid, I = isopapuanic acid, X = impurity.

Papuanic Acid.—A bright yellow oil (3.27 g) was obtained after evaporation of solvent from fraction 3. The oil was soluble in all common organic solvents, and attempts to crystallize it were unsuccessful. A yellow solid was obtained, however, upon refrigeration of pure papuanic acid: mp 73–77°; nmr (CCl_4) (integrated intensities measured) τ −2.34 (s, 1), −1.76 (s, 1), 4.90 (t, 1), 5.89 (m, 1), 6.28 (s, 3), 6.3–6.6 (m, 1), 6.81 (d, 2), 7.18 (d, 2), 7.50 (m, 1), 8.28 (s, 3), 8.34 (s, 3), 8.51 (d, 3), 8.73, 8.84 (d), 9.16 (t, 3) (Figure 1) (HR-60); uv max 286 mμ (ε 13,300), 357 (3300); ir (CCl_4) 3.35 (m), 5.84 (s), 6.11 (s), 6.31 (w), 6.95 (m), 7.21 (w), 7.43 (w), 7.70 (w), 7.86 (w), 8.63 (m), 8.75 (m), 9.11 μ (m); $[\phi]_{589}$ +350° (c 1.91 × 10^{-1}, EtOH).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.37; H, 8.28; mol wt, 432.255.

Isopapuanic Acid.—Fraction 7 contained a greenish yellow oil (1.29 g) after evaporation of the solvents. A portion of this material (0.51 g) in 25 ml of hexane was extracted with Na_2CO_3 (0.14 g) in 25 ml of water. The aqueous phase was acidified with 5% HCl to pH 7 and extracted once with 25 ml of ether. The ethereal solution was dried, filtered, and evaporated to give a bright yellow oil (0.24 g). Isopapuanic acid is soluble in all common organic solvents and could not be crystallized [nmr (CCl_4) (integrated intensities measured) τ −2.32 (s, 1), −0.98 (s, 1), 4.88 (t, 1), 5.44 (m, 1), 6.26 (s, 3), 6.35–6.65 (m, 1), 6.79 (d, 2), 7.15 (d, 2), 7.40 (m, 1), 8.26 (s, 3), 8.31 (s, 3), 8.63 (d), 8.73, 8.82 (d), 9.16 (t, 3) (Figure 2) (HR-60); uv max 280 mμ (ε 12,700), 360 (3000); ir (CCl_4), 3.35 (m), 5.84 (s), 6.11 (s), 6.30 (w), 6.95 (m), 7.21 (w), 7.42 (w), 7.66 (w), 7.75 (m), 8.61 (m), 8.78 (m), 9.15 μ (w); $[\phi]_{589}$ −100° (c 8.90 × 10^{-2}, EtOH)].

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.64; H, 8.52; mol wt, 432.255.

Dihydropapuanic Acid.—Papuanic acid (97 mg, 2.24 × 10^{-4} mol) was treated with hydrogen in ethanol using prereduced platinum oxide catalyst. Reaction was complete in 1/2 hr, at which time 5.9 ml (5.1 ml at STP, 2.28 × 10^{-4} mol) of hydrogen had been consumed. The molecular weight of papuanic acid calculated from this value is 434 ± 10. The solution was filtered, and the solvent was evaporated to give a yellow oil: nmr (CCl_4) (integrated area measured) τ −2.40 (s, 1), −1.38 (s, 1), 5.81 (m, 1), 6.25 (s, 3), 6.3–6.7 (m, 1), 7.16 (d, 2), 7.45 (t, 2), 7.3–7.7 (m, 1), 8.50 (d, 3), 8.81 (d), 9.06 (d), 9.16; uv max 285 mμ (ε 13,500), 356 (3260); ir (CCl_4) 3.43 (m), 3.51 (m), 5.84 (s), 6.11 (s), 6.32 (w), 7.00 (m), 7.21 (w), 7.42 (w), 7.66 (m), 8.40 (w), 8.60 (w), 8.78 (m), 8.91 (m), 9.30 μ (w).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.33; H, 8.91.

Dihydroisopapuanic Acid.—Isopapuanic acid was similarly reduced using prereduced platinum oxide and hydrogen at 1 atm. Hydrogen uptake was complete after 20 min of brisk stirring. The solution was filtered and evaporated to give a yellow oil: nmr (CCl_4) τ −2.32 (s, 1), −0.2 (broad, 1), 5.48 (m, 1), 6.24 (s, 3), 6.3–6.7 (m, 1), 7.18 (d, 2), 7.48 (t, 2), 7.4–7.7 (m, 1), 8.61 (d), 8.74, 8.82 (d), 9.05 (d), 9.17; uv max 287 mμ (ε 12,700), 358 (3250); ir (CCl_4) 3.44 (m), 3.51 (w), 5.85 (s), 6.12 (s), 6.32 (w), 6.97 (m), 7.21 (w), 7.45 (w), 7.70 (w), 7.85 (2), 8.42 (w), 8.60 (m), 8.75 (m), 8.94 (m), 9.25 μ (w).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.35; H, 8.65.

Papuanolide (8).—Papuanic acid (72 mg) was dissolved in 5 ml of 2:1 acetic anhydride–pyridine and allowed to stand at room temperature for 1/2 hr. The excess reagents were removed *in vacuo* to give a light yellow oil (72 mg): nmr (CCl_4) (integrated areas measured) τ 4.93 (t, 1), 5.87 (m, 1), 6.25 (s, 3), 6.80 (d and m), 7.30 (d, 2), 7.85 (m, 1), 8.27 (s, 3), 8.33 (s, 3), 8.53 (d), 8.70, 8.93 (d), 9.13; uv max 231 mμ (ε 22,000), 269 (12,100), 328 (4000); ir (CCl_4) 3.45 (s), 3.52 (m), 5.60 (s), 5.89 (s), 6.25 (s), 6.95 (s), 7.23 (m), 7.45 (m), 8.02 (w), 8.42 (w), 8.80 (s), 9.12 (s), 9.37 μ (w).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.44; H, 8.08.

Isopapuanolide (8).—Isopapuanic acid (59 mg) was treated with 2 ml of 2:1 acetic anhydride–pyridine at room temperature for 1/2 hr. The reagents were removed *in vacuo* to give a nearly colorless oil (57 mg): nmr (CCl_4) τ 4.93 (t, 1), 5.44 (m, 1), 6.24 (s, 3), 6.78 (d, 2), 6.5–7.0 (m, 1), 7.40 (d, 2), 7.8–8.2 (m, 1), 8.27 (s, 3), 8.33 (s, 3), 8.64 (d), 8.91 (d), 9.12 (t, 3); uv max 231 mμ (ε 21,400), 270 (10,100), 329 (3600); ir (CCl_4) 3.33 (m), 5.57 (s), 5.86 (s), 6.22 (s), 6.93 (s), 7.22 (w), 8.01 (w), 8.40 (w), 8.85 (s), 9.10 μ (m).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.48; H, 8.10.

Cyclodemethylation of Papuanic and Isopapuanic Acids.—A mixture of papuanic and isopapuanic acids (520 mg) was dissolved in 10 ml of acetic anhydride in a 50-ml boiling flask. Hydriodic acid (50%, 7 ml) was added very carefully, and the mixture was heated under reflux at 135° for 3 hr. The cooled reaction mixture was poured into 20 ml of water containing 4 g of $NaHSO_3$. The organic substances were extracted with benzene, washed with 10% aqueous bisulfite, and dried (Na_2SO_4). A light orange oil (460 mg) was obtained after evaporation of the benzene. Chromatography of a portion of this oil (50 mg) gave two fractions, one containing the *trans* isomers (28 mg) and one the *cis* (21 mg).

Sublimation of the *trans* isomers gave a mixture of cyclodemethylpapuanic acid and cyclodemethylepiisopapuanic acid as a light yellow solid: mp 53–57°; nmr (CCl_4) τ 5.90 (m, 1), 6.37 (m, 1), 7.24, 7.36, 7.46, 7.57, 8.18, 8.29, 8.50 (d, 3), 8.62, 8.67, 8.70, 8.74, 8.88, 9.14 (t, 3) (HR-60 with CAT); uv max 218 mμ (ε 21,300), 299 (19,400), 344 (3400); ir (CCl_4) 3.43 (m), 3.50 (w), 5.84 (s), 6.10 (s), 6.27 (w), 6.91 (m), 7.21 (w), 7.40 (m), 8.61 (m), 8.92 μ (m).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 69.06; H, 8.21.

Sublimation of the *cis* isomers gave a similar mixture of cyclodemethylisopapuanic acid and cyclodemethylepipapuanic acid as a yellow glassy solid: mp 44–50°; nmr (CCl_4) τ −2.12 (s, 1), −0.62 (broad, 1), 5.48 (m, 1), 6.2–6.5 (m, 1), 7.24, 7.37, 7.45, 7.55, 8.16, 8.28, 8.40, 8.61 (d), 8.67, 8.76, 8.84 (d), 9.15 (t, 3); uv max 217 mμ (ε 21,000), 300 (19,500), 345 (2760).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 69.04; H, 8.36.

Methyl Cyclodemethylpapuanate and Its Stereoisomers (26).—The mixture of cyclodemethyl acids prepared above (80 mg) was treated with methanol and a few drops of concentrated H_2SO_4. The solution was refluxed for 2 hr, poured into an excess of 5% $NaHCO_3$, and extracted twice with ether. The ethereal extract was washed with water, dried, and evaporated to give 61 mg of a yellow oil. Tlc showed two spots with identical rust-colored fluorescences. Separation by preparative tlc gave 37 mg (43%) of a yellow oil corresponding to the upper spot and 18 mg (21%) corresponding to the lower spot. The material from the upper spots (*trans*) had nmr (CCl_4) τ −2.22 (s, 1), 5.90 (m 1), 6.50 (s, 3), 7.48 (t), 8.29 (t), 8.53 (d), 8.65 (s), 8.84 (d), 9.17 (t); ir (CCl_4) 5.75 (s), 6.13 (s), 6.27 (m), 6.91 μ (s); uv max 298 mμ (ε 18,900), 342 (2450).

Anal. Calcd for $C_{25}H_{36}O_6$: 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.34; H, 8.55; mol wt, 432.253.

The material from the lower spot (*cis*) had nmr (CCl_4) τ −2.15 (s, 1), 5.45 (m, 1), 6.48 (s, 3), 7.48 (t), 8.27 (t), 8.61 (d), 8.63 (s), 8.82 (d), 9.15 (t); uv max 298 mμ (ε 19,800), 342 (2780); ir (CCl_4) 5.75 (s), 6.14 (s), 6.29 (m), 6.94 μ (m).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.59; H, 8.54; mol wt, 432.250.

Cyclodemethylpapuanolide (9).—Cyclodemethylpapuanic acid (50 mg) prepared as described above from pure papuanic acid was treated with dicyclohexylcarbodiimide (40 mg) in 5 ml of dichloromethane. After 15 min, 5 ml of 80% acetone was added. The solvents were evaporated, and the material was taken up in 5 ml of CH_2Cl_2. Precipitated dicyclohexylurea was removed by filtration, and the solution was chromatographed on a preparative tlc plate. A light yellow glass was obtained (35 mg): nmr

(CCl_4) τ 5.86 (m, 1), 6.85 (m, 1), 6.85 (m, 1), 7.40, 7.6–7.9 (m, 1), 8.11, 8.23, 8.32, 8.54 (d), 8.67, 8.75, 8.87 (d), 9.12; uv max 240 (ϵ 19,600), 285 (13,700), 320 sh (3360); ir (CCl_4) 3.44 (m), 3.53 (m), 5.60 (s), 5.90 (s), 6.22 (s), 6.90 (s), 7.23 (w), 7.54 (m), 8.11 (m), 8.61 (s), 8.83 (s), 8.94 μ (s).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.17; H, 8.28.

Cyclodemethylisopapuanolide (9).—Cyclodemethylisopapuanic acid prepared from pure isopapuanic acid was dehydrated with dicyclohexylcarbodiimide as described above. A light yellow oil was obtained: ir (CCl_4) 3.43 (m), 3.51 (w), 5.60 (s), 5.90 (m), 6.21 (s), 6.90 (m), 7.22 (w), 7.53 (w), 8.09 (m), 8.62 (s), 8.84 (s), 8.92 μ (s).

Demethyldihydropseudopapuanolide and Demethyldihydropseudoepipapuanolide (6).—Dihydropapuanic acid (198 mg) dissolved in 2 ml of acetic anhydride was mixed carefully with 1 ml of 50% HI. The solution was heated on a steam bath for 10 min, poured into 15 ml of 10% $NaHSO_3$, stirred, and extracted twice with ether. The combined ethereal extracts were washed twice with water and dried. Preparative tlc yielded demethyldihydropseudopapuanolide (78 mg) and demethyldihydropseudoepipapuanolide (34 mg).

Demethyldihydropseudopapuanolide was sublimed to give a light yellow solid, mp 94–98°. A sample was dissolved in hot acetone–water and cooled to −15° to give light yellow crystals: mp 91–95°; nmr (CCl_4) τ −2.14 (s, 1), 5.87 (m, 1), 6.75 (m, 1), 7.36, 7.45, 7.57, 8.48 (s), 8.65, 8.80 (d), 9.07 (d); uv max 216 mμ (ϵ 26,000), 287 (15,200), 351 (3300); ir (CCl_4) 3.39 (m), 5.60 (s), 6.12 (s), 6.90 (s), 7.24 (m), 7.43 (w), 7.66 (w), 7.85 (w), 8.05 (w), 8.32 (w), 8.60 (m), 8.80 (s), 9.50 μ (w).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.67; H, 8.51; mol wt, 402.240. Found: C, 71.84; H, 8.59; mol wt, 402.242.

Sublimation of demethyldihydropseudoepipapuanolide yielded a light yellow solid: mp 94–97°; nmr (CCl_4) τ −1.94 (s, 1), 5.5 (m, 1), 6.8 (m, 1), 7.35, 7.45, 7.57, 8.59 (d), 8.81 (d), 9.06 (d); uv max 215 mμ (ϵ 27,400), 286 (16,200), 352 (3500); ir (CCl_4) 3.39 (s), 5.60 (s), 6.11 (s), 6.90 (s), 7.22 (m), 7.43 (w), 7.66 (w), 7.85 (w), 8.05 (w), 8.60 (m), 8.80 μ (s).

Nitric Acid Oxidation of Papuanic Acid.—Papuanic acid (400 mg) in a 50-ml boiling flask fitted with a reflux condenser was treated with 20 ml of 50% HNO_3. This mixture was heated gently on a steam bath for 3 days. After the solution had cooled, solid Na_2CO_3 was added until it was basic to litmus. The solution was evaporated to dryness and concentrated HCl (2 ml) and CH_2Cl_2 (25 ml) were added. The layers were separated, and the CH_2Cl_2 solution was dried, filtered, and evaporated to give a light yellow oil (82 mg). An ethanolic solution of this oil was treated with Norit and filtered to obtain a colorless solution. The ethanol was evaporated, and the oil was dissolved in 1 ml of benzene, to which was rapidly added 5 ml of hexane. A white solid began to form, and the solution was refrigerated. The resulting crystals were filtered, washed with hexane, and air dried to give 10.4 mg (6%) of *n*-pentylsuccinic acid: mp 79–83° after sublimation; mmp 79–82° with an authentic sample of racemic *n*-pentylsuccinic acid; ir ($CHCl_3$) 3.45 (m), 5.84 (s), 7.05 (w), 7.80 (w), 8.05 μ (w); ORD (*c* 0.104, EtOH) $[\phi]_{589}$ +43°, $[\phi]_{500}$ +60°, $[\phi]_{350}$ +160°, $[\phi]_{250}$ +630°, $[\phi]_{225}$ +1560°, $[\phi]_{207}$ 0°.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.23; H, 8.62.

Synthetic *n*-Pentylsuccinic Acid.—Succinic anhydride (30.0 g) was placed in a 250-ml boiling flask fitted with a Dean–Stark water trap, together with *p*-toluenesulfonic acid monohydrate (1.25 g), 50 ml of absolute ethanol, 100 ml of benzene, and 0.5 ml of water. In the course of 54 hr of refluxing, 14 ml of ethanol–water was drawn off. After an initial distillation of the benzene and ethanol, diethyl succinate (51 g, 98%) was distilled at 101° (15–20 mm).

A three-neck 200-ml flask was fitted with a reflux condenser and a mechanical stirrer. Diethyl succinate (10.4 g, 0.06 mol) and freshly distilled *n*-valeraldehyde (4.3 g, 0.05 mol) were added to KO-*t*-Bu (6.15 g, 0.055 mol) in 60 ml of refluxing *t*-butyl alcohol (distilled from Na) over a 10-min period. The solution was stirred and refluxed for 2.5 hr. After distillation of most of the solvent under reduced pressure, the residue was acidified with 50 ml of 10% HCl. The remainder of the butanol was removed, and the resulting mixture was extracted with three 50-ml portions of ether. The yellow extracts were washed with 50 ml of water and four 25-ml portions of 10% Na_2CO_3. The carbonate extracts were combined and washed with 50 ml of ether which was added to the previous ethereal solution. This was dried, filtered, and evaporated to give a 67% recovery of diethyl succinate (6.95 g).

Excess concentrated HCl (50 ml) was added to the carbonate extracts, which were then extracted with three 50-ml portions of ether. The ethereal extracts were dried and evaporated to yield a light yellow oil (2.0 g). This was dissolved in CCl_4 and filtered to remove succinic acid (0.14 g).

The CCl_4 was evaporated, and the residue (1.86 g) was refluxed with 15 ml of 10% NaOH for 22 hr. Additional NaOH (1 g) was added and heating continued for several hours. The solution was cooled and extracted with two 10-ml portions of CH_2Cl_2. The aqueous solution was treated with Norit, heated, and filtered, before being acidified with 10 ml of concentrated HCl. Extraction of the acidic solution with four 20-ml portions of ether, followed by evaporation of the ether, gave a soft yellow solid (1.14 g), mp 147–154°.

The entire crude product was dissolved in glacial acetic acid and reduced at 1 atm of hydrogen over Adams catalyst. After hydrogen uptake had ceased, the solution was filtered, and the solvent was evaporated. The product was dissolved in 20 ml of benzene, and 10 ml of hexane was added. Crystals of succinic acid (0.151 g) formed and were filtered off. The filtrate was evaporated, and the remaining oil was dissolved in 15 ml of 2:1 hexane–CCl_4. Upon refrigeration white crystals of *n*-pentylsuccinic acid (0.386 g, 4%) formed and were filtered, washed with hexane, and air dried: mp 73–77° [sublimation and repeated crystallization from benzene–hexane raised the melting point to 80–82° (lit.[19] mp 80°)]; nmr (CH_2Cl_2) τ −1.34 (s, 2), 7.10, 7.30, 7.33, 7.42, 7.48, 7.65, 8.57, 8.66, 8.72, 9.12 (t, 3); ir ($CHCl_3$) 3.30 (w), 3.45 (m), 3.80 (w), 5.85 (s), 7.02 (w), 8.03 (w), 10.65 μ (w).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.57; H, 8.65.

Nitric Acid Oxidation of Isopapuanic Acid.—Isopapuanic acid (460 mg) was placed in a 50-ml boiling flask fitted with a reflux condenser. A 25-ml portion of 50% HNO_3 was added, and a spontaneous reaction began. After the reaction had subsided the mixture was heated gently on a steam bath for 2 days. The cooled solution was treated with solid $NaHSO_3$ until no more brown gases were given off and was then evaporated to a thick oil. The oil was dissolved in CH_2Cl_2, dried, and evaporated to give a yellow oil (129 mg). This was dissolved in 1 ml of benzene; 5 ml of hexane was added rapidly; and the solution was refrigerated. *n*-Pentylsuccinic acid (13 mg, 6%) was obtained by filtration: mp 80–85°; mmp 78–84° with authentic racemic *n*-pentylsuccinic acid; ir ($CHCl_3$) 3.45 (m), 3.52 (w), 5.84 (s), 6.25 (w), 7.00 (w), 7.75 μ (w); ORD (*c* 0.129, EtOH), $[\phi]_{589}$ +45°, $[\phi]_{500}$ +66°, $[\phi]_{350}$ +184°, $[\phi]_{250}$ +758°, $[\phi]_{225}$ +1835° (peak).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.53; H, 8.45.

3-Bromodihydropapuanic Acid (31a).—Dihydropapuanic acid (165 mg) was dissolved at room temperature in 1 ml of glacial acetic acid which was 1 *M* in Br_2. After 30 hr the acetic acid and bromine were evaporated to give a bright yellow oil (241 mg). This was chromatographed on three preparative plates, and three fractions were taken. Fraction i (least mobile) contained 3-bromodihydroepipapuanic acid (**31b**) (65 mg); ii contained both isomers (50 mg); and iii (most mobile) contained **31a** (48 mg): nmr (CCl_4) τ −1.45 (s, 1), −1.24 (s, 1), 6.0–6.7 (m, 2), 6.24 (s, 3), 7.18 (d, 2), 7.50 (t, 2), 8.20 (s, 3), 8.42 (d), 8.56, 8.75, 8.80, 8.86, 9.08 (d), 9.17; uv max 292 mμ (ϵ 12,700), 367 (2830); ir (CCl_4) 3.40 (m), 3.50 (m), 5.86 (s), 6.12 (s), 6.17 (m), 6.32 (w), 6.95 (m), 7.20 (m), 7.45 (w), 7.68 (w), 8.30 (w), 8.74 (m), 8.90 μ (s).

Anal. Calcd for $C_{25}H_{37}O_6Br$: C, 58.47; H, 7.26. Found: C, 58.66; H, 7.32.

3-Bromodihydroepipapuanic Acid (31b).—This material was isolated as described above: nmr (CCl_4) τ −1.50 (s, 1), −1.20 (s, 1), 5.34 (q, 1), 6.26 (s, 3), 6.3–6.8 (m, 1), 7.18 (d, 2), 7.51 (t, 2), 8.20 (s, 3), 8.50 (d), 8.76, 8.79, 9.08 (d), 9.16; uv max 296 mμ (ϵ 12,800), 373 (2800); ir (CCl_4) 3.39 (m), 3.49 (w), 5.85 (s), 6.11 (s), 6.18 (m), 6.35 (w), 7.00 (m), 7.22 (w), 7.52 (w), 7.71 (m), 8.38 (w), 8.85 μ (m).

3-Bromodihydroisopapuanic Acid (32a).—Dihydroisopapuanic acid (185 mg) was dissolved in 1 ml of glacial acetic acid, 1 *M* in Br_2, and left for 18 hr at room temperature. After evaporation of the acetic acid and bromine, a bright yellow oil was obtained

(19) F. Wrede and A. Rothhaas, *Z. Physiol. Chem.*, **226**, 95 (1934).

(255 mg). A portion of this (235 mg) was separated into two fractions by preparative tlc. Fraction i (less mobile) contained a mixture of the two isomers (86 mg), and fraction ii (more mobile) contained **32a** (10 mg): nmr (CCl_4) τ −1.48 (s, 1), −1.10 (s, 1), 5.32 (q, 1), 6.25 (s, 3), 6.3–6.8 (m, 1), 7.17 (d, 2), 7.52 (t, 2), 8.19 (s, 3), 8.50 (d), 8.76, 8.80, 9.08 (d), 9.18; uv max 294 mμ (ε 11,600), 369 (2460); ir (CCl_4) 3.42 (m), 5.84 (s), 6.13 (s), 6.35 (w), 7.00 (w), 7.27 (w), 7.55 (w), 7.75 (w), 8.41 (w,) 8.91 (m), 9.15 (w), 9.35 μ (w).

Anal. Calcd for $C_{25}H_{37}O_6Br$: C, 58.47; H, 7.26. Found: C, 58.73; H, 7.11.

3-Bromodihydroepiisopapuanic Acid (32b).—Fraction i from above was chromatographed on a preparative tlc plate to give **32a** (12 mg) and **32b** (61 mg): nmr (CCl_4) τ −1.43 (s, 1), −0.90 (broad, 1), 6.27 (s, 3), 6.1–6.9 (m, 2), 7.20 (d, 2), 7.50 (t, 2), 8.21 (s, 3), 8.45 (d), 8.58, 8.66, 8.77, 8.80, 9.10 (d), 9.19; uv max 296 mμ (ε 12,800), 369 (2600); ir (CCl_4) 3.42 (m), 5.89 (s), 6.15 (s), 6.20 (sh), 6.35 (w), 7.00 (w), 7.27 (w), 7.53 (w), 7.75 (w), 8.37 (w), 8.80 (m), 8.94 μ (s).

Neopapuanic Acid (12) from Papuanic Acid.—3-Bromodihydropapuanic acid (41 mg) was refluxed in 15 ml of isopropylamine for 4 hr. After solvent evaporation, the product was chromatographed on a preparative plate to give neopapuanic acid (21 mg): nmr (CCl_4) τ −2.70 (s, 1), 6.24 (s, 3), 6.58 (m), 7.05, 7.17, 7.31, 7.45, 7.71 (s, 3), 8.13 (s, 3), 8.48, 8.61, 8.82, 9.07 (d), 9.19; uv max 249 mμ (ε 22,500), 340 (4240); ir (CCl_4) 3.40 (s), 3.49 (m), 5.85 (s), 6.06 (s), 6.27 (m), 6.97 (m), 7.28 (w), 7.51 (m), 7.75 (w), 8.37 (m), 8.82 μ (m).

Anal. Calcd for $C_{25}H_{36}O_6$: Mol wt, 432.251. Found: Mol wt, 432.255.

Neopapuanic Acid (12) from Isopapuanic Acid.—3-Bromodihydroepiisopapuanic acid (38 mg) was refluxed in 15 ml of isopropylamine for 5 hr. The solvent was evaporated, and the product was chromatographed on a preparative plate to give neopapuanic acid (21 mg): nmr (CCl_4) τ −2.74, (s, 1), 6.23 (s, 3), 6.57 (m, 1), 7.03, 7.16, 7.33, 7.47, 7.68 (s, 3), 8.10 (s, 3), 8.45, 8.58, 8.75, 8.78, 9.05 (d), 9.18; uv max 248 mμ (ε 21,900), 341 (4160); ir (CCl_4) 3.40 (s), 3.50 (m), 5.85 (s), 6.06 (s), 6.27 (m), 6.95 (m), 7.27 (w), 7.50 (m), 7.75 (w), 8.36 (m), 8.80 μ (m).

Anal. Calcd for $C_{25}H_{36}O_6$: Mol wt, 432.251. Found: Mol wt, 432.255.

Neopapuanolide (13). A.—Neopapuanic acid from papuanic acid (2.6 mg) was dissolved in 1 ml of 2:1 acetic anhydride–pyridine and left at room temperature for 1/2 hr. The reagents were evaporated to give a colorless oil: nmr (CCl_4) τ 6.17 (s, 3), 6.6–7.1 (m, 1), 7.25, 7.30, 7.70 (s, 3), 8.16 (s, 3), 8.66, 8.75, 9.02 (d), 9.11; uv max 240 mμ (ε 30,000), 270 sh (7100), 313 (7000); ir (CCl_4) 3.41 (s), 3.51 (m), 5.61 (s), 6.07 (s), 6.23 (m), 6.85 (w), 6.95 (m), 7.20 (w), 7.35 (w), 7.52 (m), 7.80 (w), 8.13 (w), 8.42 (w), 8.81 μ (s); ORD (c 4.6×10^{-2}, EtOH) $[\phi]_{589}$ +325°, $[\phi]_{500}$ +600°, $[\phi]_{400}$ +1750°; ORD (c 2.3×10^{-3}) $[\phi]_{375}$ +3100°, $[\phi]_{346}$ +6000° (peak), $[\phi]_{333}$ 0°, $[\phi]_{320}$ −13,100° (trough), $[\phi]_{306}$ 0°, $[\phi]_{290}$ +14,400°, $[\phi]_{282}$ +16,300° (peak), $[\phi]_{267}$ +10,600° (trough), $[\phi]_{263}$ +11,200° (peak), $[\phi]_{250}$ 0°.

Anal. Calcd for $C_{25}H_{34}O_5$: Mol wt, 414.241. Found: Mol wt, 414.242.

B.—Neopapuanic acid (4.2 mg) was treated with 1 ml of 2:1 acetic anhydride–pyridine at room temperature for 1/2 hr. The reagents were evaporated, and a colorless oil was obtained [uv max 240 (ε 29,200), 270 sh (6850), 313 (6800); ir (CCl_4) 3.42 (s), 3.50 (m), 5.60 (s), 6.06 (s), 6.24 (m), 6.83 (w), 6.95 (m), 7.05 (w), 7.15 (w), 7.31 (w), 7.47 (m), 7.75 (w), 8.06 (w), 8.40 (w), 8.81 μ (s); ORD (c 8.0×10^{-2}, EtOH) $[\phi]_{589}$ +175°, $[\phi]_{500}$ +430°, $[\phi]_{400}$ +1400°; ORD (c 8.0×10^{-3}) $[\phi]_{375}$ +1160°, $[\phi]_{344}$ +4900° (peak), $[\phi]_{334}$ 0°, $[\phi]_{320}$ −13,400° (trough), $[\phi]_{305}$ 0°, $[\phi]_{283}$ +13,600° (peak), $[\phi]_{268}$ +8200° (trough), $[\phi]_{263}$ +9000° (peak), $[\phi]_{252}$ 0°].

3,4,6,7-Tetrahydro-2,6-dioxo-8,8-dimethyl-4-*n*-pentyl-5-hydroxy-2H,8H-benzo[1,2-*b*:5,4-*b*']dipyran (15).—Excess aluminum chloride, senecioyl chloride (185 mg, 1.38 mmol), and 5-hydroxy-4-*n*-pentyl-7-methoxydihydrocoumarin (14, 187 mg, 0.71 mmol) were mixed in 8 ml of $C_6H_5NO_2$. The reaction mixture was allowed to stand at room temperature for 2 days, after which it was poured into ice and dilute HCl. The solution was heated on a steam bath for 1/4 hr, cooled, and extracted twice with ether. The ethereal extract was washed twice with water before the ether was evaporated, and the $C_6H_5NO_2$ was removed by steam distillation. The pot residue was extracted with CH_2Cl_2, which was dried and evaporated to give 200 mg of a yellow oil. Column chromatography gave 143 mg (59%) of product **15** as white crystals: mp 99–100° after crystallization from hexane–CH_2Cl_2; nmr ($CDCl_3$) τ −1.28 (s, 1), 3.98 (s, 1), 6.70 (m, 1), 7.26 (m, 4), 8.53 (s, 6), 9.25 (t, 3); uv max 283 mμ (ε 15,000), 342 (3130); ir (CH_2Cl_2) 5.61 (s), 6.09 (s), 6.27 μ (m).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.73; H, 7.26.

Methylation of **15** with excess dimethyl sulfate and solid K_2CO_3 in acetone yielded a methyl ether (**16**) much more mobile than **21** on tlc comparison.

Clemmensen Reduction of 3,4,6,7-Tetrahydro-2,6-dioxo-8,8-dimethyl-4-*n*-pentyl-5-hydroxy-2H,8H-benzo[1,2-*b*:5,4-*b*']dipyran.—The chromone lactone **15** (380 mg) was treated 1.75 hr at room temperature with 16 g of freshly amalgamated zinc, 23 ml of glacial acetic acid, and 6 ml of concentrated HCl. The solution was decanted into water, neutralized with $NaHCO_3$, and extracted with ether. The extracts were washed with water and 5% $NaHCO_3$, dried, and evaporated to yield 380 mg of oil, shown by tlc to be largely a mixture of two products, **18** (more mobile) and **17**, with **17** predominating. Samples of the individual compounds were obtained by chromatography of this mixture, but methylation with dimethyl sulfate and K_2CO_3 in acetone led in both cases to products chromatographically distinct from **23**.

A similar reduction carried out for 16 hr led to the same two products, but with **18** predominating.

3,4,9,10-Tetrahydro-2,2-dimethyl-5-hydroxy-10-*n*-pentyl-4,8-dioxo-2H,8H-benzo[1,2-*b*:3,4-*b*']dipyran (22).—Into a 100-ml pear-shaped flask containing 75 ml of anhydrous ether was placed 3,4,9,10-tetrahydro-2,2-dimethyl-5-methoxy-10-*n*-pentyl-4,8-dioxo-2H,8H-benzo(1,2-*b*:3,4-*b*')dipyran[1b] (**21**, 860 mg). Excess aluminum chloride was added. The flask was fitted with a condenser equipped with a drying tube, and the solution was refluxed for 31 hr, after which it was poured into a mixture of dilute HCl and ice. The solution was heated on the steam bath for 1/2 hr, cooled, and extracted three times with ether. The ethereal extract was washed twice with water, dried, and evaporated to give 810 mg of crude product. Preparative tlc gave 500 mg (62%) of white crystalline product: mp 86–87° after recrystallization from hexane–CH_2Cl_2; nmr (CCl_4) τ −1.40 (s, 1), 3.95 (s, 1), 6.75 (m, 1), 7.28 (m, 4), 8.49 (s, 6), 9.11 (t, 3); uv max 283 mμ (ε 15,500), 342 (3250); ir (CCl_4) 5.60 μ (s), 6.07 (s), 6.14 (s), 6.25 (m).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.88; H, 7.33.

A small sample of the hydroxy compound was remethylated with dimethyl sulfate and K_2CO_3 in acetone. Tlc comparison showed the product to be identical with **21**.

3,4,9,10-Tetrahydro-2,2-dimethyl-5-hydroxy-10-*n*-pentyl-8-oxo-2H,8H-benzo[1,2-*b*:3,4-*b*']dipyran (24).—The chromanone **22** (250 mg) and 4 ml of concentrated HCl were added to 14 ml of glacial acetic acid, 3 ml of CH_2Cl_2, and 5 g of freshly amalgamated zinc. The mixture was stirred for 4 hr, poured into water, and neutralized with solid $NaHCO_3$. The solution was extracted three times with ether, which was washed twice with water, dried, and evaporated to give 240 mg of solid crude product. Preparative tlc gave 108 mg (45%) of white crystalline **24**: mp 163.5–165.5° after recrystallization from hexane; nmr ($CDCl_3$) τ 3.78 (s, 1), 6.76 (m, 1), 7.33 (m, 4), 8.22 (t), 8.67 (s), 9.03 (t); ir (CCl_4) 2.80 μ (w), 3.00 (w), 5.66 (s), 6.17 (s).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.59; H, 8.35.

Methylation of a small sample of **24** with dimethyl sulfate, K_2CO_3, and acetone yielded a product (**23**) identical with that obtained[1b] by Clemmensen reduction of **21**.

Synthetic Methyl Cyclodemethylpapuanate (26) and Its Stereoisomers.—Tiglic acid (38 mg, 0.38 mmol) was mixed thoroughly with finely powdered chroman **24** (76 mg, 0.24 mmol). The mixture was placed in a small weighing bottle (12 ml), and approximately 9 g of polyphosphoric acid was added. A magnetic stirring bar was placed in the bottle, which was stoppered and put on a Thermix hot plate maintained at 130°. After being stirred 1/2 hr the hot, dark red solution was dumped into ice–water. After dissolution of the polyphosphoric acid, the solution was extracted three times with ether. The combined ether layers were washed twice with 5% $NaHCO_3$, dried, and evaporated to give 65 mg of yellow oil. Tlc showed three similar fluorescent spots, which were identical chromatographically in all respects with the three spots representing a mixture of stereo-

isomeric cyclodemethylpapuanolides prepared from mixed papuanic and isopapuanic acids.

A portion of this material (57 mg) was refluxed with methanol and a trace of H_2SO_4 for 2 hr. The solution was poured into an excess of 5% $NaHCO_3$ and extracted twice with ether. The ethereal extract was washed with water, dried, and evaporated to give 55 mg of crude product as a yellow oil. This showed two identically fluorescent spots on tlc, and separation by preparative plates gave 34 mg (16%) of products in fractions i (more mobile), 14 mg, and ii, 18 mg. Both fractions were identical in all respects on tlc with the spots constituting natural 26 prepared from mixed papuanic and isopapuanic acids. For analysis the oils were sublimed (100°, 10^{-5} torr).

Fraction i: nmr (CCl_4) τ −2.22 (s, 1), 5.90 (m, 1), 6.50 (s, 3), 7.48 (t), 8.29 (t), 8.53 (d), 8.65 (s), 8.84 (d), 9.17 (t) (HR-60); uv max 298 mμ (ϵ 19,200), 342 (2720); ir (CCl_4) 5.75 (s), 6.13 (s), 6.27 (m), 6.91 μ (s).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.61; H, 8.55; mol wt, 432.250.

Fraction ii: nmr (CCl_4) τ −2.15 (s, 1), 5.45 (m, 1), 6.48 (t, 3), 7.48 (t), 8.27 (t), 8.61 (d), 8.63 (s), 8.82 (d), 9.15 (t) (HR-60); uv max 298 mμ (ϵ 19,600), 342 (2730); ir (CCl_4) 5.75 (s), 6.14 (s), 6.29 (m), 6.94 μ (s).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.57; H, 8.60; mol wt, 432.253.

Epipapuanic Acid (29b).—Papuanic acid (130 mg) was dissolved in 5 ml of 95% ethanol, 0.1 *N* in KOH. The bright yellow solution was left at room temperature for 6 hr. The ethanol was evaporated, and the remaining solution was acidified with 10% HCl. The water-insoluble material was dissolved in CH_2Cl_2, which was dried (Na_2SO_4) and evaporated to give a yellow oil (125 mg). The mixture was separated by preparative tlc to give papuanic acid (48 mg) and epipapuanic acid (19 mg): nmr (CCl_4) τ −2.20 (s, 1), 4.93 (t, 1), 5.50 (m, 1), 6.30 (s 3), 6.3–6.7 (m, 1), 6.83 (d, 2), 7.19 (d, 2), 7.4–7.7 (m, 1), 8.30, 8.34, 8.62 (d), 8.77 (d), 9.16 (t, 3); uv max 285 mμ (ϵ 13,000), 358 (3200); ir (CCl_4) 3.35 (m), 5.85 (s), 6.11 (s), 6.31 (w), 6.95 (m), 7.21 (w), 7.43 (w), 7.66 (w), 7.75 (w), 8.62 (m), 8.77 (m), 9.15 μ (m); ORD $[\phi]_{589}$ +265° (*c* 1.50 × 10^{-1}, EtOH).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.21; H, 8.53.

Epiisopapuanic Acid (30b).—Isopapuanic acid (87 mg) was dissolved in 5 ml of 0.1 *N* KOH in 95% ethanol. After 6 hr at room temperature the ethanol was evaporated, and the residue was acidified with 10 ml of 10% HCl. The organic materials were extracted with ether and dried (Na_2SO_4). The isomers were separated by preparative tlc to give isopapuanic acid (23 mg) and epiisopapuanic acid (49 mg, more mobile): nmr (CCl_4) τ −2.28 (s, 1), 4.95 (t, 1), 5.88 (m, 1), 6.30 (s, 3), 6.35–6.70 (m, 1), 6.83 (d, 2), 7.18 (d, 2), 7.3–7.7 (m, 1), 8.27 (s, 3), 8.32 (s, 3), 8.50 (d, 3), 8.81 (d), 9.17 (t, 3); uv max 284 mμ (ϵ 13,100), 357 (3200); ir (CCl_4) 3.43 (m), 3.50 (w), 5.83 (s), 6.10 (s), 6.30 (w), 6.91 (m), 6.99 (m), 7.20 (w), 7.42 (m), 7.70 (m), 7.85 (m), 8.40 (w), 8.60 (m), 8.75 (m), 9.10 (m), 9.22 μ (w); ORD $[\phi]_{589}$ −140° (*c* 1.93 × 10^{-1}, EtOH).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.57; H, 8.51.

Bromination of Dihydrodemethylpseudopapuanolide.—Dihydropapuanic acid (101 mg) was dissolved in 2 ml of acetic anhydride, and 1 ml of 50% HI was added carefully. The solution was heated to 100° for 20 min, cooled, and poured into 20 ml of 10% $NaHSO_3$. After extraction with two 20-ml portions of ether, the combined extracts were washed with water, dried, and evaporated to give a yellow oil (87 mg). This was dissolved in 1 ml of glacial acetic acid, 1 *M* in Br_2, and left at room temperature for 12 hr. The solvent and bromine were evaporated, and the resulting bright yellow oil was chromatographed on a preparative plate. Three fractions were obtained [(i) (most mobile) 3-bromodihydrodemethylpseudoepipapuanolide (34 mg), (ii) 3-bromodihydrodemethylpseudopapuanolide (18 mg), and (iii) 3-bromodihydropapuanic acid (both epimers, 18 mg)].

3-Bromodihydrodemethylpseudopapuanolide (28).—The melting point of this compound after crystallization from ethanol was 89–93°: nmr (CCl_4) τ −2.14 (s), 5.9–6.7 (m), 7.22, 7.29, 7.40, 7.46, 8.13 (s, 3), 8.36 (d), 8.61, 8.72, 9.03 (d); uv max 295 mμ (ϵ 14,700), 363 (2950); ir (CCl_4) 3.40 (m), 3.48 (w), 5.60 (s), 6.13 (s), 6.90 (m), 7.25 (w), 7.52 (w), 7.70 (w), 8.05 (w), 8.35 (w), 8.85 μ (s).

3-Bromodihydrodemethylpseudoepipapuanolide.—Fraction ii exhibited the following data: nmr (CCl_4) τ −1.30 (s, 1), 5.32 (q, 1), 6.72 (m), 7.33, 7.45, 7.56, 8.17 (s, 3), 8.50 (d), 8.65, 8.74, 8.86, 9.06 (d); uv max 292 mμ (ϵ 13,800), 359 (2960); ir (CCl_4) 3.39 (m), 3.50 (w), 5.59 (s), 6.13 (s), 6.25 (w), 6.90 (m), 7.22 (w), 7.37 (w), 7.73 (w), 8.01 (m), 8.40 (w), 8.84 μ (s).

Registry No.—Demethyldihydropseudoepipapuanolide, 17278-15-8; papuanolide, 17230-49-8; isopapuanolide, 17230-50-1; cyclodemethylpapuanolide, 17230-51-2; cyclodemethylisopapuanolide, 17278-16-9; dihydropapuanic acid, 17230-77-2; dehydroisopapuanic acid, 17230-78-3; cyclodemethylpapuanic acid, 17230-79-4; cyclodemethylepiisopapuanic acid, 17230-80-7; cyclodemethylisopapuanic acid, 17278-24-9; cyclodemethylepipapuanic acid, 17230-81-8; demethyldihydropseudopapaunolide, 17230-82-9; 3-bromodihydrodemethylpseudoepipapuanolide, 17230-83-0; **12**, 17230-52-3; **13**, 17230-53-4; **15**, 17230-54-5; **22**, 17230-55-6; **24**, 17230-56-7; **26** (*trans*), 17230-57-8; **26** (*cis*), 17278-25-0; **28**, 17230-58-9; **29a**, 17230-75-0; **29b**, 17230-59-0; **30a**, 17230-76-1; **30b**, 17230-60-3; **31a**, 17278-17-0; **31b**, 17230-61-4; **32a**, 17230-73-8; **32b**, 17230-74-9.

Acknowledgments.—We wish to express our thanks to Dr. P. van Royen for a generous supply of *C. papuanum* bark.

The Effect of Magnesium Halides on the Reaction of Phosphonates with Phenylmagnesium Bromide

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The effect of magnesium chloride and bromide on the rate of reaction of diethyl phenylphosphonate with phenylmagnesium bromide has been investigated in diethyl ether, tetrahydrofuran, and benzene. Contrary to previous reports the reaction is not accelerated but is retarded by the addition of these magnesium halides. Possible explanations for these results are presented.

The reaction of diethyl phenylphosphonate with phenylmagnesium bromide has been reported to be accelerated by the addition of magnesium bromide.[1] On the basis of this report it was proposed that the magnesium bromide and the diethyl phenylphosphonate formed an activated complex in which the phosphoryl group was coordinated to the magnesium through the oxygen atom. Similar reasoning was used to explain the facile formation of triphenylphosphine oxide from diethyl phosphorochloridate and phenylmagnesium bromide in diethyl ether. Subsequently, several authors have cited this work as evidence for the proposal that increasing the positive character of the phosphorus atom increases its susceptibility to nucleophilic attack.[2] Although this concept seems highly reasonable, recent evidence concerning the substitution reactions of phosphoryl halides suggests the opposite may be true.[3] Furthermore, the fact that trimethylaluminum, a relatively good Lewis Acid, failed to give substitution reactions with dialkyl alkylphosphonates[4] was puzzling in view of the reported effect of magnesium halides on the substitution reactions of phosphorus esters. In an attempt to resolve this matter and to answer several questions raised in an earlier study,[5] the effect of magnesium halides on the reaction rate of diethyl phenylphosphonate with phenylmagnesium bromide was reinvestigated.

Results

The reaction of diethyl phenylphosphonate with phenylmagnesium bromide in the absence and in the presence of magnesium halides was investigated in tetrahydrofuran (THF), diethyl ether, and benzene. The principal part of our study was carried out using THF as the solvent since the reaction is homogeneous and can be followed quite nicely by gas chromatographic analysis of hydrolyzed aliquots taken at time intervals. In contrast, the reactions in diethyl ether and benzene became heterogeneous. In all cases, however, control reactions of diethyl phenylphosphonate with phenylmagnesium bromide were run under the same conditions as the reactions with added magnesium halides. Furthermore, the triphenylphosphine oxide was isolated in several cases, and the relative yields were found to be directionally consistent with the gas chromatographic analyses. Results of analysis of ^{31}P nmr spectra were also directionally consistent, although two of the signals overlapped, making quantitative analysis by this method difficult. Additional confirmation of our results was made in several cases by titration of the remaining phenylmagnesium bromide. (See the Experimental Section and ref 16).

The effect of 1 equiv of added magnesium halide on the rate of reaction of phenylmagnesium bromide with diethyl phenylphosphonate in THF at 68° is illustrated in Figure 1 which shows the percentage of phenylmagnesium bromide reacted as a function of time. Figures 2–4 merely exemplify the effect of 1 equiv of magnesium halide on the percentages of starting diethyl phenylphosphonate, the intermediate ethyl diphenylphosphinate, and the triphenylphosphine oxide, respectively, in THF at 68°. In all cases the data for MgClBr were intermediate between $MgBr_2$ and $MgCl_2$; consequently, for simplicity these data are recorded in the Experimental Section. The isolated yields of triphenylphosphine oxide after 6 hr were 55–59% in the absence of magnesium halides and 19–25% in the presence of magnesium halides.

Essentially the same effect was observed when the reactions were carried out in diethyl ether at 34°, although the over-all reaction is much slower than in THF at 68°. This is illustrated in Figure 5. At some point between 22 and 90 hr the reaction mixture became heterogeneous. The final analysis was therefore made on the total hydrolysis products. For simplicity the different percentages of starting material, intermediate, and product are given in the tables in the Experimental Section.

In benzene at 72° the reaction of diethyl phenylphosphonate with phenylmagnesium bromide became heterogeneous in a short time and could not be followed as in THF or diethyl ether. Under the conditions used by Burger and Dawson,[1] but in the absence of added magnesium bromide, a mixture of 9.8% diethyl phenylphosphonate, 11.8% ethyl diphenylphosphinate, and 78.4% triphenylphosphine oxide was obtained. In contrast, under the same conditions in the presence of magnesium bromide, a mixture of 23.4% diethyl phenylphosphonate, 21.6% ethyl diphenylphosphinate, and 55% triphenylphosphine oxide was obtained. The isolated yields of triphenylphosphine oxide from the two experiments were 58 and 30%, respectively.

Discussion

From these results it is readily obvious that the reaction of diethyl phenylphosphonate with phenylmag-

(1) N. D. Dawson and A. Burger, *J. Org. Chem.*, **18**, 207 (1953).

(2) (a) K. D. Berlin and G. B. Butler, *Chem. Rev.*, **60**, 243 (1960); (b) K. D. Berlin, T. H. Austin, and K. L. Stone, *J. Amer. Chem. Soc.*, **86**, 1787 (1964); (c) K. D. Berlin and M. E. Peterson, *J. Org. Chem.*, **32**, 125 (1967); (d) K. D. Berlin and R. U. Pagilagan, *ibid.*, **32**, 129 (1967).

(3) R. S. Drago, V. A. Mode, J. G. Kay, and D. L. Lydy, *J. Amer. Chem. Soc.*, **87**, 5010 (1965).

(4) H. R. Hays, unpublished results. Upon heating mixtures of trimethylaluminum and dialkyl alkylphosphonates elimination of olefin and formation of methane and aluminum phosphonates were observed. For further details see the Experimental Section.

(5) H. R. Hays, *J. Org. Chem.*, submitted for publication.

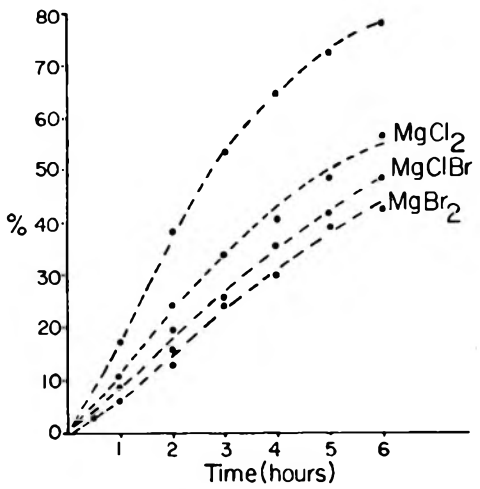


Figure 1.—The effect of MgX_2 on the percentage of C_6H_5MgBr reacted *vs.* time: $C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr$, THF, 68°.

$$\% C_6H_5MgBr = \frac{\% (C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt + 2 \times \% (C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}}{2}$$

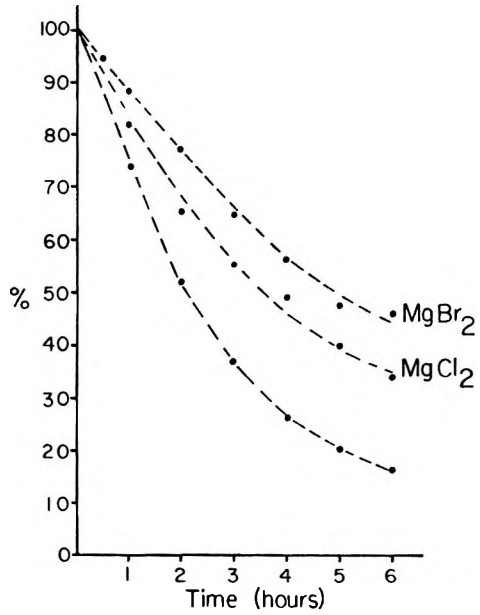


Figure 2.—The effect of MgX_2 on the percentage of $C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2$ not reacted *vs.* time: $C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr$, THF, 68°.

nesium bromide is not accelerated but is retarded by the addition of magnesium chloride or bromide. Several possible explanations of the data have been considered.[6] For example, preliminary results of a related study of substituted phosphonate esters and phenylmagnesium bromide show that their reactivity is increased by electron-withdrawing substituents attached to the phosphorus atom.[7] That is, in a series of phosphorus esters with nearly the same P→O bond

(6) Worthy of note is the fact that magnesium bromide also retards the addition of methylmagnesium bromide to pinacolone and suppresses the tendency of magnesium alkoxides to give enolization of ketones. See H. O. House and D. D. Traficante, *J. Org. Chem.*, **28**, 355 (1963).

(7) H. R. Hays, to be submitted for publication.

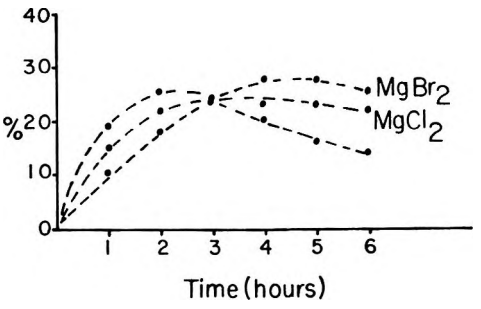


Figure 3.—The effect of MgX_2 on the percentage of $(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt$ *vs.* time: $C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr$, THF, 68°.

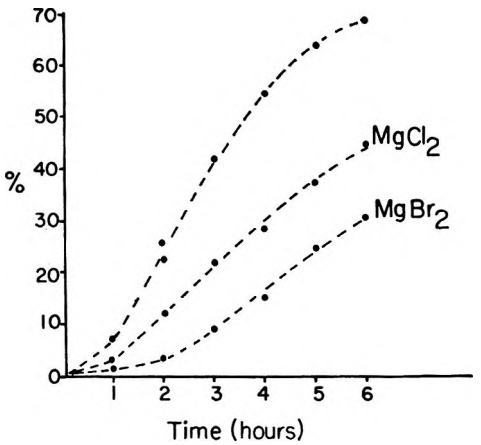


Figure 4.—The effect of MgX_2 on the percentage of $(C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}$ formed *vs.* time: $C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr$, THF, 68°.

strengths and ground-state energies, the pentacovalent transition state is stabilized by electrophilic substituents. Thus the fact that magnesium halides retard the reaction under study is not due to electronic destabilization of the transition state as a result of polarization of the phosphoryl bond by the magnesium halide.

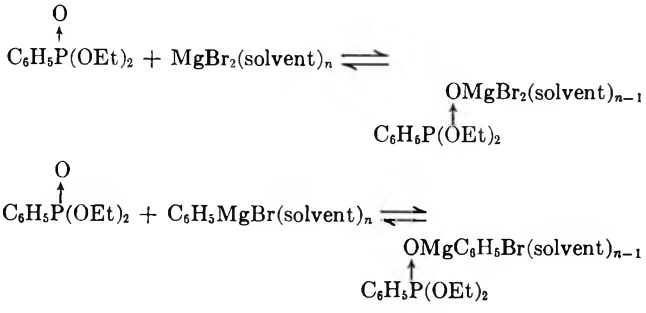
Conceivably, the complex of diethyl phenylphosphonate with the magnesium halide, if formed,[8] might be sterically hindered to attack by the solvated Grignard reagent. That is, a bimolecular, rather than a termolecular, mechanism may be involved in the latter case. Smith and coworkers[9] have recently reported evidence that methylmagnesium bromide and 2,4-dimethyl-4′-methylmercaptobenzophenone react by a bimolecular mechanism rather than the termolecular mechanism reported for benzophenone.[10]

(8) This is not meant to imply that diethyl phenylphosphonate and magnesium halides as such do not form complexes. The question is whether such complexes are formed in the presence of phenylmagnesium bromide, which may also be capable of complexing with magnesium halides. See the following discussion.

(9) (a) S. G. Smith and G. Su, *J. Amer. Chem. Soc.*, **88**, 3995 (1966); S. G. Smith and J. Billet, *ibid.*, **89**, 6948 (1967); (b) H. R. Hays, *ibid.*, submitted for publication. Preliminary kinetic data on the reaction of ethyl diphenylphosphinate and phenylmagnesium bromide are consistent with the rapid formation of a bimolecular complex which then proceeds to products by a first-order process. Thus the magnesium halide could be competing with the phenylmagnesium bromide for the phosphonate ester.

(10) E. C. Ashby, R. B. Duke, and H. M. Neumann, *ibid.*, **89**, 1964 (1967).

In an attempt to gain information about complex formation, the phosphorus nmr spectra of diethyl phenylphosphonate with magnesium bromide and diethyl phenylphosphonate with phenylmagnesium bromide were recorded in THF and diethyl ether. Aside from a slight broadening of the phosphorus signals and small differences in the chemical shifts (less than 1–2 ppm), the spectra were essentially the same as that of diethyl phenylphosphonate. These results coupled with the results of a recent study of the basicity of various phosphoryl compounds[11] and the pK_B's of THF[12] and diethyl ether[12] suggest that the diethyl phenylphosphonate complexes shown below are relatively weak complexes.



Another possibility may be that the magnesium halide forms a complex with the phenylmagnesium bromide thus deactivating the Grignard reagent. Ashby and coworkers have isolated the related complex $EtMg_2Cl_3$ by fractional crystallization from THF.[13] In addition a similar complex between magnesium bromide and magnesium alkoxides has been proposed to explain the negative effect of magnesium bromide on the enolization of ketones.[6] Whether or not such a complex possesses a structure bridged through the halogen atoms or is ionic in nature appears speculative at this time.[14]

Several other possible explanations of the results were considered. These are repression of the Schlenck equilibrium (*i.e.*, diphenylmagnesium concentration), a medium effect, and the possibility that diethyl phenylphosphonate might react with the magnesium halide.[15] All of these are believed unlikely for the following reasons. First, kinetic evidence regarding the reaction of ethyl diphenylphosphinate with phenylmagnesium bromide[9b] indicates the reactive species is phenylmagnesium bromide and not diphenylmagnesium. The fact that complex formation is also shown to be important suggests the negative effect of magnesium halides is not due to a medium effect. Second, no evidence of reaction was observed when diethyl phenylphosphonate and magnesium bromide were heated in refluxing THF for 6 hr. No ethyl bromide or ethylene could be detected in the ir spectra of the THF vapors, and 67% of the diethyl phenylphosphonate was recovered. This is in contrast to diethyl phenylphosphonate and magnesium iodide which did react upon heating in refluxing THF.

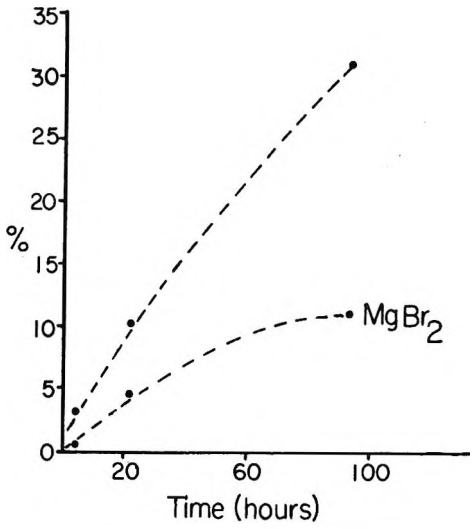


Figure 5.—The effect of $MgBr_2$ on the percentage of C_6H_5MgBr reacted *vs.* time: $C_6H_5\overset{\overset{O}{\uparrow}}{P}(OEt)_2 + 2C_6H_5MgBr$, Et_2O, 34°.

The findings of this study indicate that another explanation is required for the fact that diethyl phosphorochloridate reacts so readily with phenylmagnesium bromide in diethyl ether to produce triphenylphosphine oxide.[1] An investigation of this reaction is presently underway.

Experimental Section

Materials.—Diethyl phenylphosphonate was prepared from commercial phenylphosphonyl chloride, ethanol, and triethylamine in ether. Ethyl diphenylphosphinate was prepared by oxidation of ethyl diphenylphosphinite, obtained from commercial diphenylchlorophosphine, ethanol, and triethylamine in ether. Reference triphenylphosphine oxide was obtained by the oxidation of commercial triphenylphosphine with hydrogen peroxide. The purity of the products was confirmed by gas chromatography and by their infrared and proton and phosphorus nmr spectra.

Phenylmagnesium bromide in ether was obtained from a commercial source. Upon displacement of the diethyl ether with THF and subsequent refluxing, the percentage of biphenyl impurity increased, presumably as a result of the coupling of phenylmagnesium bromide with bromobenzene impurity. Consequently, phenylmagnesium bromide was prepared in THF using 100% excess magnesium and reaction temperatures of 30–40°. When prepared in this manner and using the procedure recently reported by Watson and Eastham, the phenylmagnesium bromide titration showed a nearly quantitative yield.[16] Only a trace of biphenyl was observed in the gas chromatograms.

Magnesium bromide and magnesium chlorobromide were prepared by the addition of dibromoethane and 1-bromo-2-chloroethane, respectively, to magnesium in diethyl ether. Magnesium chloride was obtained commercially.

All solvents were freshly distilled over lithium aluminum hydride.

Reaction of Diethyl Phenylphosphonate with Phenylmagnesium Bromide. A. In THF.—To the magnesium halide (0.1 mol) under argon 70 ml of tetrahydrofuran was added. Upon addition of 21.4 g of diethyl phenylphosphonate (0.1 mol) small heat effects resulted in a temperature rise of a few degrees. Surprisingly in the case of magnesium bromide, a secondary factor, perhaps a negative heat of solution, resulted in a slower over-all temperature drop of a few degrees. Both the magnesium bromide and the chloro bromide dissolved upon subsequent stirring, whereas a part of the magnesium chloride remained insoluble. Upon addition of 84 ml of warm 2.4 *M* phenylmagnesium bromide,

(11) P. Haake, R. D. Cook, and G. H. Hurst, *J. Amer. Chem. Soc.*, **89**, 2650 (1967).

(12) E. M. Arnett in "Progress in Physical Organic Chemistry," Vol. 1, S. G. Cohen, A. Streitwieser, and R. W. Taft, Ed., Interscience Publishers, New York, N. Y., 1963, p 325.

(13) E. C. Ashby and W. E. Becker, *J. Amer. Chem. Soc.*, **85**, 119 (1963).

(14) E. C. Ashby, *Quart. Rev.* (London), **21**, 259 (1967).

(15) The complex of methyl diphenylphosphinate and magnesium iodide is known to readily form methyl iodide and the magnesium salt of diphenylphosphinic acid. See K. D. Berlin and R. U. Pagilagan, *Chem. Commun.*, **19**, 687 (1966).

(16) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

the reaction vessel and control experiment were placed in an oil bath preheated to 68–70°. (The phenylmagnesium bromide crystallizes from a 2.4 *M* solution upon cooling to room temperature.) In the control experiments 84 ml of 2.4 *M* phenylmagnesium bromide in warm THF was added to the 70 ml of THF followed by the addition of 21.4 g of the diethyl phenylphosphonate (0.1 mol). As in the case of the magnesium halides a slight temperature rise was observed; however, the only differences in the phosphorus nmr spectrum were less than 1–2 ppm differences in the chemical shifts and a slight broadening of the diethyl phenylphosphonate signal. Diethyl phenylphosphonate (25% in THF) for example, had a phosphorus chemical shift of −17.3 ppm *vs.* −17.7 ppm in the presence of an equivalent amount of phenylmagnesium bromide and −17.3 ppm in the presence of magnesium bromide. Likewise, no significant difference was observed in the phosphorus nmr spectrum in diethyl ether of diethyl phenylphosphonate (−17.5 ppm) and magnesium bromide (−18.3 ppm).[17] After heating for the times shown in Tables I, II, III, and IV, 5-ml samples were removed and hydrolyzed with an equivalent amount of cold ammonium chloride solution. The resultant organic phases were separated, dried over molecular sieves, and analyzed as quickly as possible by gas chromatography to give the percentage compositions shown in Tables I, II, III, and IV. A 5 ft column of 10% SE 30 on Chromosorb W was used over the temperatures 130–250°. The percentage of phenylmagnesium bromide reacted was taken as one-half of the sum of the ethyl diphenylphosphinate and twice the amount of triphenylphosphine oxide. That this is a close approximation was shown by the agreement with the percentage of remaining phenylmagnesium bromide as determined by the titration procedure of Watson and Eastham.[16] Phosphorus nmr spectral analysis of the mixtures were also in good agreement with the results shown except that low percentages of ethyl diphenylphosphinate were not observed. In addition, work-up of several of the reactions listed in Tables I and II (magnesium halide) by hydrolysis with ammonium chloride solution, followed by removal of the THF and digestion with diethyl ether, gave 55–59% of triphenylphosphine oxide (Table I) and 19–25% of triphenylphosphine oxide (Table II) after 6 hr. After 23 hr at 68°, yields of 41 and 12% of crystalline triphenylphosphine oxide, mp 152–153°, were obtained in the absence and presence of added magnesium bromide, respectively. To check the possibility of side reactions, 21.4 g of diethyl phenylphosphonate, magnesium bromide (0.1 mol), and 70 ml of THF were heated at 68° for 6 hr using a 45° condenser with a subsequent Dry Ice trap. No evidence of ethyl bromide formation was observed in the ir spectrum of a small amount of diethyl ether, and THF collected in the Dry Ice trap. Upon work-up 67% of the diethyl phenylphosphonate was recovered. Very little if any C alkylation of the phenylmagnesium bromide to give ethylbenzene was observed in the reaction of diethyl phenylphosphonate with phenylmagnesium bromide in the presence of magnesium bromide at 68° in THF.

B. In Diethyl Ether.—Essentially the same procedure as in A was followed with the exception that the oil bath was preheated to 34°. At some point between 22 and 94 hr the control reaction became heterogeneous, necessitating work-up at that point. The results obtained from this study are given in Tables V and VI.

TABLE I

$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr$, THF, 68°

Time, hr	$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2$, %	$(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt$, %	$(C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}$, %	C_6H_5MgBr reacted, %
1	74.5	19.5	6	15.7
2	52.5	25.1	22.4	35.0
3	33.2	23.8	43.0	54.9
4	25.1	21.7	53.2	64.0
5	21.4	15.6	63.0	70.8
6	20.1	13.4	66.5	73.2
23	2.2	4.6	93.1	94.3

TABLE II

$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr + MgBr_2$, THF, 68°

Time, hr	$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2$, %	$(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt$, %	$(C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}$, %	C_6H_5MgBr reacted, %
1	88.0	10.6	1.4	6.7
2	79.0	16.8	4.2	12.6
3	64.1	23.6	12.3	24.1
4	56.1	29.0	14.9	29.4
5	45.9	29.0	24.8	39.4
6	46.3	23.6	30.1	41.9
23	24.8	18.7	56.5	63.8

TABLE III

$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr + MgClBr$, THF, 68°

Time, hr	$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2$, %	$(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt$, %	$(C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}$, %	C_6H_5MgBr reacted, %
1	83.3	14.5	2.2	9.4
2	70.1	21.4	8.5	19.2
3	65.1	20.6	14.3	24.6
4	49.9	26.4	23.7	36.9
5	41.8	25.0	33.2	40.7
6	39.4	22.8	37.8	49.2

TABLE IV

$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr + MgCl_2$, THF, 68°

Time, hr	$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2$, %	$(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt$, %	$(C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}$, %	C_6H_5MgBr reacted, %
1	82.2	14.7	3.1	10.4
2	64.8	22.4	12.8	24.0
3	54.7	23.5	21.8	33.5
4	49.0	23.0	28.0	39.5
5	40.3	23.0	36.7	48.2
6	32.8	22.4	44.8	56.0

TABLE V

$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr$, Et_2O, 34°

Time, hr	$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2$, %	$(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt$, %	$(C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}$, %	C_6H_5MgBr reacted, %
1.5	98.2	1.8	...	0.9
4.5	94.0	5.5	0.5	3.0
22	83.0	13.7	3.3	10.1
94	56.7	23.7	19.55	31.4

TABLE VI

$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2 + 2C_6H_5MgBr + MgBr_2$, Et_2O, 34°

Time, hr	$C_6H_5\overset{O}{\overset{\uparrow}{P}}(OEt)_2$, %	$(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}OEt$, %	$(C_6H_5)_3\overset{O}{\overset{\uparrow}{P}}$, %	C_6H_5MgBr reacted, %
1.5	99.6	0.4	...	0.2
4.5	98.9	1.1	...	0.6
22	91.5	7.9	0.6	4.5
94	81.7	14.3	4.0	11.1

(17) Significant differences were observed in the nmr spectra of the more basic phosphoryl compounds: $(C_6H_5)_3PO$ in THF −23.5 ppm, + $MgBr\cdot OEt$ −33.8 ppm; $(C_6H_5)_2O{=}POEt$ in THF −28.2 ppm, + $MgBr_2$ −30.0 ppm; $(C_6H_5)_2O{=}POEt$ in THF + $(C_6H_5)MgBr$ −34.4 ppm.

C. In Benzene.—The procedure of Burger and Dawson ($MgBr_2$) was repeated with a control experiment. In the latter case the reaction became heterogeneous in about 2 hr. After 6 hr in benzene (oil bath temperature of 73°) the reactions were worked up to give 24.5 and 24 g of crude material, respectively. Gas chromatographic analysis indicated 23.4% diethyl phenylphosphonate, 21.6% ethyl diphenylphosphinate, and 55% triphenylphosphine oxide from Burger and Dawson's conditions with $MgBr_2$ and 9.8% diethyl phenylphosphonate, 11.8% ethyl diphenylphosphinate, and 78.4% triphenylphosphine oxide from the control experiment. Following digestion with diethyl ether, 30 and 58% yields of triphenylphosphine oxide were isolated from the run containing magnesium bromide and the control experiment, respectively.

Reactions of Trimethylaluminum. A. With Dodecylphosphonyl Dichloride.—To 14.5 g of trimethylaluminum (0.2 mol) under argon was added *very slowly* 28 g of dodecylphosphonyl dichloride (0.1 mol). Care was required during the addition to keep the temperature below 45° as several of these reactions blew up. After stirring overnight and heating slowly to 130° over a period of 8 hr, the mixture was cooled and solvolyzed cautiously with 50 ml of ethanol. Addition of ice-cold 1:1 hydrochloric acid gave a solution which was extracted with diethyl ether. Following removal of the ether, dissolution in chloroform, and water washing, distillation gave 17 g (71%) of dimethyldodecylphosphine oxide, mp 83–84°. Use of 0.2 mol of trimethylaluminum to 0.3 mol of dodecylphosphonyl dichloride gave a mixture of largely diethyl dodecylphosphonate and ethyl dodecylmethylphosphinate in about a 2:1 ratio.

B. With Dialkyl Alkylphosphonates.—Upon adding 16.5 g of trimethylaluminum to 200 ml of THF considerable heat was evolved. Addition of 30.6 g of diethyl dodecylphosphonate gave a relatively small heat effect. After refluxing 3.5 hr work-up as above gave 88% recovered diethyl dodecylphosphonate. No evidence of substitution products could be detected in the gas chromatograph or the phosphorus nmr spectrum of the crude product.

Addition of 30.6 g of diethyl dodecylphosphonate to 16.5 g of trimethylaluminum at 10° resulted in considerable heat evolution. Upon heating slowly to 70° for 3 hr, 100° for 1 hr, and reflux for 8 hr, (130–135°) ethylene and methane gas were evolved. Work-up in the manner as above gave a solid that was insoluble in water and diethyl ether. Recrystallization from acetone gave 12.3 g (43%) of aluminum tris(ethyl dodecylphosphonate).

Anal. Calcd for $C_{42}H_{90}P_3O_9Al$: C, 58.8; H, 10.6; Al, 3.1. Found: C, 59.2; H, 10.6; Al, 2.8.

Again no substitution products were detected in the crude products.

Phosphorus nmr spectra of a 3:1 mixture of diethyl ethylphosphonate–trimethylaluminum showed a signal at −32.2 ppm with a shoulder at −35.2 ppm.

In THF diethyl ethylphosphonate (−32.5 ppm) and trimethylaluminum (1:1) gave only one signal at −33.5 ppm.

Registry No.—Phenylmagnesium bromide, 100-58-3; magnesium chloride, 7786-30-3; magnesium bromide, 7789-48-2; diethyl phenylphosphonate, 1754-49-0; diethyl ethylphosphonate, 78-38-6; trimethylaluminum 75-24-1; dimethyldodecylphosphine, 871-95-4; aluminum tris(ethyl dodecylphosphonate), 17448-03-2.

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Synthesis and Acetolysis of Mixed Trialkyl Phosphites

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A number of mixed trialkyl phosphites were prepared by reaction of the appropriate mono- or dialkyl chlorophosphite and alcohol in an inert solvent in the presence of N,N-dimethylaniline. Reaction of these mixed trialkyl phosphites with acetic acid at 125° resulted in formation of a mixture of acetate esters and dialkyl phosphites. Analysis of the acetate esters produced in this manner served as a means of determining the nature of the acetolysis of various alkyl groups from trialkyl phosphites.

The dealkylation reactions of phosphite esters with hydrogen halides yielding an alkyl halide and a phosphite ester with one less alkyl group have been extensively studied by Gerrard and his coworkers.[2] They found that (1) the reactions of trialkyl phosphites with a hydrogen halide were faster than those of dialkyl phosphites and monoalkyl phosphites; (2) the removal of the alkyl group occurred with inversion of configuration in the trialkyl and dialkyl phosphites, whereas extensive racemization was observed in the reactions of monoalkyl phosphites having an optically active alkyl group; and (3) the order of reactivity of the hydrogen halides with a given trialkyl halide was HI > HBr > HCl. Reactions of trialkyl phosphites with sulfuric acid yielding sulfate esters have been reported.[3] Similarly, reactions of trialkyl phosphites with mono- and dialkyl phosphates yielding the trialkyl phosphates are known.[4] Carboxylic acids have been reported to react at elevated temperatures (110–170°) with equivalent amounts of triethyl phosphite yielding the ethyl carboxylate and diethyl phosphite.[5] Esterification of furylacrylic acid was accomplished by heating the acid for 3 hr at 150–160° with triethyl phosphite.[6] Reactions of dialkyl phosphites with carboxylic acids are also known but occur more slowly at the conditions used for the reactions with trialkyl phosphites.[7]

The work described in this article is concerned with the acetolysis reactions of several mixed trialkyl phosphites. The purpose of this study was to determine

(1) Taken from the Ph.D. thesis submitted by J. A. D. to the University of Kansas, 1966.

(2) W. Gerrard, *J. Chem. Soc.*, 1464 (1940); W. Gerrard, *ibid.*, 85 (1944); W. Gerrard, *ibid.*, 848 (1945); M. C. Berla and W. Gerrard, *ibid.*, 2309 (1949); W. Gerrard and E. G. G. Whitbread, *ibid.*, 914 (1952); V. F. G. Cooke and W. Gerrard, *ibid.*, 1978 (1955); T. M. Cook, E. J. Coulson, W. Gerrard, and H. R. Hudson, *Chem. Ind.* (London), 1506 (1962); E. J. Coulson, W. Gerrard, and H. R. Hudson, *J. Chem. Soc.*, 2364 (1965).

(3) A. E. Arbuzov and P. I. Alimov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 268 (1951).

(4) C. Walling, F. W. Stacey, S. E. Jamison, and E. S. Huyser, *J. Amer. Chem. Soc.*, **80**, 4546 (1958).

(5) G. Kamami', V. A. Kukhtin, and O. A. Strogova, *Tr. Kazansk. Khim. Teknol. Inst.*, **21**, 155 (1956).

(6) A. E. Arbuzov and V. M. Zoroastrova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1030 (1960).

(7) F. W. Hoffmann and H. D. Wiess, *J. Amer. Chem. Soc.*, **79**, 4759 (1957).

TABLE I

SYNTHESIS OF MIXED TRIALKYL PHOSPHITES

$(RO)_2PCl + R'OH \longrightarrow (RO)_2POR' + HCl$

$(RO)_2PCl$	R'OH	Product	Bp, °C (mm)	% yield	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
Ethyl	2-Octanol	Diethyl-2-octyl phosphite (III)	74–80 (0.5–1.0)	31	57.57	10.87	12.38	57.55	10.83	12.45
Ethyl	*d*-(+)-2-Octanol[a]	Diethyl-(+)-*d*-2-octyl phosphite (IV)[b]	74–80 (0.5–1.0)	30	...	...	...	...	...	...
Ethyl	*trans*-Crotyl alcohol	Diethyl-*trans*-crotyl phosphite (V)	60–61 (12)	21	49.99	8.92	16.12	49.66	8.79	16.42
Ethyl	α-Methyallyl alcohol	Diethyl-α-methallyl phosphite (VI)	44–46 (0.5–1.0)	10	49.99	8.92	16.12	50.09	8.82	16.10
Ethyl	*exo*-Norbornyl alcohol	Diethyl-*exo*-norbornyl phosphite (VII)	64 (0.3)	15	56.88	9.11	13.34	56.87	9.18	13.03
Ethyl	*endo*-Norbornyl alcohol	Diethyl-*endo*-norbornyl phosphite (VIII)	62–64 (0.3)	17	56.88	9.11	13.34	57.16	9.16	13.82

$ROPCl_2 + 2R'OH \longrightarrow (R'O)_2POR + 2HCl$

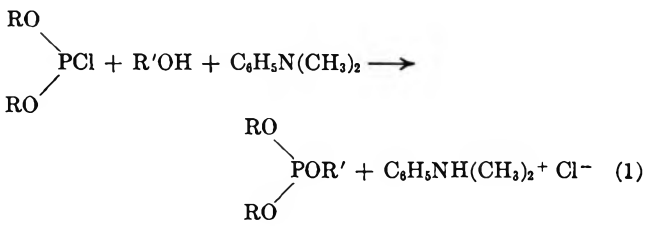
$ROPCl_2$										
Ethyl	Isopropyl alcohol	Ethyldiisopropyl phosphite (II)[c]	75–77 (25)	18	...	...	...	...	...	...
Isopropyl	Ethyl alcohol	Diethylisopropyl phosphite (I)	61–63 (20)	43	46.66	9.51	17.19	46.74	9.35	16.74
Cyclohexyl	Ethyl alcohol	Diethylcyclohexyl phosphite (IX)	122–125 (20)	17	54.53	9.61	14.07	54.87	9.71	14.24

[a] $[\alpha]^{27}D$ +9.2 (c 10.0, ethanol). [b] $[\alpha]^{26}D$ +4.8 (*c* 10.2, ethanol). [c] Lit. bp 65–65.5 (18 mm). G. Kamai' and R. M. Kharrasova *Zh. Obshch. Khim.*, **27**, 953 (1957).

both the relative ease of removal of various alkyl groups and the structure of the acetate esters in cases where isomers could be formed in order to deduce mechanisms for these dealkylation reactions.

Results

With the exception of ethyldiisopropyl phosphite and diethylcyclohexyl phosphite, the mixed trialkyl phosphites used in this study were synthesized by reaction of diethyl chlorophosphite and the appropriate alcohol in either diethyl ether or pentane in the presence of N,N-dimethylaniline. The mixed phosphites prepared in



$$\begin{matrix} RO \\ \diagdown \\ \quad PCl \\ \diagup \\ RO \end{matrix} + R'OH + C_6H_5N(CH_3)_2 \longrightarrow \begin{matrix} RO \\ \diagdown \\ \quad POR' \\ \diagup \\ RO \end{matrix} + C_6H_5NH(CH_3)_2^+ Cl^- \quad (1)$$

this manner and used in the acetolysis studies are listed in Table I. Ethyldiisopropyl phosphite was prepared by reaction of ethyl dichlorophosphite with isopropyl alcohol in the same manner employed for the other phosphites. Diethylcyclohexyl phosphite was prepared by reaction of cyclohexyl dichlorophosphite with ethanol in the pentane in the presence of N,N-dimethylaniline.

The acetolysis reactions were accomplished by heating a mixture of about equivalent amounts of the mixed trialkyl phosphite and acetic acid sealed in a Pyrex tube at 125° for about 12 hr. During this period, an appreciable amount of the trialkyl phosphite reacted, but little, if any, of the dialkyl phosphite produced in the reaction underwent acetolysis. We found that when reaction of the dialkyl phosphite was allowed to occur by using more than an equivalent of acetic acid and a longer period of heating, a heterogeneous mixture resulted owing to the insolubility of the monoalkyl phosphite in the nonpolar mixture of acetate esters and dialkyl phosphites. The results shown in Tables II–V were obtained from reactions in which no evidence of acetolysis of the dialkyl phosphite was observed. The relative reactivity ratios $k_{ROAc}/k_{R'OAc}$ were determined from the amounts of the acetate esters as determined by gas chromatographic analysis of

TABLE II

ACETOLYSIS OF MIXED TRIALKYL PHOSPHITES

Phosphite	Phosphite, mmol	HOAc, mmol	Ethyl acetate	Alkyl acetate	k_{ROAc}/k_{EtOAc}[a]
Ethyldiisopropyl phosphite (II)	5.14	5.22	0.74	2.13	1.43
	5.48	6.02	0.87	2.52	1.45
	5.34	4.74	0.75	2.15	1.43
Diethylisopropyl phosphite (I)	5.66	5.72	2.07	1.14	1.10
	5.63	5.86	2.37	1.21	1.02
Diethyl-2-octyl phosphite (III)	4.03	4.51	0.81	1.04	2.5
	4.10	4.53	0.74	10.3	2.8

[a] Corrected for statistical factor.

TABLE III

ACETOLYSIS REACTIONS OF DIETHYL-*trans*-CROTYL PHOSPHITE (V) AND DIETHYL-α-METHALLYL PHOSPHITE (VI)

Phosphite	Phosphite, mmol	HOAc, mmol	Ethyl acetate	Crotyl acetate	α-Methallyl acetate	k_{ROAc}/k_{EtOAc}[a]
Diethyl-*trans*-crotyl phosphite	5.60	5.88	1.13	2.33	0.96	5.9
	5.24	5.26	1.72	2.02	1.26	3.8
Diethyl-α-methallyl phosphite	5.36	5.16	0.42	0.90	1.89	13.3
	5.26	5.20	0.48	0.87	1.97	11.8
	5.22	5.36	0.43	0.88	2.20	14.7

[a] Determined from the combined crotyl and α-methallyl acetates and statistically corrected.

TABLE IV

REACTIONS OF DIETHYL *exo*- AND *endo*-NORBORNYL PHOSPHITES WITH ACETIC ACID

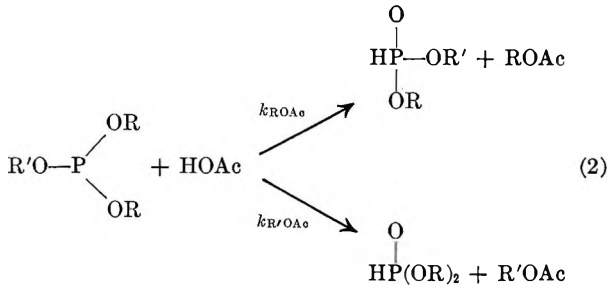
Phosphite	Phosphite, mmol	Acetic acid, mmol	Ethyl acetate, mmol	Norbornyl acetate, mmol	*exo*-Norbornyl acetate, %	k_{ROAc}/k_{EtOAc}
Diethyl-*exo*-norbornyl	4.46	4.55	3.01	1.25	100	0.83
phosphite (VII)	4.31	4.41	3.63	1.50	100	0.83
Diethyl-*endo*-norbornyl	4.31	4.42	1.79	0.64	75	0.71
phosphite (VIII)	4.33	4.37	2.04	0.79	82	0.77

TABLE V

ACETOLYSIS OF DIETHYLCYCLOHEXYL PHOSPHITE (IX)

Phosphite, mmol	HOAc, mmol	Ethyl acetate	Cyclohexyl acetate	Cyclohexene
4.56	4.50	1.78	0.37	1.10
4.77	4.72	2.13	0.43	1.49
4.71	4.98	2.74	0.47	1.50
4.67	0.48	0.16		0.72
4.50	0.58	0.23		0.64

the reaction mixtures. In all cases, two or more runs were made for each mixed phosphite.



(2)

The acetolysis reactions of diethylisopropyl phosphite and ethyldiisopropyl phosphite showed that the secondary alkyl group was removed somewhat more readily than the primary group and that the ease of removal was dependent on the particular phosphite used (Table II). In the case of diethyl-*dl*-2-octyl phosphite, the secondary alkyl group is relatively more reactive toward acetolysis than the isopropyl group. Acetolysis of diethyl-(+)-2-octyl phosphite (IV) (93% optical purity) yielded (−)-2-octyl acetate with an optical purity of 84–89% indicating a total inversion of 92–94% in the reaction. The results of these experiments indicate that secondary alkyl groups are removed more readily than primary ethyl groups and that acetolysis reactions occur with over 90% inversion of configuration.

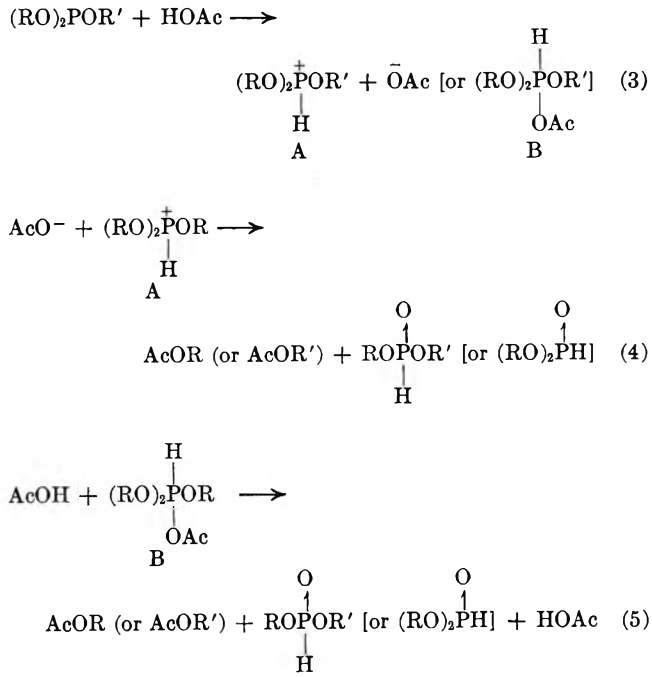
The crotyl group was removed about five times faster than the ethyl group in the acetolysis of diethyl-*trans*-crotyl phosphite. Furthermore, the acetolysis of the crotyl group gave a mixture of crotyl and α-methallyl acetates in which the former predominated (Table III). Diethyl-α-methallyl phosphite reacted with acetic acid yielding a mixture of acetate esters in which α-methallyl acetate predominated over the crotyl acetate. In this case, the acetolysis of the α-methallyl group, a secondary group, was about 13 times more facile than that of the ethyl group.

Diethyl-*exo*-norbornyl phosphite reacted in a somewhat anomalous manner in that the norbornyl group underwent acetolysis with complete retention of configuration (Table IV). The norbornyl acetate formed from the acetolysis of the diethyl-*endo*-norbornyl phosphite is mainly that resulting from inversion of configuration at the reaction site although some retention was observed. It is also interesting to note that the norbornyl group is less reactive than the ethyl group in both cases toward acetolysis.

The course of the acetolysis of diethylcyclohexyl phosphite was unusual in that cyclohexene was a major reaction product (Table V). The alkene did not result from pyrolysis of cyclohexyl acetate since heating a mixture of this ester with diethyl phosphite did not yield any detectable amounts of cyclohexene. Interestingly, reaction of diethylcyclohexyl phosphite with about 10 mol % acetic acid resulted in formation of a greater than stoichiometric amount of cyclohexene along with ethyl acetate. These observations suggest that acetic acid may play what amounts to a catalytic role in forming cyclohexene from this mixed trialkyl phosphite and that the reaction path for acetolysis of this phosphite ester is different from those of the others in which no detectable amounts of alkene were observed.

Discussion

A plausible mechanism for the acetolysis of mixed trialkyl phosphites having only primary and secondary alkyl groups is one in which either the phosphonium ion (A) or the pentacovalent adduct (B) undergoes nucleophilic attack by acetate ion or acetic acid, respectively, producing the acetate ester and a dialkyl phosphite. The 92–94% inversion of configuration observed in the acetolysis of the (+)-2-octyl group of diethyl-(+)-2-octyl phosphite (IV) indicates that an SN2 displacement on the alkyl group is the predominant course of reaction in these simpler systems. The fact that complete inversion is not observed suggests that some fragmentation of the phosphonium ion (A) (SN1

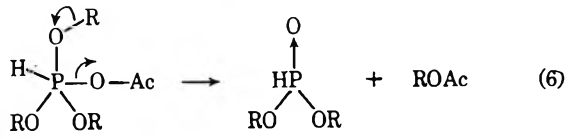


(3)

(4)

(5)

reaction) competes with the SN2 displacement. It is also possible, however, that an SNi reaction of the pentacovalent species yielding an acetate with retention of configuration may occur.[8] Evidence supporting



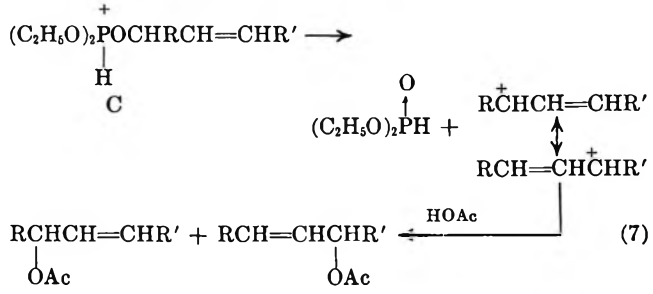
(6)

the SNi reaction is found in the reactions of the diethylnorbornyl phosphites (VII and VIII) and will be discussed subsequently in this article.

One explanation for the higher reactivity of secondary alkyl groups with respect to primary may be the greater role relief of steric factors in the leaving groups play relative to steric effects in the region of the carbon atom undergoing nucleophilic attack. Nucleophilic attack at the isopropyl group (of either A or B) will result in displacement of diethyl phosphite, a relatively strain-free species. On the other hand, attack on an ethyl group, although preferable from the standpoint of the steric requirements for the alkyl group undergoing attack, results in displacement of ethylisopropyl phosphite. Both the displaced dialkyl phosphite and the species undergoing attack contain phosphorus with a tetrahedryl configuration and consequently subjected to steric problems caused by secondary alkyl groups. Nucleophilic attack at the secondary alkyl group would result in relief of steric strain in the phosphorus moiety whereas attack at the ethyl group would have no effect in relieving steric strain.

The observation that an isopropyl group is relatively more reactive than an ethyl group in ethyldiisopropyl phosphite (II) than in diethylisopropyl phosphite (I) (see Table II) can also be explained in terms of similar steric factors. The relief of strain resulting from removal of one of the two isopropyl groups from the reaction intermediate derived from II yielding ethyl isopropyl phosphite is likely more pronounced than that resulting from removal of the single isopropyl group in the reaction of I. It should also be noted that the 2-octyl group in III, probably because of its size and the larger number of possible conformations it can assume, introduces more strain than the smaller isopropyl group and is more reactive toward acetolysis relative to ethyl than is the isopropyl group in I or II.

The acetolysis reactions of the allylic groups of diethyl-*trans*-crotyl phosphite (V) and the diethyl-α-methylallyl phosphite (VI) also showed SN2 character. Both phosphites gave a mixture of crotyl acetate and α-methylallyl acetate, but the acetate with the allylic structure present in the parent phosphite predominated in each case (Table III). Although the formation of the isomeric allylic acetate may have resulted from some ionization of the phosphonium cation yielding the allylic carbonium ion (SN1 path shown in reaction 7), other routes to the isomeric acetates are also available. One is an SN2′ attack of either the phosphonium



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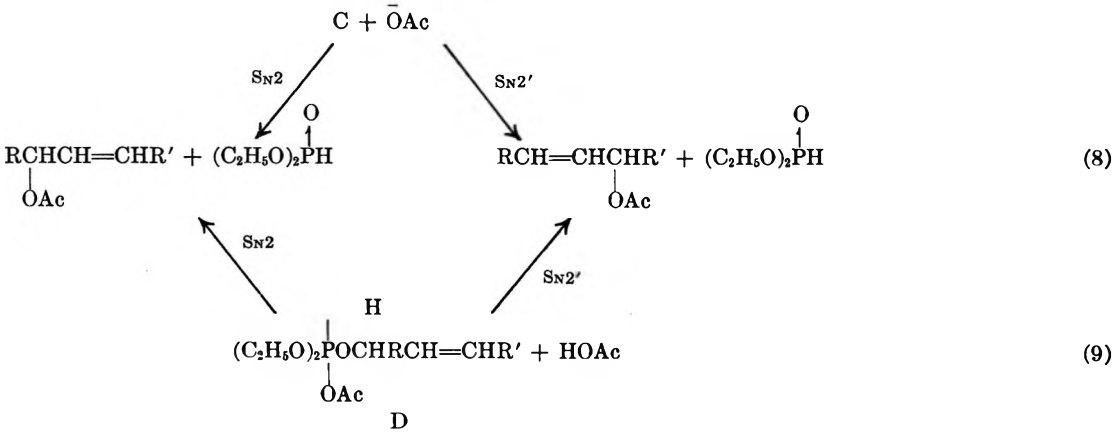


(8)

(9)

R = H; R′ = CH_3 for V; and R = CH_3 and R′ = H for VI

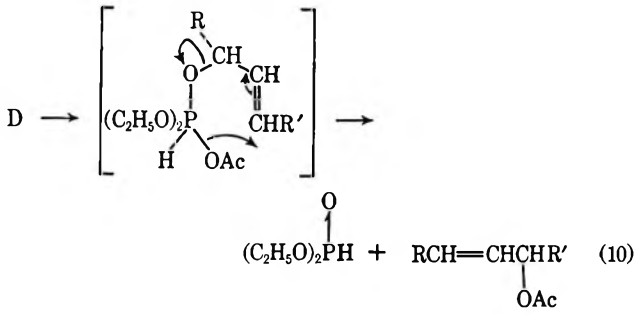
ion (C, eq 8) or the pentacovalent adduct (D, eq 9) at the unsaturated linkage[9] competing with the SN2 reaction. If this were the case, more crotyl acetate, the rearranged product, would have been expected from the reaction of VI with the less hindered γ carbon and hindered α carbon than α-methallyl acetate, the rearranged product, from V. The amounts of the isomeric acetate were about the same. Another possible explanation is that the isomeric acetates resulted from an SNi′ reaction[10] of the pentacovalent adduct as shown in reaction 10.

The allylic groups in both V and VI are more reactive toward SN2 displacement than the ethyl group. It is interesting that the reactivity of the secondary α-methylallyl group in VI is markedly more reactive than the primary crotyl group in V. This observation is consistent with the preferential displacement on a

(8) Reactions of pentavalent phosphorus species yielding products with retention of configuration have been reported by Huckel and Pietrzak who found menthyl chloride produced in the reaction of menthol with PCl_5: W. Huckel and H. Pietrzak, *Ann.*, **540**, 250 (1939).

(9) R. H. de Wolfe and W. G. Young, *Chem. Rev.*, **56**, 769 (1956).

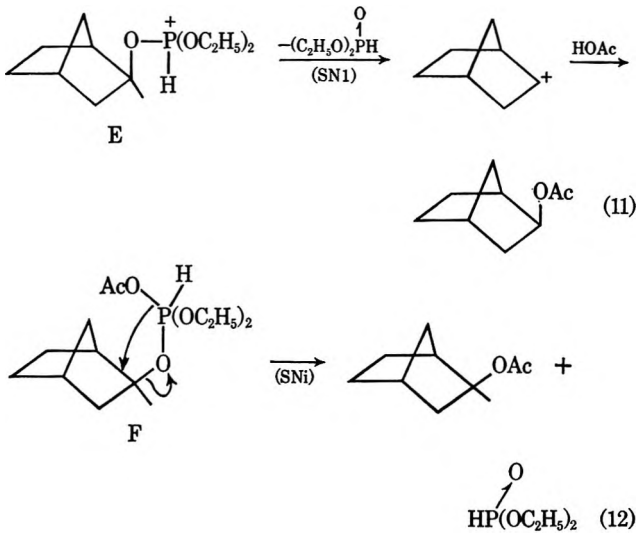
(10) J. D. Roberts, W. G. Young, and S. Winstein, *J. Amer. Chem. Soc.*, **64**, 2127 (1942); W. G. Young, F. F. Caserio, and D. Brandon, *Science*, **117**, 473 (1953); F. F. Caserio, G. E. Dennis, R. H. DeWolfe, and W. G. Young, *J. Amer. Chem. Soc.*, **77**, 4182 (1955).



(10)

secondary alkyl group because of relief of strain in the displaced dialkyl phosphite.

The formation of only *exo*-norbornyl acetate in the acetolysis reactions of diethyl-*exo*-norbornyl phosphite (VII) suggests that the norbornyl cation, which could result from the fragmentation of the protonated species E (reaction 11), is an intermediate in the reaction. Although the norbornyl cation would yield exclusively the *exo*-norbornyl acetate,[11] this acetate could result from an SNi reaction of the pentacovalent species F (reaction 12). Steric hindrance is very likely responsible for the lack of any *endo*-norbornyl acetate resulting from an SN2 attack of the norbornyl moiety of either E or F.

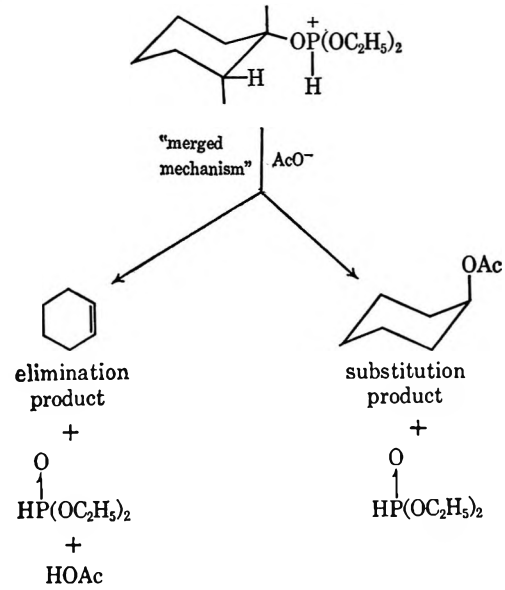


(11)

(12)

The formation of both the *endo*- and *exo*-norbornyl acetates in the reactions of VIII (see Table IV) supports the suggestion that SNi reactions may occur in these systems. In this case, steric hindrance toward SN2 attack at the norbornyl moiety from the *exo* side is not as great, and the SN2 reaction yielding *exo*-norbornyl acetate can compete with the SNi reaction yielding the isomeric *endo*-norbornyl acetate. Indeed, it becomes difficult to conceive of a mechanism in this case other than the SNi mechanism to account for the formation of *endo*-norbornyl acetate.

The formation of cyclohexene as the major product of the acetolysis of the cyclohexyl moiety of diethylcyclohexyl phosphite (IX) requires some explanation. Cyclohexyl acetate, the expected product resulting from acetolysis of the cyclohexyl moiety, was not a precursor of the alkene since it proved to be relatively stable under the conditions of our experiments. The alkene may have resulted from the nucleophilic attack on the cyclohexyl moiety in a "merged mechanism."[12] The expected preferred conformers for either the cation or the pentacovalent species would be those in which the leaving group (the diethyl phosphite moiety) would most likely be in an equatorial position. The preferential formation of the alkene by attack of a β hydrogen by a relatively weak nucleophile (AcO^- or AcOH) rather than the SN2 product is similar to reactions of other cyclohexane derivatives with weakly nucleophilic reagents. It is interesting to note also that the amount of fragmentation of IX into diethyl phosphite and cyclohexene is larger than the amount of acetic acid originally present. This "catalytic effect" of acetic



acid on the fragmentation of IX into cyclohexene and diethyl phosphite is consistent with the "merged mechanism" concept for the reaction of this mixed phosphite.

Experimental Section

Preparation of Mixed Trialkyl Phosphites (Table I).—Diethyl chlorophosphite was prepared by refluxing a 2:1 molar mixture of triethylphosphite and phosphorus trichloride for approximately 1 hr, during which time the liquid assumed a yellow color. Distillation of the mixture gave diethyl chlorophosphite (bp 32–42° at 25 mm) in about 80% yield. Diethylcrotyl phosphite (V), diethyl-α-methylallyl phosphite (VI), diethyl-2-octyl phosphite (III), diethyl-*exo*-norbornyl phosphite (VII), diethyl-*endo*-norbornyl phosphite (VIII), and diethyl-(±)-2-octyl phosphite (IV) were prepared from diethyl chlorophosphite as follows. About 10 g of the alcohol and an equivalent amount of N,N-dimethylaniline in 125 ml of dry Skelly F was added slowly to a mixture of diethyl chlorophosphite in an amount equivalent to the alcohol which was dissolved in 250 ml of Skelly F. The reaction mixture was vigorously stirred with cooling in an ice bath during the addition. The amine hydrochloride was filtered from the reaction mixture, and the Skelly F was removed under reduced pressure. The remaining residues were subjected to vacuum distillation and yielded the mixed phosphites in the amounts shown in Table I.

Diethylisopropyl phosphite (I) and diethylcyclohexyl phosphite (IX) were prepared in the following manner. Phosphorus trichloride (68.8 g, 0.5 mol) was dissolved in 700 ml of dry diethyl ether and an equimolar amount of either isopropyl alcohol or cyclohexanol and N,N-dimethylaniline was added slowly to the phosphorus trichloride–ether mixture with vigorous stirring and cooling of the flask by means of an ice bath. When addition of the alcohol was completed, ethanol (45 g, 1.0 mol) and N,N-dimethylaniline (121 g, 1.0 mol) were added with stirring to the

(11) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1154 (1952).

(12) S. Winstein, D. Darwish, and H. J. Holness, *ibid.*, **78**, 2915 (1956); E. Eliel and R. G. Haber, *ibid.*, **81**, 1249 (1959).

mixture. The amine hydrochloride was filtered from the reaction mixture; the ether was removed under vacuum; and the remaining residue was distilled. The mixed phosphites were formed in the amounts shown in Table I.

Ethyl dichlorophosphite (50 g, 0.34 mol), prepared by reaction of equimolar amounts of phosphorus trichloride and ethanol in dry diethyl ether,[13] was added to a mixture of N,N-dimethylaniline (82.4 g, 0.67 mol) and isopropyl alcohol (40.8 g, 0.68 mol) dissolved in 500 ml of dry Skelly F. During the addition of the ethyl dichlorophosphite, the reaction flask was cooled in an ice bath, and the mixture was stirred vigorously. After removal of the amine hydrochloride by filtration and the Skelly F by distillation at atmospheric pressure, the remaining residue was distilled under vacuum yielding ethyldiisopropyl phosphite (see Table I).

In all cases, the ir and nmr spectra of the mixed phosphite esters were consistent with their assigned structures.

Reactions of Mixed Phosphites with Acetic Acid.—The quantities of acetic acid and mixed phosphites shown in Tables II–V were sealed in Pyrex tubes and heated for approximately 12 hr in a constant temperature oil bath set at 125°. During this period of heating, the mixtures remained homogeneous. Upon cooling, the tubes were opened, and an accurately weighed amount of the reaction mixture was added to a known amount of an inert compound (chlorobenzene, toluene, tetralin or anisole) which served as an internal standard for the gas chromatographic analysis. The amounts of the ethyl acetate and other alkyl acetate produced in the reaction were determined from comparison of their gas chromatographic peak areas with that of the internal standard. Duplicate or triplicate runs were made for each mixed phosphite.

Separation of *exo*- and *endo*-norbornyl acetates could not be accomplished by gas chromatographic analysis. The compositions of these norbornyl acetates produced in these reactions (Table IV) were determined by ir analysis of the norbornyl acetates which were separated from the reaction mixtures by preparative gas chromatography using a 10 ft × $^3/_8$ in. column packed with 30% phenyldiethanolamine on Chromosorb W. Acetolysis of 0.99 g (4.3 mmol) of diethyl-*exo*-norbornyl phosphite with 0.26 g (4.4 mmol) of acetic acid at 125° for 12 hr yielded on isolation 50.9 mg of *exo*-norbornyl acetate with an ir spectrum identical with that of an authentic sample. Acetolysis of diethyl-*endo*-norbornyl phosphite (1.00 g, 4.3 mmol) with acetic acid (0.26 g, 4.4 mmol) at 125° for 12 hr yielded on isolation 25.9 mg of norbornyl acetates. Ir analysis showed the characteristic absorption at 1072 cm^{-1} displayed by *exo*-norbornyl acetate as well as an absorption at 1039 cm^{-1} found in the spectrum of an authentic sample of *endo*-norbornyl acetate. The amounts of the *endo*- and *exo*-norbornyl acetates were determined from the relative intensities of the absorptions by comparing them with the intensities observed for synthetic mixtures of the two esters.

Acetolysis of Diethyl-(+)-2-octyl Phosphite.—Diethyl-(+)-2-octyl phosphite (2.01 g, 8.03 mmol) and acetic acid (0.481 g, 8.01 mmol) were heated for 12 hr at 125°. The 2-octyl acetate formed was separated from the reaction mixture by preparative gas chromatography on a 20 ft × $^3/_8$ in. column packed with 30% Carbowax on Chromosorb P. The isolated 2-octyl acetate, which amounted to 0.142 g, had a specific rotation of $[\alpha]^{27}D$ −2.6 (c 11.2, ethanol). In a similar reaction employing 1.15 g (4.62 mmol) of diethyl-(+)-2-octyl phosphite and 0.28 g (4.7 mmol) of acetic acid, 0.125 g of 2-octyl acetate was isolated which had $[\alpha]^{27}D$ −2.7 (c 10.0, ethanol).

Registry No.—I, 17448-38-3; II, 14540-27-3; III, 17448-39-4; IV, 17448-40-7; V, 17448-41-8; VI, 17448-42-9; VII, 17448-43-0; VIII, 17448-44-1; IX, 17448-45-2.

(13) R. W. Young, K. H. Wood, R. J. Joyce, and G. W. Anderson, *J. Amer. Chem. Soc.*, **78**, 2126 (1956).

The Synthesis of Methyl 13,16-Cycloatisan-18-oate (Methyl *anti*-Trachylobanate)[1,2]

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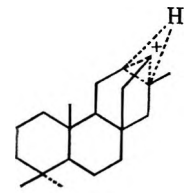
The synthesis of the pentacyclic diterpene methyl 13,16-cycloatisan-18-oate, the enantiomer of methyl trachylobanate, is described. The successful route involved as the initial step the condensation of methyl levopimarate with *n*-butyl crotonate. The major adduct whose structure and stereochemistry were elucidated was transformed by oxidation with potassium permanganate, ozonolysis, reduction with chromous chloride, and oxidative decarboxylation to 8-carboxymethyl-2,5a,8-trimethyl-1H-3,10a-Δ^1-decahydroethanophenanthren-12-one (**30a**). Cationically induced cyclization of the major alcohol obtained by hydride reduction of **30** gave the title compound. Other approaches to the trachylobane system are presented.

The trachylobanes or *ent*-13,16-cycloatisanes[3-5] (**1**) comprise a class of interesting pentacyclic diterpenes which were isolated[4] from the seed pods of *Trachylobium verrucosum* Oliv. Their importance stems from the circumstance that their occurrence in nature completes the array of diterpenoids theoretically derivable from the ion A which has been suggested[6] as the common intermediate leading to tetracyclic diterpenes and in fact helps to substantiate current notions concerning the biogenesis of diterpenes in general.



A

Our interest in the transformation of common resin acids into diterpenes with novel skeletons[7,8] prompted us to examine possible routes to the partial synthesis of this interesting pentacyclic skeleton. We have

(1) Resin Acids. XIV. A preliminary communication has appeared. W. Herz, R. N. Mirrington, and H. Young, *Tetrahedron Lett.*, 405 (1968).

(2) Supported in part by grants from the Petroleum Research Fund of the American Chemical Society and the National Science Foundation (GP-6362).

(3) In deference to the discoverers[4] of this series of compounds, we shall refer to **1a** as trachylobane and **1b** as trachylobanic acid. However, in accordance with a proposal for systematic nomenclature subscribed to by most workers in this area,[5] the preferred systematic name for **1a** is enantiomeric 13,16-cycloatisane (**2a**) or *ent*-13,16-cycloatisane; **1b** would then be *ent*-13,16-cycloatisan-18-oic acid. The preferred[5] common names for **2a** and **2b** are *anti*-trachylobane and *anti*-trachylobanic acid.

(4) G. Hugel, L. Lods, J. M. Mellor, D. W. Theobald, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1974 (1963); 2282, 2888 (1965). G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *ibid.*, 2894 (1965).

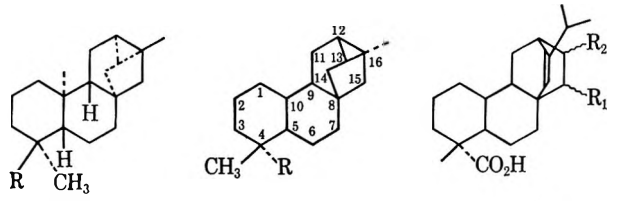
(5) J. W. Rowe, in preparation.

(6) E. Wenkert, *Chem. Ind.* (London), 282 (1955).

(7) W. Herz and R. N. Mirrington, *J. Org. Chem.*, **30**, 3195 (1965).

(8) W. Herz, A. R. Pinder, and R. N. Mirrington, *ibid.*, **31**, 2257 (1966).

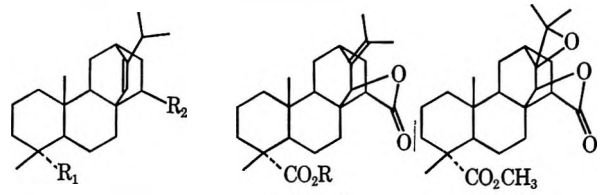
achieved our objective and now report the synthesis of methyl 13,16-cycloatisan-18-oate (**2c**), the enantiomer of methyl trachylobanate[9] (**1c**, methyl *anti*-trachylobanate),[5] which confirms the structure and stereochemistry assigned previously to the trachylobanes.



1a, R = CH_3
b, R = CO_2H
c, R = CO_2CH_3

2a, R = CH_3
b, R = CO_2H
c, R = CO_2CH_3

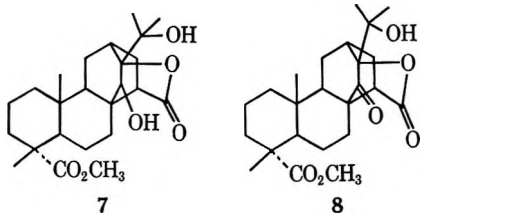
3



4a, $R_1 = R_2 = CO_2H$
b, $R_1 = R_2 = CO_2CH_3$
c, $R_1 = CO_2CH_3$; $R_2 = CO_2H$

5a, R = H
b, R = CH_3

6



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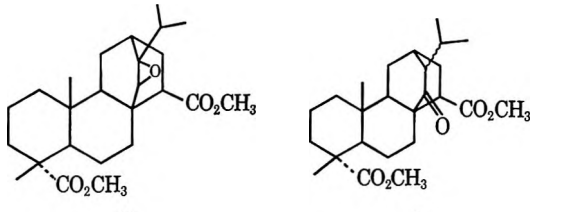

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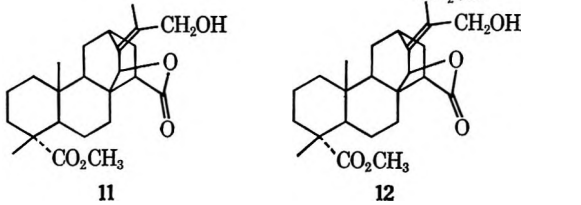


11

12

Levopimaric acid was chosen as starting material because of its availability and, more importantly, because the isopropyl group in the well-known 2,2,2-bicyclooctene system **3**,[10] easily prepared by diene synthesis of levopimaric acid with a variety of dienophiles,[11] can be readily removed[11,12] from adducts **3** (R_1 = *endo*-COOH) by permangante oxidation followed by ozonolysis.[13]

Our initial attempts to prepare a compound of type **3** (R_1 = *endo*- or *exo*-COOH, R_2 = *exo*- or *endo*-methyl) suitable for conversion into **2b** by condensation of levopimaric acid with crotonic acid or methyl or ethyl crotonate were not promising. We therefore explored the use of **4a**, prepared by hydrolysis of the adduct of levopimaric acid and methyl acrylate,[11a] which was oxidized with alkaline potassium permanganate in the described[11a] manner, the crude product being methylated with diazomethane. In spite of many trials the reported[11a] high yield of the acid corresponding to the ester lactone **5b** could not be repeated and never exceeded 40–50%. Instead the formation of by-products, which were the result of further oxidation and were very difficult to separate, except by tedious chromatography, interfered with the smoothness of the operation. Apparently the oxidizing agent attacked the initial product **5a** as rapidly as it attacked starting material. This led to the isolation of two new products, the epoxy lactone **6** (6%, configuration of the isopropyl group based on the most likely direction of attack by the oxidizing agent), whose structure was established by epoxidation of **5b** and comparison of samples, and the diol **7** (14%). The structural assignment of the latter derives from (1) presence of a δ-lactone frequency superimposed on the ester band in the ir spectrum; (2) presence in the nmr spectrum of a singlet proton at 4.35 ppm characteristic of hydrogen under hydroxyl flanked by fully substituted carbon atoms and two superimposed methyl singlets at 1.38 ppm indicative of the dimethyl carbinol grouping; (3) oxidation of **7** with chromic acid to the ketone alcohol **8**, whose physical properties were consonant with the proposed structure. Hydroxyketo lactone **8** was subjected to base treatment in the hope that it might undergo a retroaldol reaction, thus resulting in the desired loss of the isopropyl group, but no useful products could be isolated.

Several alternative routes to **5a** were investigated in efforts to improve the yield. Epoxidation of **4b** gave **9** which on treatment with acid invariably furnished **10**, instead of the hoped-for diol or **5a**. The exclusive operation of the pinacol rearrangement is understandable if the pronounced steric hindrance to displacement of the epoxide function, apparent from inspection of models, is taken into account, hydride migration being preferable to rear-side attack by an external nucleophile.

The action of bromine on **4a** or **4c** was also studied with a view to obtaining the bromo lactone which it was hoped could be converted into **5**, perhaps spontaneously. Partial realization of this objective was achieved under radical conditions (see Experimental Section) but offered no significant improvements. Worthy of note is the observation that addition of bromine in chloroform–methanol solution resulted after methylation and chromatography over alumina in the isolation of a bromo lactone (**13a** or **b**, 15%) and a hydroxy lactone (**11**, 25%). The latter substance must be the product of allylic bromination at one of the vinyl methyl groups in the presumed intermediate

(9) The French workers[4] reported the isolation of trachylobanic acid (**1b**). They did not report its physical properties but characterized it as the methyl ester **1c**.

(10) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. 3, Cambridge University Press, Cambridge, 1952, p 431.

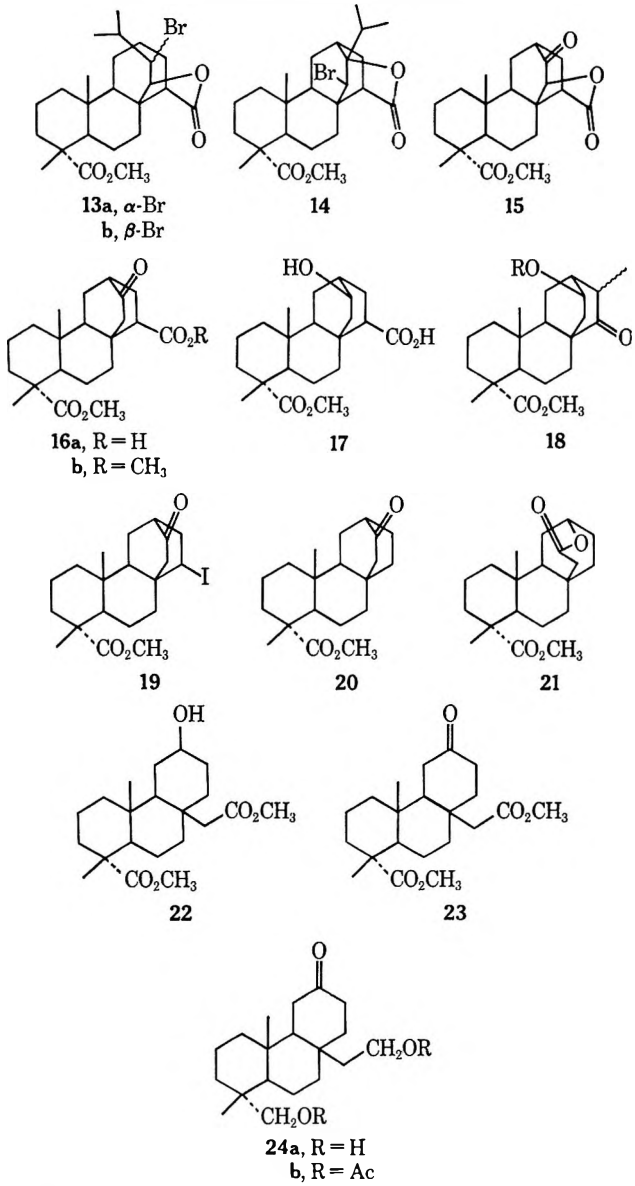
(11) For leading references, see (a) N. J. Halbrook, R. V. Lawrence, R. L. Dressier, R. C. Blackstone, and W. Herz, *J. Org. Chem.*, **29**, 1017 (1964); (b) W. Herz, R. C. Blackstone, and M. G. Nair, *ibid.*, **31**, 1800 (1966); **32**, 2992 (1967).

(12) (a) L. H. Zalkow, R. A. Ford, and J. P. Kutney, *ibid.*, **27**, 3535 (1962), and references cited therein; (b) L. H. Zalkow and D. R. Brannon, *ibid.*, **29**, 1296 (1964).

(13) Ozonolysis proceeds very slowly, if at all, when R_2 is also *endo* (except R_2 = H).[12a]

5a, the halogen being replaced by hydroxyl under the basic conditions of chromatography. When the bromination was conducted in chloroform, a dihydroxy lactone **12** was isolated as well. Structures of **11** and **12** were apparent from the nmr spectra which exhibited only one (for **11**) and no (for **12**) vinyl methyl singlets, as contrasted with **5b** which had two, and displayed signals corresponding to one (for **11**) and two (for **12**) hydroxymethyl groups. Ozonolysis of **11** and **12** to **15** (*vide infra*) confirmed the assignments.

The nature of the bromo lactone (**13a** or **b**) requires comment. Because it could not be dehydrohalogenated by treatment with base or acid, it probably did not represent the bromo lactone intermediate on the route from **4a** to **5**, **11**, or **12** which apparently undergoes spontaneous dehydrohalogenation. The alternative formula **14** was, however, ruled out on the basis of the ir spectrum which clearly identified it as a γ-lactone (carbonyl band at 1785 cm^{-1}).[14] It is therefore



possible that bromo lactonization of **4a** results in the formation of both C-13 epimeric bromo lactones **13a** and **13b** by *cis* as well as by the usual *trans* mode of addition to the bridge double bond, because, as has already been mentioned earlier, the peculiar geometry of levopimaric acid adducts interferes greatly with attack from the side of ring A.[15,16] Only one of the two epimers might then be favorably disposed conformationally or sterically for the elimination reaction which leads to **5**.[17]

Ozonolysis of **5b** proceeded smoothly to the keto lactone **15** which was reduced to **16a** in 90% yield with chromous chloride. Contrary to expectations, reduction of **16a** with various metal hydrides did not effect exclusive or even predominant formation of hydroxy acid **17** by reagent approach from the unhindered side. Instead, a difficultly separable mixture of epimers was produced from which a small amount of **17** was eventually isolated by preparative tlc.[18] This result interfered with the projected route to trachylobanic acid which required protection of the C-13 hydroxyl group of **17**, degradation of the carboxyl group at C-15 to a ketone, methylation to **18**, and intramolecular base-catalyzed alkylation at C-16 *via* the mesylate or tosylate.

In exploring an alternate path to **2b**, **17a** was converted into **19** (configuration at C-15 tentative) in 79% yield by the Barton modification[19] of the Hunsdiecker reaction. Reduction of **19** with tri-*n*-butyltin hydride[20] proceeded quantitatively and afforded the previously reported[21] ketone **20**. Treatment of this now readily available substance with *m*-chloroperbenzoic acid furnished the lactone **21** whose nmr spectrum (H-12 triplet at 4.56, AB system of H-14a and H-14b centered at 2.75 ppm) demonstrated that the Baeyer–Villiger oxidation had taken the expected course.

An attempt to reduce the lactone to the hydroxyaldehyde with diisoamylborane was not successful, so recourse was had to a more circuitous route. Hydrolysis of **21** and reesterification furnished **22**, which on dehydration gave a mixture of olefins, since ring C had reverted into the chair form on opening of the lactone bridge, thus making the hydroxyl group equatorial. Oxidation of **22** with Jones reagent yielded **23** which was converted into the ketodiol **24a**, characterized as the diacetate **24b**, *via* the ketal, lithium aluminum hydride reduction, and deketalization. An attempt to prepare **24a** more directly by hydride reduction of **21** and oxidation of the secondary hydroxyl group of the resulting triol with N-bromoacetamide was not satisfactory because of poor yields in the first step due to solubility problems and failure to achieve selective oxidation in the second.

The proposed route to the trachylobanes from **24a** required elaboration into a 8-formylmethyl-Δ^{12}-13-methyl derivative which in the form of its tosylhydra-

(14) The nmr signal of H-14 at 4.85 ppm is also more nearly in the range of hydrogen under lactone ether oxygen than of R_2CHBr.

(15) A similar instance of *cis* addition to the 13,14 bridge of maleopimaric anhydride has been claimed recently.[16]

(16) N. Langlois and B. Gastambide, *Bull. Soc. Chim. Fr.*, 2966 (1965).

(17) Because of the appearance of the C-10 methyl signal at the somewhat deshielded frequency of 1.08 ppm, we tentatively assign formula **13b**, the product of the usual *trans*-bromo lactonization reaction, to the unreactive bromo lactone.

(18) The assignment was based on a comparison of the C-10 methyl frequency at 1.10 ppm with the C-10 methyl frequencies of **31** and **32** (*vide infra*).

(19) D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 2438 (1965).

(20) H. G. Kuivila, *Advan. Organometal. Chem.*, **1**, 47 (1964); see also H. O. House, S. G. Boots, and V. K. Jones, *J. Org. Chem.*, **30**, 2519 (1965).

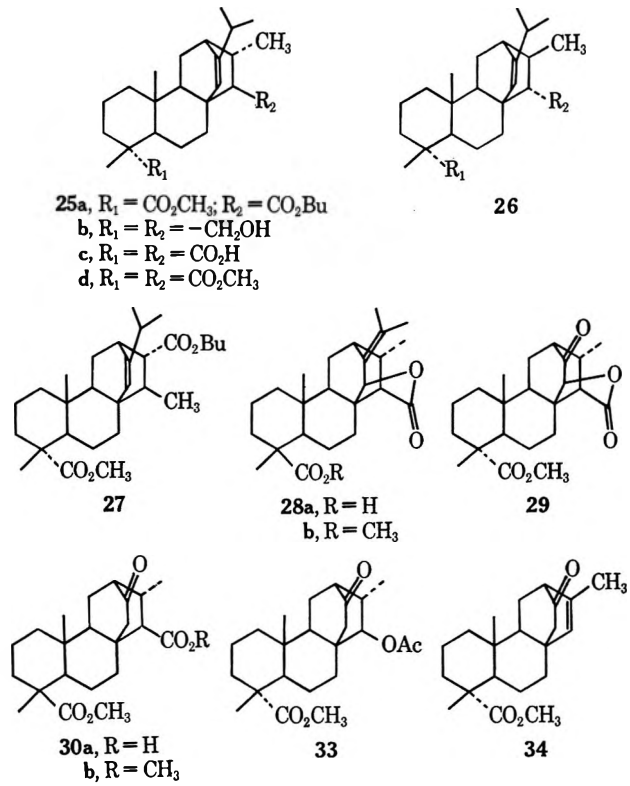
(21) L. H. Zalkow and N. N. Girotra, *ibid.*, **28**, 2037 (1963).

zone was expected to undergo intramolecular cyclization to **2b** in an aprotic medium.[22] However, the number of steps envisaged in this and the preceding scheme prompted us to reexamine the more direct approach requiring a Diels–Alder reaction between levopimaric acid and a crotonic derivative which, it will be recalled, had been studied earlier without success. After considerable experimentation it was finally discovered that the reflux temperature of a mixture of methyl levopimarate and *n*-butyl crotonate provided optimum conditions for the formation of two adducts in approximately 60% total yield. Isomerization to abietic acid and disproportionation to dehydroabietic acid accounted for the remainder of starting material. The yield of the two adducts (52 and 7%) was based on glpc analysis since they could not be separated satisfactorily by column chromatography. In practice the mixture was hydrolyzed directly, most of the diacid corresponding to the major adduct, crystallizing on acidification. The mother liquors were converted into the methyl esters which were separated by column chromatography.

Lithium aluminum hydride reduction of the two adducts separately yielded the same diols obtained by reduction of the methyl esters. Hence hydrolysis of the adducts was not accompanied by epimerization, and the acids or methyl esters could be used to assign structures to the adducts. The reactions to be discussed subsequently clearly demonstrate that the carbobutoxy group of the major adduct is attached to C-15 of the basic carbon skeleton and that its orientation is *endo* to the unsaturated bridge or β. If the configuration of the dienophile were maintained during the diene synthesis, the orientation of the C-16 methyl group of the major adduct should be *trans* to the carbobutoxy group or α, as in **25a**. Evidence for the correctness of this formulation will be presented in the sequel together with a discussion of the probable configuration of the minor adduct.

Oxidation of the dibasic acid **25c** obtained from the major adduct whose nmr spectrum was comparable to that of **4b**[11a] but had an extra signal attributable to the secondary methyl group presented the same difficulties encountered during the oxidation of **4c**, due to facile further oxidation of the primary product. In practice it proved simplest to carry out the oxidation with a limited amount of oxidizing agent at low temperature for a short time period. This resulted in the formation of the desired lactone **28a** in about 35% yield, mixed with a considerable amount of starting material and some over-oxidation products. Separation was effected by partitioning with carbon tetrachloride in which **27a** was insoluble and converting the acid into the methyl ester **28b**. That **28b** was a γ-lactone was revealed by the ir spectrum which had carbonyl bands at 1783 (γ-lactone) and 1730 cm^{-1} (ester). That the lactone ring was closed to C-14 was shown by the nmr spectrum which, just like that of **5b**, displayed a singlet at 4.83 and two vinyl methyl signals at 1.77 and 1.71 ppm. The lactone carbonyl of **28b**, and hence the carbobutoxy group of **25a**, was therefore attached to C-15 and had the β orientation.

(22) For analogies, see G. Büchi and J. D. White, *J. Amer. Chem. Soc.*, **86**, 2884 (1964); G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *ibid.*, **87**, 935 (1965); M. Schwarz, A. Besold, and E. R. Nelson, *J. Org. Chem.*, **30**, 2425 (1965).



25a, $R_1 = CO_2CH_3$; $R_2 = CO_2Bu$
b, $R_1 = R_2 = -CH_2OH$
c, $R_1 = R_2 = CO_2H$
d, $R_1 = R_2 = CO_2CH_3$

26

27

28a, R = H
b, R = CH_3

29

30a, R = H
b, R = CH_3

33

34

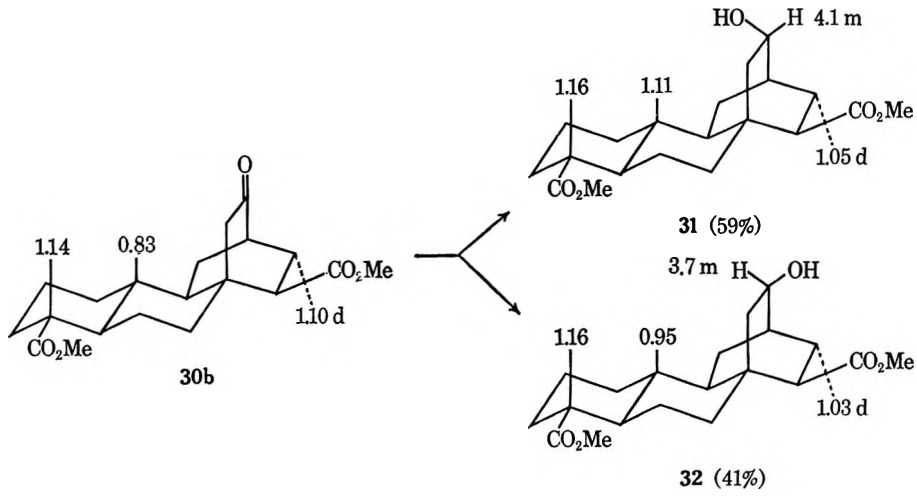
Our experience with the lower homolog **5b** now saved us the trouble of further experimentation and resulted in uniformly high yields. Ozonolysis of **28b** proceeded quantitatively. The resulting keto lactone **29** which possessed the required spectral properties — carbonyl bands at 1797, 1745 (γ-keto lactone), and 1723 cm^{-1} (ester) — was converted with chromous chloride in quantitative yield into **30a** which was further characterized as the methyl ester **30b**. Sodium borohydride reduction of the latter gave two epimeric alcohols **31** and **32** (Scheme I) in 59 and 41% yield,[23] respectively, the examination of whose nmr spectra permitted assignment of configuration to the C-16 methyl group, although this was not relevant to the contemplated synthesis.

The premise that the predominating direction of attack by hydride ion should lead to epimer **31** was supported by the nmr spectrum of the major product which displayed chemical shifts for C-10 methyl and H-13 significantly lower than those found for the corresponding signals in the nmr spectrum of the minor product. In a compound of formula **31**, C-10 methyl would be deshielded by C-13 hydroxyl, and H-13 would be deshielded by C-15 carbomethoxy, compared with the effects to be expected in a substance of formula **32**. Hence, the major epimer was indeed **31**. Since the chemical shift of the methyl doublet (C-16 methyl) was the same in both **31** and **32**, the secondary methyl group of **32** is not subject to the deshielding influence of a hydroxyl group and must be α in **32**, **31**, and all of their precursors. This settled the structure of the major Diels–Alder adduct as **25a**.

With this matter clearly established, some comments on the structure of the minor Diels–Alder adduct for

(23) In view of the obstruction generally interposed to attacks from the side of ring A, this relatively even proportion of products was somewhat surprising, but may to a certain extent be due to interference by the carbomethoxy group.

SCHEME I



which we adopt the tentative formula **26a** are in order. Failure to obtain a saturated lactone by acid treatment of **26c** or a hydroxylated or unsaturated lactone by permanganate oxidation indicated that the carbobutoxy group of the minor adduct should be *exo* to the bridge double bond. Furthermore in the nmr spectra of **26b–d**, the signal of C-16 methyl group appeared at considerably higher field (*ca.* 0.8 ppm) than in the nmr spectra of **25b–d** (*ca.* 1.05 ppm).[24,25] This observation could be accounted for by assuming that the secondary methyl group of the minor adduct and its derivatives was *endo* to, hence shielded by, the bridge double bond and required that its structure be formulated as **26a** or **27**.

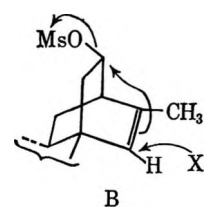
An attempt to distinguish between these two possibilities encountered unexpected complications with which we shall deal in a subsequent report. For reasons too involved to discuss here we have, however, tentatively adopted **26a** as the structure of the minor adduct.

We now return to the sequence of reactions which led to the synthesis of methyl *anti*-trachylobanate. Oxidative decarboxylation of **30a** with lead tetraacetate in the conventional manner resulted in a 45% yield of **33** (*endo* configuration of acetate suggested by the coupling constant of H-15). When the reaction was carried out in the presence of cupric acetate as recommended by Kochi,[26] the main product, formed in 79% yield, was the olefin **34**. This was evident from the nmr spectrum which exhibited not a methyl doublet like the precursor **30a** or **33**, but a narrowly split signal at 1.75 ppm characteristic of vinyl methyl which was spin coupled to the signal of a vinyl proton at 5.8 ppm. Small amounts of **29** and **33** were also formed.

Reduction of **34** with lithium tri-*t*-butoxyaluminum hydride furnished two epimeric alcohols in 82 and 16% yield. The major isomer was assigned formula **35** on steric grounds and because of the nmr spectra (Scheme II). In the major isomer the signal of C-10 methyl is found farther downfield, due to deshielding by the hydroxyl group, and the signal of H-13 is much farther upfield, due to shielding by the π-electron system of the double bond, as would be expected if the hydroxyl group were oriented toward ring A. Because the minor isomer **36** could be reoxidized to **34**, the over-all yield of the desired isomer **35** was better than 90%.

When an attempt was made to protect the hydroxyl group of **35** through the mesylate prior to hydroboration of the double bond, spontaneous cyclization of **35** to a compound possessing the trachylobane skeleton took place unexpectedly. The structure of **37**, which was isolated in 60% yield, was manifested in the nmr spectrum (Scheme II) which, instead of the vinyl methyl and vinyl proton signals of precursor **35**, displayed a methyl singlet at 1.21 and a singlet at 3.30 ppm characteristic of hydrogen under hydroxyl. Further proof for the pentacyclic nature of the new alcohol was provided by its oxidation in 85% yield to **38** which was clearly a cyclopropyl ketone as revealed by the uv spectrum [λ_{max} 211 and 285 nm (ϵ_{max} 2620 and 72)].

The cyclization of the bicyclo[2.2.2]octenol **35** is formally analogous to the acetolysis of bicyclo[2.2.2]-oct-5-en-2-ol tosylate[27] which leads to the predominant formation of tricyclo[2.2.2.$0^{2,6}$]octan-3-ol owing to participation by the 2,3 double bond. Hence, the formation of **37** might be represented by process B (X = H_2O). Since evidence for the formation of a mesylate could not be procured, it is also possible that mesyl chloride acts as a Lewis acid which, assisted by the double bond of **35**, produces a stabilized cationic inter-



B

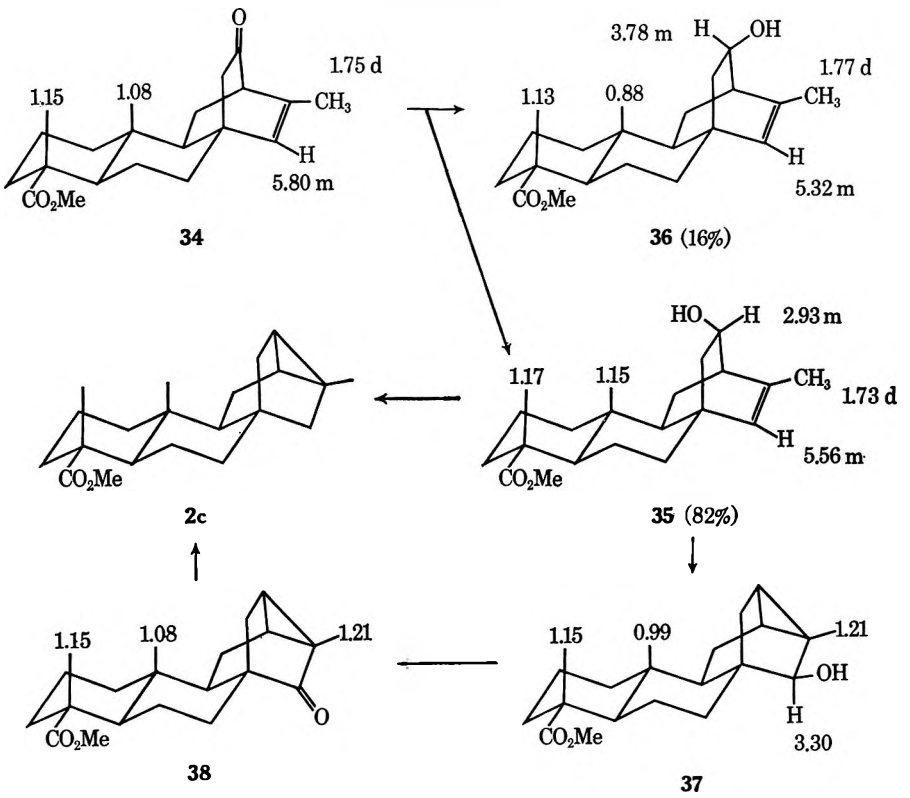
(24) Although this signal is generally a doublet, it is a singlet in **25b, c,** and **d** and some esters of **25c** not reported in this paper, presumably because *endo* H-16 in these compounds is shielded by the bridge double bond, thus reducing $\Delta\delta$ 16-methyl, H-16 to a value smaller than $J_{16\text{-Me, H-16}}$. Other reports of this phenomenon have appeared.[25]

(25) G. Slomp, Jr., and B. R. McGarvey, *J. Amer. Chem. Soc.*, **81**, 2200 (1959); F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961); J. I. Musher, *Spectrochim. Acta*, **16**, 835 (1960).

(26) J. K. Kochi, *J. Amer. Chem. Soc.*, **87**, 1811 (1965); J. D. Bacha and J. K. Kochi, *Tetrahedron*, **24**, 2215 (1968). According to these authors, the formation of olefin is due to the circumstance that cupric ion is a far better oxidizing agent for the intermediate radical than tri- or tetravalent lead and that the oxidation with cupric ion proceeds directly to alkene, if a β hydrogen is present, rather than through a carbonium ion which can rearrange or collapse to acetate.

(27) N. A. LeBel and J. E. Huber, *J. Amer. Chem. Soc.*, **85**, 3193 (1963).

SCHEME II



mediate which then reacts with added nucleophile to form **37**.

The facile cyclization of **35** to **37** suggested that addition of hydride ion to a solution of the mesylate or cationic intermediate might, by the process adumbrated in B (X = H^-), lead directly to methyl 13,16-cycloatisanoate (**2c**).[28] In fact the reaction proceeded as hoped for though only in about 17% yield and gave material identical in all respects (ir, nmr, glpc, tlc) with methyl trachylobanate (**1c**). The analogous cyclization of the *anti*-tosylate of bicyclo[2.2.2]oct-5-en-ol under the influence of lithium aluminum hydride has been described recently.[29]

Although substitution of boron trifluoride for methanesulfonyl chloride effected a yield improvement to 40%, **2c** from this as well as from the preceding cyclization experiment could not be freed satisfactorily from small amounts of contaminants, possibly rearrangement products,[29] which lowered the melting point of the synthetic material to 105–110° as compared with the reported mp 110–112°. A somewhat purer sample of **2c** was therefore prepared in 60% yield from **38** *via* the ethylene thio ketal. This material, mp 109–111°, was indistinguishable from authentic methyl trachylobanate (**1c**)[30] in all respects, but had the opposite rotation.

Experimental Section[31]

Oxidation of 4a with Alkaline Permanganate.—The high yield of lactone **5a** reported previously could not be realized. The experiment which follows illustrates the separation of the minor products. The benzene solvate of diacid **4a**,[11a] 3.78 g (8.2 mmol), was dissolved in 25 ml of water containing 0.8 g (20 mmol) of sodium hydroxide. The solution was cooled to 10°, and to it was added an ice-cold solution of 1.58 g (10 mmol, 3.8 equiv) of potassium permanganate in 75 ml of water. The mixture was kept in the refrigerator for 6 hr. The manganese dioxide was removed by filtration with the aid of Celite, and the colorless filtrate was acidified with 5 *N* aqueous hydrochloric acid. The precipitate was extracted with ether, and the washed and dried extract was concentrated to about 5 ml. Carbon tetrachloride was added, and the insoluble material was collected, taken up in methanol, and methylated with excess ethereal diazomethane. Removal of the solvents gave diol **7** as a colorless solid which crystallized from chloroform–methanol as needles: yield, 0.49 g (14%); mp 226–227°; ν_{max} 3550 (OH) and 1735–1725 cm^{-1} (double intensity, δ-lactone and ester); $\nu_{max}^{CHCl_3}$ 3550 (OH), 1755 (δ-lactone), and 1725 cm^{-1} (ester); nmr 4.39 (H-14), 3.69 (methoxyl), 3.48 (methanol of crystallization), 1.38 (6 H, isopropyl), 1.20 (C-4 methyl), and 1.12 ppm (C-10 methyl). This compound clung tenaciously to methanol which could not be removed completely, even after drying at 100° (1 mm) for 18 hr. The analytical sample was dried at 78° (1 mm) for 16 hr.

Anal. Calcd for $C_{24}H_{36}O_6 \cdot 0.5CH_3OH$: C, 67.44; H, 8.77. Found: C, 67.25; H, 8.72.

The carbon tetrachloride filtrate remaining after separation of **7** was evaporated, and the residue was methylated with diazomethane to give 1.2 g of solid, mp 170–190°, which was taken up in benzene and chromatographed on 100 g of alumina. Elution benzene gave 0.05 g (1.5%) of diester **4b** which crystallized from aqueous methanol as colorless needles: mp and mmp 68–69°; ir spectrum identical with that of authentic material.

Continued elution with benzene furnished 1.05 g (33%) of lactone **5b** which crystallized from ethanol as colorless needles: mp 196–197°; $[\alpha]D$ −90° (c 0.575); ν_{max} 1780 (γ-lactone), 1725 (ester), and 1675 cm^{-1} (w) (olefin); $\nu_{max}^{CCl_4}$ 1785 (γ-lactone), 1730 (ester), and 1670 cm^{-1} (olefin); nmr 5.03 (H-14), 3.66

(28) P. R. Story and M. Saunders, *J. Amer. Chem. Soc.*, **84**, 4876 (1962); H. C. Brown and H. M. Bell, *ibid.*, **85**, 2324 (1963); S. Winstein, A. H. Lewis, and K. C. Pande, *ibid.*, **85**, 2324 (1963).

(29) R. A. Appleton, J. C. Fairlie, and R. McCrindle, *Chem. Commun.*, 690 (1967).

(30) We wish to thank Professor G. Ourisson and Dr. G. Hugel for a generous sample of **1c**.

(31) Melting points were taken in capillaries and are uncorrected. Unless otherwise specified, rotations were run in chloroform, uv spectra in 95% ethanol, ir spectra as Nujol mulls and nmr spectra in deuteriochloroform with tetramethylsilane as the internal standard. R_f values apply to thin layer chromatograms on silica gel G plates using benzene–ethyl acetate (5:1) as the solvent system unless otherwise stated. Analyses were made by Dr. F. Pascher, Bonn, Germany.

(methoxyl), 1.78, 1.73 (vinyl methyl singlets), 1.18 (C-4 methyl), and 0.73 ppm (C-10 methyl); R_f 0.70.

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.91; H, 8.56.

Elution with benzene–ether (7:3) afforded 0.20 g (6%) of epoxy lactone **6** which crystallized from benzene–hexane as colorless prisms: mp 261–262°; ν_{max} 1785 (γ-lactone) and 1725 cm^{-1} (ester); $\nu_{max}^{CCl_4}$ 1795 (γ-lactone) and 1735 cm^{-1} (ester); nmr 4.35 (H-14), 3.69 (methoxyl), 1.40 (6 H, isopropyl methyl singlets), 1.20 (C-4 methyl), and 0.83 ppm (C-10 methyl); R_f 0.3.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.26; H, 8.53.

In subsequent work use of stoichiometric amounts of potassium permanganate at pH 8.5–10 (measured on a pH meter) gave 40–50% **5a**, 40–50% starting material **4a**, and some by-products (nmr and glpc analysis). Since starting material was easily precipitated with carbon tetrachloride, in which **5a** is soluble, reasonably pure **5a** was obtained relatively readily by this procedure. Use of excess potassium permanganate resulted in a lower yield of **5a** and lower yields of starting material. Use of a large excess of potassium permanganate and destruction of excess oxidant, after 26 sec by pouring the mixture into hydroxylamine hydrochloride solution, gave a 60–70% yield of lactone **5a** when carried out on less than 1-g quantities; but on a larger scale the volume of liquid involved made this method impractical.

Oxidation of 7.—A stirred solution of 0.2 g of **7** in 20 ml of acetic acid was treated dropwise at room temperature with Jones reagent until a brown color persisted. The mixture was diluted with water and saturated with salt, and the precipitate was collected. Crystallization from aqueous methanol gave 0.16 g of **8** as colorless needles: mp 198–199°; ν_{max} 3550 (OH), 1755 (γ-keto δ-lactone), 1740 (ester), and 1705 cm^{-1} (ketone); nmr 3.68 (methoxyl), 1.47, 1.36 (isopropyl methyl singlets), 1.20 (C-4 methyl), and 0.85 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.53; H, 8.12.

Epoxidation of 5a.—A mixture of 0.27 g of **5a** and 0.30 g of *m*-chloroperbenzoic acid in 30 ml of chloroform was kept at room temperature for 18 hr then shaken successively with aqueous potassium iodide and aqueous sodium thiosulfate. The layers were separated; the aqueous layer was extracted with chloroform; and the extract was combined with the original chloroform phase and washed thoroughly with 1 *N* aqueous sodium hydroxide to remove *m*-chlorobenzoic acid. Evaporation of the washed and dried organic phase gave 0.23 g (82%) of **6** which crystallized from benzene–hexane: mp and mmp 261–262°; ir spectra identical with that of **6** above. Compound **6** was unaffected by treatment with perchloric or formic acids.

Epoxidation of 4b.—A mixture of 1.77 g of **4b** and 3.4 g of *m*-chloroperbenzoic acid in 100 ml of chloroform was kept at room temperature for 16 hr. Work-up as usual gave 1.75 g (95%) of oily **9**: R_f 0.61; $\nu_{max}^{CCl_4}$ 1725 cm^{-1} (esters) and no olefinic absorption; nmr 3.63 and 3.61 (2 methoxyls), 3.13 (H-14), 1.17 (C-4 methyl), 1.03 (d), 0.74 (d, isopropyl methyls, both J = 7 cps), and 0.83 ppm (C-10 methyl). The same epoxide was also prepared by epoxidation of diacid **4a**, methylation of the crude product, and chromatography on alumina. Elution with benzene gave oily **9** (55%); ir and nmr spectra were superimposable.

Acid Treatment of 9.—Two drops of 70% perchloric acid was added to a solution of 1.04 g of **9** in 30 ml of acetone, and the mixture was kept for 8 hr at room temperature. Water was added until incipient crystallization, and the crystalline product was collected. Crystallization from methanol gave 0.4 g of **10** as colorless needles: mp 180–181°; ν_{max} 1740–1710 (broad, esters and ketone) and no hydroxyl; nmr 3.65 and 3.61 (2 methoxyls), 1.27 (d, 6 H, isopropyl methyl), 1.12 (C-4 methyl), 0.93 (d, 6.5 H, isopropyl methyl), and 0.73 ppm (C-10 methyl); R_f 0.70.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.61; H, 9.20.

Treatment of **9** for 1 hr at 25° with 90% formic acid and dilution with water gave the same ketone **10** (mixture melting point, nmr) in 60% yield.

Bromination of 4a. A. In Methanol–Carbon Tetrachloride.—A solution of 2 g of **4a** in 50 ml of methanol was treated with excess bromine in carbon tetrachloride for 40 min at 25°, then diluted with water, and extracted with ether. The extract was washed with water, aqueous sodium thiosulfate, and water, dried, and evaporated. The residue was methylated with diazomethane to give an oil which was chromatographed on a column of 80 g of alumina prepared in benzene. Elution with benzene–ether (4:1) gave 0.3 g of bromo lactone **13** which crystallized from methanol as needles: mp 260–262° dec; $\nu_{max}^{CHCl_3}$ 1780 (γ-lactone) and 1725 cm^{-1} (ester); nmr 4.85 (H-14), 3.68 (methoxyl), 1.20 (s, C-4 methyl), 1.08 (C-10 methyl), 1.02 (d), and 0.99 (d, each 6.5 H, isopropyl methyls).

Anal. Calcd for $C_{24}H_{35}O_4Br$: C, 61.66; H, 7.54; Br, 17.09. Found: C, 61.36; H, 7.64; Br, 17.30.

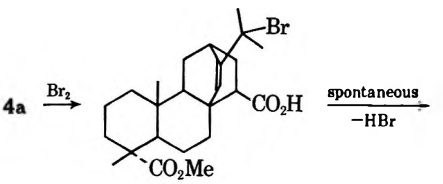
Elution with benzene–ether (7:3, 1:1) gave 0.5 g of **11** which crystallized from acetone–hexane as needles: mp 241–243°; ν_{max} 3500 (OH), 1760 (γ-lactone), and 1715 cm^{-1} (ester); nmr 5.01 (H-14), 4.18 (2 H, C=C—CH_2OH), 3.68 (s, methoxyl), 1.87 (vinyl methyl), 1.19 (C-4 methyl), and 0.73 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.11; H, 8.55.

B. In Chloroform.—A solution of diacid **4a** in chloroform was treated with bromine in chloroform for 10 hr at 25°. Copious fumes of HBr were evolved shortly after addition. The mixture was worked up and methylated as above, and the product was chromatographed on alumina. Benzene–ether (9:1) eluted 1.6 g of **13**; benzene–ether (4:1, 1:1) gave 6.4 g of **11**. Finally, ether–methanol (4:1) gave 2.8 g of dihydroxy lactone **12** which crystallized from acetone–hexane as colorless needles: mp 218–219°; ν_{max} 3400 (OH), 1780 (γ-lactone), 1750 (possibly γ-lactone intermolecularly hydrogen bonded), and 1720 cm^{-1} (ester); nmr 5.15 (H-14), 4.41, 4.35 (2 H each, C=C—CH_2OH), 3.67 (s, methoxyl), 1.20 (C-4 methyl), and 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.56; H, 8.11.

C. Direct Bromination.—A mixture of 1 g of monomethyl ester **4c** and 2.1 g of sodium acetate in 10 ml of carbon tetrachloride was irradiated with a 250-W light bulb while 10 ml of 0.92 *m* solution of bromine in carbon tetrachloride was being added dropwise with stirring; the temperature was kept at −30 to −20°. Stirring was continued for 2.5 hr. Excess bromine was destroyed with sodium sulfite. The solvent was removed *in vacuo*, and the residue was taken up in ether, washed, dried, concentrated, and purified by preparative tlc. There was obtained 0.64 g of **5a** contaminated by a trace of an unknown impurity. Scaling up of this procedure reduced the yield. When the bromination was carried out at 0° or higher, the formation of side product complicated the reaction mixture. Indications (nmr analysis) were that the reaction proceeded *via* the path shown.



i

5b $\xrightarrow{Br_2}$ further bromination products

The presence of intermediate i was suggested by the nmr spectrum which revealed a component containing a vinyl proton at C-14 and four tertiary methyl groups, two of them attached to carbon containing halogen.

Iodo Lactonization of 4a.—A solution of 7.25 g of **4a** in 250 ml of water containing 25 g of sodium bicarbonate was mixed with a solution of 10 g of iodine and 19.24 g of potassium iodide in 60 ml of water, stirred for 7 days at room temperature (a longer reflux period did not increase the per cent conversion), acidified with 10% sulfuric acid solution, and extracted thoroughly with ether. The ether extracts were washed with water, thiosulfate, and water, dried, and evaporated. The residue was refluxed with 200 ml of N,N-dimethylformamide for 2 hr; the solvent was removed at reduced pressure; and the residue was methylated with ethereal diazomethane. The crude product, 5.85 g, was chromatographed over 210 g of Alcoa alumina F-20. Elution with benzene (1400 ml) and ether–benzene (1:19, 400 ml) furnished 3.0 g of **4b**. Further elution with ether–benzene (1:9, 1,4,2,3) gave 1.9 g of **5b**.

Ozonolysis of 5b.—A slow stream of ozone was passed through a solution of 2.5 g of **5b** in 50 ml of chloroform until a potassium

iodide trap became discolored, and passage of ozone was continued for 1 hr (total time about 3 hr). The solution was shaken successively with aqueous potassium iodide, aqueous sodium thiosulfate, and water, dried, and evaporated. The solid residue (15) crystallized from either ethanol or acetone as colorless plates: mp 263–264°; yield, 1.2 g; ν_{max} 1805 (γ-lactone), 1735 (ester), and 1720 cm^{-1} (ketone); nmr 4.31 (H-14), 3.70 (methoxyl), 1.18 (C-4 methyl), and 0.77 (C-10 methyl).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.31; H, 8.13.

The same substance was obtained by ozonolysis of 11 and 12.

Chromous Chloride Reduction of 15.—A solution of 0.2 g of 15 in 100 ml of methanol was deaerated by cautious addition of Dry Ice. Excess 2 *M* chromous chloride in 2 *N* hydrochloric acid was added, and after 0.5 hr the mixture was diluted with water, saturated with salt, and extracted thoroughly with ether. The extracts were washed with water and then extracted well with 2 *N* aqueous sodium hydroxide solution. The ether layer was washed again with water, dried, and evaporated to give a trace of starting material. The alkaline washings were cooled in ice and acidified with excess 5 *N* hydrochloric acid. The white precipitate of 16a was collected, washed well with water, and dried by suction. Crystallization from methanol gave 0.18 g of colorless prisms: mp 271–272°; ν_{max} 1725 (ester and ketone) and 1690 cm^{-1} (acid); nmr 8.66 (broad, COOH, removed by shaking with D_2O), 3.68 (methoxyl), 1.15 (C-4 methyl), and 0.82 (C-10 methyl).

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.14; H, 8.37.

The methyl ester 16b was prepared by treating 16a with ethereal diazomethane and was crystallized from aqueous methanol as colorless needles: mp 132–133°; R_f 0.63; ν_{max} 1730–1720 cm^{-1} (broad, two esters and ketone); nmr 3.68 (two methoxyls), 1.16 (C-4 methyl), and 0.83 (C-10 methyl).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.21; H, 8.51.

$NaBH_4$ Reduction of 16a.—A solution of 0.2 g of 16a in 40 ml of methanol was mixed with 2 ml of aqueous 2 *N* sodium hydroxide solution containing 42 mg of $NaBH_4$. Tlc indicated little reduction after 4 hr at room temperature, so a large excess of $NaBH_4$ was added, and the mixture was left overnight, diluted with water, acidified, and worked up in the usual way. Tlc of the crude product (0.2 g) indicated the presence of two main products. Preparative tlc (4% methanol–chloroform developed twice, then 10% isopropyl alcohol–chloroform developed twice) resulted in the isolation of crystalline 17 which was recrystallized from carbon tetrachloride and then had mp 260–262°; nmr 4.1 (c, H-13), 3.74 (methoxyl), 1.18 (C-4 methyl), and 1.10 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.02; H, 9.11; O, 21.98.

Repetition of the reduction and acetylation of the crude product with acetic anhydride resulted in a 1:1 mixture (nmr spectrum) of epimeric acetates which could not be separated by tlc. Reduction followed by reflux with acetic anhydride resulted in a gummy neutral fraction (lactone bands at 1760 and 1730 cm^{-1}) and a small yield of acid, mainly 17a. Reduction with sodium borohydride or lithium tri-*t*-butoxyaluminum hydride also gave mixtures of epimers.

8-Carboxymethyl-5a,8-dimethyl-1-iodo-1H-3,10a-dodecahydroethanophenanthren-12-one (19).—A mixture of 0.3 g (0.83 mmol) of 17a and 0.50 g (1.15 mmol) of lead tetraacetate in 15 ml of carbon tetrachloride was refluxed under nitrogen for 10 min and then irradiated with a 250-W lamp while a solution of iodine in carbon tetrachloride was added dropwise. When the iodine color persisted (after about 4 hr), the mixture was cooled and filtered, and the precipitate of lead acetate was washed well with chloroform. The filtrate and washings were washed successively with aqueous sodium thiosulfate, water, 2 *N* aqueous sodium hydroxide, and water, dried, and evaporated under reduced pressure at 40° to prevent decomposition. The residual colorless oil crystallized from methanol at 0° to give 0.29 g (79%) of iodide 19 as colorless needles: mp 163–164°; R_f 0.82; ν_{max} 1725 cm^{-1} (ester and ketone); nmr 4.33 (t, broad, 7.5 H, H-16), 3.66 (methoxyl), 1.14 (C-4 methyl), and 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{20}H_{29}IO_3$: C, 54.05; H, 6.58; I, 28.56. Found: C, 54.40; H, 6.40; I, 28.71.

Reduction of 19 with Tri-*n*-butyltin Hydride.—A solution of crude 19 (from 6 g of acid 17a) in 50 ml of benzene was stirred at room temperature for 18 hr with a excess (about 10 ml) of tri-*n*-butyltin hydride.[20] The reaction mixture was shaken with dilute hydrochloric acid to convert excess reagent into the chloride, and the dried organic phase was concentrated and poured onto a column of alumina prepared in hexane. Elution with hexane gave tri-*n*-butyltin chloride and iodide, while elution with benzene–ether (9:1) gave 4.1 g of 20 (78% from 17a) which crystallized from hexane and had mp 129–130° (lit.[21] mp 129–130°); R_f 0.62.

Baeyer–Villiger Oxidation of 20.—A mixture of 4.8 g of 20 and 9.0 g of *m*-chloroperbenzoic acid in 400 ml of chloroform was refluxed for 18 hr. The cooled solution was washed with 1 *N* aqueous sodium hydroxide and water, dried, and evaporated to furnish a solid which was purified by chromatography on alumina in hexane. Elution with benzene–ether (4:1) gave 3.0 g of 21 which crystallized from methanol as colorless needles: mp 187–188°; ν_{max} 1735–1720 cm^{-1} (broad, ester and lactone); nmr 4.56 (t, H-12, $J \cong 3$ cps), 3.65 (methoxyl), 3.00 (*ca.* d), 2.53 (broad, 1 H each, C-14 methylene, $J_{doublet} = 1.5$ cps), 1.17 (C-4 methyl), and 0.98 ppm (C-10 methyl).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.50; H, 8.56.

Preparation of 23.—A mixture of 3.6 g of 20 and 3.5 g of sodium hydroxide in 150 ml of 10% aqueous ethanol was refluxed for 2 hr, then poured into water, and extracted once with ether to remove traces of neutral material. The aqueous layer was acidified with 5 *N* hydrochloric acid, saturated with salt, and extracted with ether thrice. The extracts were washed with brine, dried, concentrated, and treated with excess ethereal diazomethane. Removal of the solvent afforded 3.0 g of 22 as an oil: $\nu_{max}^{CHCl_3}$ 3500 (OH) and 1730 cm^{-1} (esters); nmr 3.68, 3.66 (methoxyls sitting on H-12 multiplet), 2.57 (two protons, CH_2–CO_2Me), 1.17 (C-4 methyl), and 0.86 ppm (C-10 methyl).

The crude alcohol 22 was oxidized with Jones reagent in acetone until a brown color persisted. The product was isolated with ether. Evaporation of the washed and dried extract gave 23 as an oil which slowly crystallized from aqueous 2-propanol: mp 118–120°; nmr 3.68 (two methoxyls), 2.70 (2 H, CH_2CO_2Me), 1.20 (C-4 methyl), and 0.90 ppm (C-10 methyl). The yellow dinitrophenylhydrazone was crystallized from methanol and had mp 212–213°.

The ketone also formed a crystalline ketal which crystallized from aqueous methanol as colorless needles: mp 87–88°; ν_{max} 1725 cm^{-1} (esters) and no hydroxyl absorption; nmr 3.94 (4 H, ketal), 3.65, 3.62 (methoxyls), 2.54 (2 H, CH_2CO_2Me), 1.16 (C-4 methyl), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.57; H, 8.62.

Preparation of 24b.—A solution of 0.4 g of the preceding ketal in anhydrous ether was added to a suspension of lithium aluminum hydride in anhydrous ether, and the mixture was refluxed for 1.5 hr. Excess reagent was decomposed with wet ether, methanol, and 1 *N* HCl. The washed and dried ether layer was evaporated, and the residue was treated with aqueous hydrochloric acid in acetone at 25° for 1 hr. The mixture was diluted and saturated with salt, and the product was isolated with ether to give 24a, contaminated with some ethylene glycol.

The crude diol was acetylated to the keto diacetate 24b, which was purified by chromatography on a column of silica gel prepared in hexane. Elution with benzene–ether (4:1) gave pure 24b as an oil: $\nu_{max}^{CCl_4}$ 1740 (two acetates) and 1705 cm^{-1} (ketone); nmr 4.16 (t, 2 H, $-CH_2$–CH_2–OAc, $J = 7.5$ cps), 3.94, 3.65 (AB quartet, 2 H, CH_2OAc a tC-4, $J_{AB} = 11$ cps), 2.06 (two acetates), 0.94 (C-4 methyl), and 0.87 ppm (C-10 methyl).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 70.38; H, 9.24. Found: C, 70.19; H, 9.16.

Diels–Alder Reaction of Methyl Levopimarate and *n*-Butyl Crotonate.—Crystalline methyl levopimarate, prepared from 30 g of levopimaric acid and diazomethane in ether, was dissolved in 30 ml of freshly distilled *n*-butyl crotonate and refluxed in a nitrogen atmosphere (liquid temperature 190–200°) for 18 hr. An additional 30 ml of *n*-butyl crotonate was added slowly to maintain the temperature at 190–200°. Distillation at 50–80° (0.05 mm) resulted in removal of excess crotonate; the residue on glpc (glass column packed with 5% SE-30 on Anakrom S. D.) exhibited two low retention time peaks corresponding to two adducts in a 7.5:1 ratio. Chromatography over 550 g of alumina (acid washed and activated at 250°) and elution with hexane–ether (99:1, 24:1, 19:1) gave 6 g of a mixture containing methyl abietate, butyl crotonate, and unidentified substances

Elution with hexane–ether (19:1, 93:7, 9:1, 17:3, 4:1, 3:1, 10:3) gave 23 g of a mixture of **25a** and **26a**. Elution with hexane–ether (5:2, 2:1, 1:3) and ether gave 3.8 g of pure **25a** as an oil: glpc single peak on 5% SE-30 column at 264°; $\nu_{max}^{CCl_4}$ 1730; nmr 5.53 (H-14), 3.97 (t, $-CO_2CH_2CH_2CH_2CH_3$), 3.65 (methoxyl), 1.13 (C-4 methyl), 1.06 (d, isopropyl and C-16 methyl), 1.03 (t, $-CH_2CH_3$), and 0.63 ppm (C-10 methyl); total yield of **25a** and **26a**, 59%.

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11; O, 13.95. Found: C, 75.74; H, 10.08; O, 14.18.

Rechromatography of the mixture did not provide pure **26a**, although glpc indicated the presence of **25a**, **26a**, and a third component in small amount. This substance had a retention time on an SE-30 column very close to that of **25a**, and its peak was masked in the presence of a large amount of the latter.

A small sample of pure **26a** was obtained in one run which utilized methyl levopimarate from 10 g of levopimaric acid. The initial chromatogram over 300 g of Alcoa F-20 alumina resulted in separation of 2.2 g of forerun, 2.8 g of mixture, and 2.1 g of **25a**. The mixture was rechromatographed over 300 g of alumina. Hexane and benzene–hexane (1:19, 1:9, 1:6, 1:4, 2:3, 3:2) eluted nothing. Benzene–hexane (4:1) eluted 0.4 g of **26a**: nmr 5.40 (broad H-14), 4.07 (t, 6 H, $-OCH_2CH_2CH_2CH_3$), 3.58 (methoxyl), 1.12 (C-4 methyl), 1.00 (d, 6.5 H, isopropyl), 0.80 (d, 7 H, C-16 methyl), 0.60 ppm (C-10 methyl). The triplet of $-CH_2CH_3$ was masked.

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11; O, 13.95. Found: C, 75.69; H, 10.01; O, 14.08.

In subsequent runs the crude reaction mixture from 50 g of levopimaric acid was hydrolyzed with sodium hydroxide, and the free acids were crystallized from acetonitrile–carbon tetrachloride. This furnished 25 g of pure **25c** (*vide infra*). The mother liquors were concentrated, and the residue was methylated with diazomethane. Elution from 1 kg of Merck acid-washed alumina with hexane–ether (19:1, 9:1) yielded 10.5 g of high R_f material. Elution with hexane–ether gave 3.5 g of **26d**: nmr 5.42 (broad H-14), 3.66 and 3.62 (methoxyls), 1.12 (C-4 methyl, shifted to 1.27 ppm in benzene), 1.03 (d, 6.5 H, isopropyl, resolved into two doublets at 1.0 and 0.98 ppm in benzene), 0.75 (d, 7 H, C-16 methyl), and 0.60 ppm (C-10 methyl).

Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68; O, 15.36. Found: C, 74.78; H, 9.78; O, 15.11.

Elution with hexane–ether (17:3) gave 6 g of a mixture of **25d** and **26d**. Continued elution with hexane–ether (17:3, 2:3, 1:4) and ether gave 6.5 g of **25d**: ν_{max}^{film} 1730 and 1648 (weak) cm^{-1}; nmr 5.27 (broad H-14), 3.60 and 3.57 (methoxyls), 1.13 (C-4 methyl), 1.07 (C-16 methyl), 1.03 (d, 6.5 H, isopropyl), and 0.63 ppm (C-10 methyl).

Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68; O, 15.36. Found: C, 74.72; H, 9.92; O, 15.05.

Hydrolysis of 5.6 g of **25a** with 100 ml of ethanol and 10 ml of water containing 10 g of sodium hydroxide for 18 hr, dilution with water, ether extraction, and acidification gave after the usual work-up and crystallization of the solid residue from acetonitrile–carbon tetrachloride 4.7 g of **25c**: mp 217–220° dec; $\nu_{max}^{CCl_4}$ 1690 cm^{-1}; nmr 5.33 (broad, H-14), 1.12 (C-4 methyl), 1.02 (d, 6.5, H isopropyl), 1.07 (C-16 methyl), and 0.62 ppm (C-10 methyl). The analysis was unsatisfactory owing to solvent retention.

Hydrolysis of **26a** in the same manner gave **26c**: mp 286–289°; nmr 5.51 (broad, H-14), 1.12 (C-4 methyl), 1.03 (6.5 H, isopropyl), 0.81 (d, 6.5 H, C-16 methyl), and 0.61 ppm (C-10 methyl).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.35; O, 16.47. Found: C, 73.97; H, 9.27; O, 16.65.

Lithium Aluminum Hydride Reductions of 25a, 25d, 26a, and 26d.—A mixture of 0.2 g of **25a** and 0.1 g of lithium aluminum hydride in anhydrous ether was refluxed for 2.5 hr. The product **25b**, isolated in the usual way, crystallized from methanol as colorless prisms or from acetone as colorless needles: mp 187–188°; ν_{max} 3300, 1060, 1020 (–OH), and 840 cm^{-1} (olefin); nmr (acetone-d_6) 5.20 (broad, H-14), 1.05 (C-16 methyl), 1.00 (d, 6.5 H, isopropyl), 0.67 (C-14 methyl), and 0.62 (C-10 methyl); (pyridine-d_6) 5.29, 3.29 (2 H, AB quartet, J = 11 cps, C-4 CH_2OH), 3.2–4.0 (m, 2 H, C-15, CH_2OH), 1.27 1.04 (d), 0.87, and 0.69 ppm. The same substance was obtained by reduction of **25c** and **25d**.

Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.39; H, 11.12.

Lithium aluminum hydride reduction of **26a** gave an essentially quantitative yield of **26b** which was recrystallized from ethyl acetate and then melted at 162–163°: nmr (acetone-d_6–DMSO-d_6) 5.43 (broad, H-14), 4.0 (m, C-4 $-CH_2OH$), 3.8–2.9 (m, C-15 $-CH_2OH$), 1.03 (d, 6.5 H, isopropyl), 0.80 (d, 6.5 H, C-16 methyl), 0.67 (C-14 methyl), and 0.63 ppm (C-10 methyl). The same substance was obtained by reduction of **26d**.

Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18; O, 8.88. Found: C, 80.00; H, 11.12; O, 9.23.

Oxidative Lactonization of 25c.—A solution of 2.92 g of $KMnO_4$ in 50 ml of water was added as rapidly as possible to a vigorously stirred solution of 13.0 g of **25c** in 1000 ml of aqueous sodium hydroxide. Dilute sulfuric acid was also added dropwise such that the pH was maintained as close to 9 as possible. When the pH remained constant (after about 30 min), excess hydroxylamine hydrochloride was added to decompose the precipitated manganese dioxide. Acidification and work-up in the usual manner gave 14 g of a glass which was stirred with carbon tetrachloride. This resulted in separation of 5 g of the acid lactone **28a** as a solid. The soluble material was essentially pure **25c** (tlc and ir spectrum). Recrystallization of **28a** from ethanol furnished crystalline material: mp 280–285° dec; ν_{max} 1730 cm^{-1} (broad).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56. Found: C, 74.71; H, 8.91; O, 16.55.

The acid lactone was suspended in ether and converted into the methyl ester **28b** by treatment with an ethereal solution of diazomethane. After two crystallizations from ethanol, the product had mp 190–191°; $\nu_{max}^{CCl_4}$ 1783, 1730, and 1670 cm^{-1}; nmr 4.95 (broad, H-14), 3.65 (methoxyl), 1.77, 1.71 (two vinyl methyls), 1.13 (C-4 methyl), 1.10 (d, 6.5 H, C-16 methyl), and 0.71 ppm (C-10 methyl).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06; O, 15.98. Found: C, 75.07; H, 9.11; O, 15.90.

Ozonolysis of 28b.—A solution of 0.27 g of **28b** in 20 ml of chloroform was ozonized at 0–5° for 13 min. Potassium iodide solution was added, and the mixture was stirred overnight. The chloroform layer was separated, washed with saturated sodium chloride solution, dried, and evaporated. The residue of **29**, 0.26 g, was recrystallized twice from ethanol: mp 225–226°; $[\alpha]_D$ +33.6° (c 0.654, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1797, 1745, and 1723 cm^{-1}; nmr 4.27 (H-14, 3.67 (methoxyl), 1.26 (d, 7 H, C-16 methyl), 1.17 (C-4 methyl), and 0.77 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08; O, 21.36. Found: C, 70.88; H, 8.18; O, 21.20.

1-Carboxy-8-carboxymethyl-2,5a,8-trimethyl-1H-3,10a-dodecahydroethanophenanthren-12-one (30a).—A solution of 1.46 g of the preceding compound in 20 ml of tetrahydrofuran was deaerated with argon, and excess 1 *M* chromous chloride in aqueous 1 *N* HCl was added dropwise. The solution was stirred for 12 hr, and the organic solvent was removed at room temperature *in vacuo*. The residue was partitioned between water and ether, and the aqueous layer was again thoroughly extracted with ether. The combined ether layers were washed with water and extracted twice with 2 *N* sodium hydroxide solution. The combined basic extracts were acidified and worked up in the usual manner to give 1.4 g of **30a**. Two recrystallizations from ethanol gave crystals: mp 275–285° dec; ν_{max} 3160 (broad), 1725, 1695 cm^{-1}; nmr 3.67 (methoxyl), 1.14 (C-4 methyl), 1.11 (d, 6.5, H, C-16 methyl), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.25. Found: C, 69.60; H, 8.57; O, 21.54.

Methylation of 0.6 g of **30a** with ethereal diazomethane furnished 0.53 g of the diethyl ester **30b** which was recrystallized from methanol: mp 183–184°; $\nu_{max}^{CCl_4}$ 1730 cm^{-1}; nmr 3.70 (two methoxyls), 1.14 (C-4 methyl), 1.10 (d, 6.5 H, C-16 methyl), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.49. Found: C, 70.33; H, 8.85; O, 20.68.

Reduction of 30b.—To a solution of 0.43 g of the preceding ester in 20 ml of anhydrous ether was added, with stirring, 0.48 g of sodium borohydride. After stirring at room temperature for a period of 4 hr, the mixture was poured into ice–water, and the precipitated salts were dissolved by adding 1 *N* hydrochloric acid. The solution was extracted with ether. The ether was washed, dried, and evaporated, and the solid residue, 0.45 g, was separated by preparative tlc (ether–hexane, 7:10) into 0.18 g of a more polar component and 0.25 g of a less polar component. Both were recrystallized from ethyl acetate–hexane. The more polar material was **32**: mp 225–226°; $\nu_{max}^{CCl_4}$ 3500 and 1730 cm^{-1};

nmr 3.7 (m, H-13), 3.68 (two methoxyls), 1.16 (C-4 methyl), 1.03 (d, 6.5 H, C-16 methyl), and 0.95 ppm (C-10 methyl).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24; O, 20.38. Found: C, 70.15; H, 9.24; O, 20.37.

The less polar compound (**31**) had mp 172–173°; $\nu_{max}^{CCl_4}$ 3500 and 1730 cm^{-1}; nmr 4.1 (m, H-13), 3.68 and 3.66 (two methoxyls), 1.16 (C-4 methyl), 1.11 (C-10 methyl), and 1.05 (d, 6.5 H, C-16 methyl).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24; O, 20.38. Found: C, 70.25; H, 9.30; O, 20.34.

Oxidative Decarboxylation of 30a. A.—A stirred solution of 0.1 g of **30a** and 0.13 g of lead tetraacetate in 10 ml of dry benzene was refluxed in a slow stream of nitrogen. The exit gas was bubbled through calcium hydroxide solution. When carbon dioxide evolution had ceased (*ca.* 4 hr), the mixture was refluxed for an additional 30 min, cooled, and filtered, and the precipitate was washed with benzene. The combined filtrate and washings were washed with 1 *N* sodium hydroxide solution, water, and brine, dried over magnesium sulfate, and concentrated. The residue, 80 mg, was subjected to preparative tlc (ether–hexane, 1:1). The fastest moving zone contained 17 mg of **34** (*vide infra*), the next 46 mg of **33**, the slowest 18 mg of unidentified material. The sodium hydroxide washings yielded 17 mg of starting material. The main product, **33**, was recrystallized from ethanol: mp 160°; nmr 4.33 (d broad, 4 H, H-15), 3.62 (methoxyl), 2.01 (acetate), 1.20 (d, 6 H, C-16 methyl), 1.15 (C-4 methyl), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.48. Found: C, 70.58; H, 8.85; O, 20.35.

B.—A suspension of 0.1 g of anhydrous cupric acetate in 90 ml of dry benzene (distilled from calcium hydride and then from lead tetraacetate) was stirred overnight at room temperature in 1 atm of dry nitrogen. Lead tetraacetate, 1.3 g, and 1 g of **30a** was added, and the mixture was stirred and heated to 80° while a slow stream of dry nitrogen was passed through the flask to sweep carbon dioxide into a solution of calcium hydroxide. When carbon dioxide evolution ceased after *ca.* 14 hr, the mixture was cooled to room temperature. Stirring was continued overnight, the precipitated lead acetate was filtered, and the filtrate was washed with water, 1 *N* sodium hydroxide solution, water, and brine. After being dried over magnesium sulfate, the benzene solution was evaporated. Preparative tlc of the residue, 0.81 g, using ether–hexane (3:2) gave, in order of increasing R_f, 0.007 g of a mixture of **29** and an unidentified substance, 0.028 g of **29**, 0.022 g of **33**, and 0.64 g of **34** (79%). Acidification of the sodium hydroxide washings resulted in recovery of 0.080 g of starting material. Recrystallization of **34** from methanol gave material which had mp 97–98°; ν_{max} 3010 and 1725 cm^{-1}; nmr 5.80 (t, broad, 1.8 H, H-15), 3.67 (methoxyl), 1.75 (d, 1.8 H, C-16 methyl), 1.15 (C-4 methyl), and 1.08 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 14.53. Found: C, 76.41; H, 9.23; O, 14.58.

Reduction of 34.—To a solution of 0.680 g of **34** in 15 ml of anhydrous ether was added with stirring 0.765 g of lithium tri-*t*-butoxyaluminum hydride. The mixture was stirred for 6 hr and poured into ice–water. Ether (20 ml) was added, and then dilute hydrochloric acid was added to dissolve the inorganic precipitate. The ether layer was separated, washed, dried, and concentrated. Purification of the residue, 0.705 g, by preparative tlc gave 0.4 g of pure **35** and 0.3 g of a mixture of **35** and **36**. Rechromatography of the latter gave an additional 0.17 g of **35** and 0.12 g (17%) of **36**; total weight of **35** was 0.57 g (83%). The major product was recrystallized from methanol and had mp 172–173°; ν_{max} 3612, 3515 (broad), 3010, and 1730 cm^{-1}; nmr 5.56 (t, broad, H-15), 3.93 (m, H-13), 3.63 (methoxyl), 1.73 (d, 1.6 H, C-16 methyl), 1.17 (C-4 methyl, and 1.15 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.92; H, 9.70; O, 14.62.

The minor product **36** was recrystallized from methanol and had mp 140–141°; ν_{max} 3260 and 1722 cm^{-1}; nmr 5.82 (broad, H-15), 3.78 (m, H-13), 3.62 (methoxyl), 1.77 (d, 1.2 H, C-16 methyl), 1.13 (C-4 methyl), and 0.88 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.63; H, 9.63; O, 14.92.

Methyl 15β-Hydroxy-13,16-cycloatisan-18-oate (Methyl *anti*-15α-Hydroxytrachylobanate, 37).—Methanesulfonyl chloride, 0.3 ml, was added to a solution of 0.2 g of **35** in 3 ml of dry pyridine. The solution was kept at −10° for 56 hr and then poured into ice–water. The hydrolyzed mixture was extracted with ether, and the ether was washed thoroughly with water, dilute sulfuric acid, and water and dried. Removal of ether gave 0.17 g of gum which was purified by preparative tlc (ether–hexane, 1:1) to give 0.02 g of starting material and 0.12 g of **37**. The latter after recrystallization from methanol–water, had mp 104–105°; $\nu_{max}^{CCl_4}$ 3610 and 1730 cm^{-1}; nmr 3.63 (methoxyl), 3.30 (m, singlet on D_2O exchange, H-15), 1.21 (C-16 methyl), 1.15 (C-4 methyl), and 0.99 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.66; H, 9.75; O, 14.64.

Methyl 15-Keto-13,16-cycloatisan-18-oate (Methyl *anti*-15-Ketotrachylobanate, 38).—To a solution of 70 mg of **37** in 10 ml of anhydrous ether was added 10 ml of Jones reagent at room temperature. The solution was stirred for 1 hr and diluted with 50 ml of ether. The ether layer was separated, washed with water, bicarbonate solution, and water, and evaporated. The residue of **38**, 60 mg, was recrystallized from aqueous methanol and had mp 146–147°; $\nu_{max}^{CCl_4}$ 1728 cm^{-1}; λ_{max} 211 and 285 nm (ε 2620 and 72); nmr 3.59 (methoxyl), 1.21 (C-16 methyl), 1.15 (C-4 methyl), and 1.08 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.17; H, 9.32; O, 14.41. Found: C, 76.32; H, 9.15; O, 14.53.

Methyl 13,16-Cycloatisan-18-oate (Methyl *anti*-Trachylobanate, 2c). A.—A solution of 35 mg of **38** in 1 ml of 1,2-ethanedithiol and 0.3 ml of BF_3–etherate was stirred at room temperature for 3 hr, poured into water, and extracted with ether. The ether layer was washed, dried, and evaporated to yield gummy thioketal: 30 mg; $\nu_{max}^{CCl_4}$ 1725 cm^{-1}; nmr (CCl_4) 3.20 (4 H, S–CH_2–CH_2–S), 1.19 (C-16 methyl), 1.15 (C-4 methyl), and 1.02 ppm (C-10 methyl). The product was dissolved in 20 ml of ethanol and refluxed with 200 mg of Raney nickel for 12 hr, filtered, and concentrated *in vacuo*. The residue, 20 mg, was recrystallized from methanol to give needles: mp 109–111° (lit.[4] mp 110–112°); $[\alpha]^{25}D$ +46° (*c* 0.29, $CHCl_3$) (lit.[4] $[\alpha]D$ −41°); $\nu_{max}^{CCl_4}$ 1727 and 1242 cm^{-1}; nmr 3.59 (methoxyl), 1.13, 1.08, and 0.97 ppm (three methyl singlets). Ir and nmr spectra were identical with those of authentic methyl trachylobanate as were the glpc retention times on several columns.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.71; H, 10.00; O, 10.17. Found: C, 79.70; H, 10.19; O, 10.11.

B.—A solution of 100 mg of **35** in 2 ml of anhydrous pyridine was purged with dry nitrogen and cooled to −10°. Methanesulfonyl chloride (29.5 μl) was slowly added. The mixture was kept in the refrigerator for 24 hr and filtered in a nitrogen atmosphere. An excess of sodium borohydride was added to the filtrate with vigorous stirring. After 30 min at room temperature, 0.5 ml of water was added; stirring was continued for 30 min, and dilute hydrochloric acid was added to decompose the excess hydride. Work-up in the usual way and separation by preparative tlc gave 7 mg of methyl *anti*-trachylobanate, mp 105–110°, after sublimation, 60 mg of starting material, and 10 mg of unidentified substances.

C.—To a solution of 11.4 mg of sodium borohydride in 2 ml of diglyme was added dropwise 100 mg of **35** in 1.26 g of BF_3 etherate at 0° under nitrogen. The solution was stirred at room temperature for 12 hr, poured into ice–water, and extracted with ether. The ether extract was worked up in the usual way, and the crude product, 90 mg, was purified by preparative tlc (ether–hexane, 4:6). The top fraction, 40 mg, was slightly impure methyl *anti*-trachylobanate.

Registry No.—**2c**, 17458-33-2; **5b**, 17458-34-3; **6**, 17458-35-4; **7**, 17458-36-5; **8**, 17458-37-6; **9**, 17458-38-7; **10**, 17458-39-8; **11**, 17458-40-1; **12**, 17458-41-2; **13**, 17458-42-3; **15**, 17458-43-4; **16a**, 17458-44-5; **16b**, 17458-45-6; **17**, 17458-46-7; **19**, 17481-30-0; **21**, 17458-47-8; **22**, 17447-76-6; **23**, 17447-77-7; **23** (2,4-dinitrophenylhydrazine derivative), 17447-78-8; **23** (ethylene ketal), 17447-56-2; **24b**, 17447-79-9; **25a**, 17447-80-2; **25b**, 17447-81-3; **25c**, 17458-48-9; **25d**, 17458-49-0; **26a**, 17458-50-3; **26b**, 17458-51-4; **26c**, 17458-20-7; **26d**, 17458-21-8; **28a**, 17458-22-9; **28b**, 17458-23-0; **29**, 17458-24-1; **30a**, 17481-31-1; **30b**, 17481-32-2; **31**, 17458-25-2; **32**, 17458-26-3; **33**, 17458-27-4; **34**, 17458-28-5; **35**, 17458-29-6; **36**, 17458-30-9; **37**, 17458-31-0; **38**, 17458-32-1.

Alicyclic Carbohydrates. XXXV. The Synthesis of *proto*-Quercitol. 220-MHz Proton Spectrum with the Superconducting Solenoid[1-3]

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The synthesis of (−)-*proto*-quercitol, a deoxyinositol (cyclohexanepentol) stereoisomer, discovered in the leaves of *Eucalyptus populnea* in 1961, is reported. Synthesis was effected by indirect removal of the position 2 hydroxyl group of (−)-inositol. Identical procedures applied to (+)-inositol would produce the well-known (+)-*proto*-quercitol, discovered in 1849 in acorns but never synthesized. Essentially identical procedures applied to DL-inositol would constitute a total synthesis of DL-*proto*-quercitol. The (−)-inositol 3,4,5,6-tetramethyl ether was converted into its 2-tosylate, which on methylation and detosylation gave the hexol pentamethyl ether. Oxidation of the latter produced (−)-*proto*-inosose pentamethyl ether, which on reaction with 1,2-ethanedithiol, and subsequent reduction, gave a pentol pentamethyl ether. This ether on cleavage gave the desired (−)-*proto*-quercitol, whose identity was confirmed by comparisons with authentic samples of the dextrorotatory form. Racemic *proto*-quercitol was prepared by mixing the two enantiomers. To verify the diastereomeric configuration (134/25) previously assigned by chemical correlations, the proton magnetic resonance spectrum of (+)-*proto*-quercitol was recorded at 220 MHz (51.7 kG), using a superconducting solenoid spectrometer. At this high resolution, configurational interpretation was greatly facilitated.

In 1849, Braconnot[6] isolated from the acorns of an oak tree (genus *Quercus*) a colorless, crystalline compound, $C_6H_{12}O_5$, which was named quercitol. Although the cyclohexanepentol structure, **24**, of this compound was established[7] in 1885, and its configuration, **20**, in 1932,[8] no synthesis has been reported.

Since some authors have used "quercitol" as a generic name[9,10] for the ten diastereomeric deoxyinositols (cyclohexanepentols), the more explicit name, *proto*-quercitol, has recently come into use for the diastereomer **20** (or **22**). The *proto*-quercitol first discovered was dextrorotatory; in 1961, the levorotatory form, **22**, was discovered by Plouvier[11] in leaves of the tree *Eucalyptus populnea* F. Muell.

The ten quercitols constitute possibly the largest all known family of diastereomers in organic chemistry, making them interesting candidates for systematic chemical and physical studies.[12-14] Although the *proto* diastereomer was the first discovered, it was the last synthesized. The long delay in synthesis may be attributed to the fact previously suggested,[12] "... nearly every synthetic scheme used for other cyclitols would lead stereospecifically to the 'wrong' product."

In 1965, Angyal, Gorin, and Pitman[9] did carry out an epimerization of natural (−)-*vibo*-quercitol (**25**) by heating it for a long time with 95% acetic acid (containing a little sulfuric acid). The resulting equilibrium mixture was shown by vapor phase chromatography to contain acetylated *proto*-quercitol, but none was actually isolated.[9]

The procedures here described[14] are for the synthesis of (−)-*proto*-quercitol from (−)-inositol. The identical procedures applied to (+)-inositol would produce the better known (+)-*proto*-quercitol (often called "*proto*-quercitol," or simply, "quercitol") derived from acorns. Essentially identical procedures[15] applied to DL-inositol would constitute a total synthesis of DL-*proto*-quercitol. Several total syntheses[16,17] of DL-inositol, *via* the intermediates quinonetetrol **26**,[9] *myo*-inositol,[16] or 3,5-cyclohexadiene-1,2-diol (**27**),[17] have previously been reported. Synthesis of (−)- or (+)-*proto*-quercitol by the route now described will not be "total" until the resolution[18] of DL-inositol (or DL-*proto*-quercitol) has been accomplished.

(1) For preliminary communication, see G. E. McCasland, M. O. Naumann, and L. J. Durham, *Carbohyd. Res.*, **4**, 516 (1967).

(2) For papers XXXIII and XXXIV in this series, see (a) G. E. McCasland, S. Furuta, and L. J. Durham, *J. Org. Chem.*, **33**, 2841 (1968); (b) G. E. McCasland, M. O. Naumann, and S. Furuta, in "Deoxy Sugars," S. Hanessian, Ed., Advances in Chemistry Series No. 74, American Chemical Society, Washington, D. C., 1968, pp 41–55.

(3) Presented in part by G. E. McCasland to the Division of Carbohydrate Chemistry at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(4) (a) To whom any correspondence should be addressed at the University of San Francisco; (b) Postdoctoral Fellow of the U. S. Public Health Service at the University of San Francisco, 1965–1967, fellowship no. 5-F2-CA-31-318.

(5) Stanford University.

(6) H. Braconnot, *Ann. Chim. Phys.*, (3) **27**, 392 (1849). Braconnot at first thought he had isolated lactose. Quercitol was recognized as a new compound by V. Dessaignes, *Compt. Rend.*, **33**, 308 (1851). For a recent discussion of the biosynthesis of quercitol in *Quercus* species, see H. Kindl, R. Scholda, and O. Hofmann-Ostenhof, *Phytochemistry*, **6**, 237 (1967).

(7) J. Kanonnikov, *J. Prakt. Chem.*, **140**, 497 (1885).

(8) T. Posternak, *Helv. Chim. Acta*, (a) **15**, 948 (1932); (b) **24**, 1045 (1941).

(9) (a) S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 3682 (1957); (b) S. J. Angyal and C. G. MacDonald, *ibid.*, 686 (1952); (c) S. J. Angyal, P. A. J. Gorin, and M. Pitman, *ibid.*, 1807 (1965); (d) S. J. Angyal, personal communication, June 1966.

(10) In 1952, Angyal and MacDonald (ref 9) proposed that *quercitol* be adopted as a generic name for the ten diastereomeric deoxyinositols (cyclohexanepentols), and that the configurations be specified by the ten prefixes: *allo, cis, epi, gala, muco, neo, proto, scyllo, talo,* and *vibo*. We use some of these prefixes here to facilitate comparisons with previous literature, but prefer systematic fractional notation.

(11) V. Plouvier, *Compt. Rend.*, **253**, 3047 (1961). Plouvier called his new stereoisomer "L-quercitol;" although levorotatory, it actually has the D(134/25) configuration (see formulas in Chart I).

(12) For reviews on the chemistry of quercitols, see (a) T. Posternak, "Cyclitols," Holden-Day, Inc., San Francisco, Calif., 1965, Chapter IV; (b) T. Posternak, ref 12a, p 106; (c) G. E. McCasland, *Advan. Carbohyd. Chem.*, **20**, 11 (1965); (d) G. E. McCasland, *ibid.*, **20**, 21 (1965).

(13) For a review of the most recent work, see ref 2b.

(14) For previous work by us on quercitols, see (a) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953); (b) G. E. McCasland, S. Furuta, J. N. Shoolery, and L. F. Johnson, *ibid.*, **83**, 2335 (1961); (c) G. E. McCasland, S. Furuta, J. N. Shoolery, and L. F. Johnson, *ibid.*, **83**, 4243 (1961); (d) G. E. McCasland, S. Furuta, and V. Bartuska, *J. Org. Chem.*, **28**, 2096 (1963); (e) G. E. McCasland, S. Furuta, and A. Furst, *ibid.*, **29**, 724 (1964).

(15) It is possible that some of the racemic intermediates would have different solubilities than the corresponding active intermediates, and thus require different volumes of crystallizing solvents for best results.

(16) (a) H. Müller, *J. Chem. Soc.*, **101**, 2383 (1912); (b) H. G. Fletcher and G. R. Findlay, *J. Amer. Chem. Soc.*, **70**, 4050 (1948); (c) for the first synthesis of *myo*-inositol (used to make DL), see H. Wieland and R. S. Wishart, *Ber.*, **47**, 2082 (1914).

(17) M. Nakajima, I. Tomida, N. Kurihara, and S. Takei, *Chem. Ber.*, **92**, 173 (1959).

(18) See G. Tanret, *Bull. Soc. Chim.*, **17**, 921 (1897), for a possible microbiological resolution.

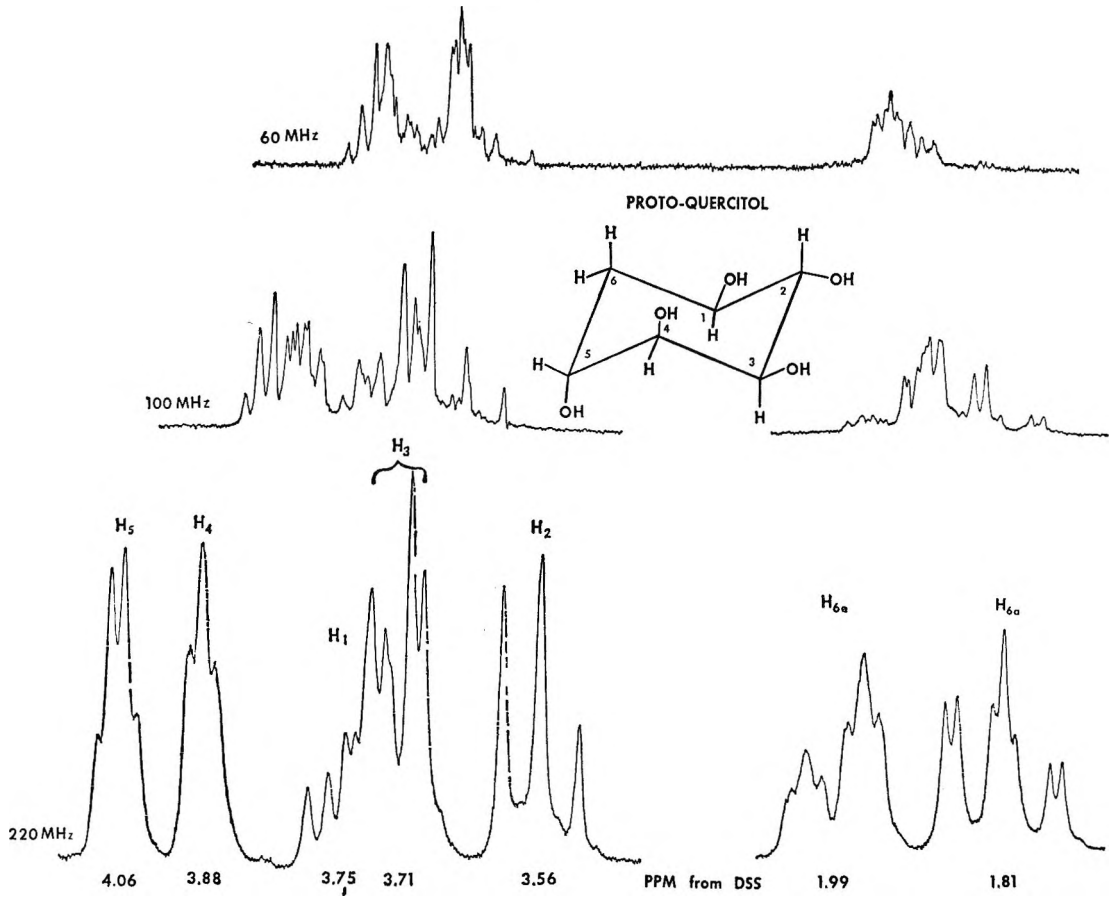


Figure 1.—Pmr spectra at 60, 100, and 220 MHz (14.1, 23.5, and 51.7 kG) of (+)-*proto*-quercitol in deuterium oxide.

Verification of Configuration by 220-MHz Pmr Spectroscopy.—Before starting our synthesis, it seemed desirable to verify the configuration **20**, of (+)-*proto*-quercitol, based on chemical correlations by Posternak.[8]

Early efforts to use proton magnetic resonance spectroscopy (pmr) to establish quercitol diastereomeric configurations were unsuccessful, with two exceptions,[14] because of complex spin–spin coupling and overlapping of the patterns at 60 MHz, and even at 100 MHz (see Figure 1).

However, when the pmr spectrum of (+)-*proto*-quercitol in deuterium oxide was observed at 220 MHz (51.7 kG), using the new superconducting solenoid spectrometer of Nelson and Weaver,[19] the patterns for individual ring protons were nearly all well separated, and configurational interpretation was greatly facilitated (see Figure 1).

The axial methylene proton H-6a (1.81 ppm) shows splittings (large, large, small) due to coupling with three protons (geminal, axial, and equatorial). (See formula in the figure). The equatorial proton H-6e similarly shows couplings (large, small, small) with the geminal and neighboring protons. The coupling constants of the axial proton H-2 triplet (3.56 ppm) indicate that the neighboring protons H-1 and H-3 also are axial. The narrowness of the patterns for H-4 and H-5 indicates that these two protons are equatorial.

The axial proton H-1 signal (3.75 ppm) is not so well separated but appears to consist of an eight-line pattern partially superposed on the axial H-3 signal (3.71 ppm), which is a pair of doublets.

The coupling constants observed for *proto*-quercitol were $J_{12} = 9.0$; $J_{23} = 9.0$; $J_{34} = 3.0$; $J_{45} = 3.1$; $J_{56e} = 3.1$; $J_{56a} = 2.9$; $J_{6a6e} = 13.8$; $J_{16e} = 5.0$; $J_{16a} = 11.5$ Hz.

These results are consistent only with the diastereomeric configuration (134/25) and the favored conformation (eeeaa) shown in the formula in Figure 1.[20] The 220-MHz pmr spectrum thus serves to confirm Posternak's configurational assignment, which was based on laborious chemical correlations.[8] These correlations involved oxidations of (+)-*proto*-quercitol to 4-deoxy-L-glucaric acid and *meso*-galactaric acid. Since the absolute configuration of L-glucaric acid is now known from X-ray studies on related compounds, Posternak's correlations serve also to establish the *absolute* L (134/25) configuration, **20**, for (+)-*proto*-quercitol.[21] This absolute assignment is confirmed by the optical rotation predictions of Whiffen.[22]

The Synthesis of (−)-*proto*-Quercitol.—Among the many possible synthetic approaches to a cyclohexanepentol considered by us were (1) introduction of a fifth hydroxyl group into a saturated or unsaturated

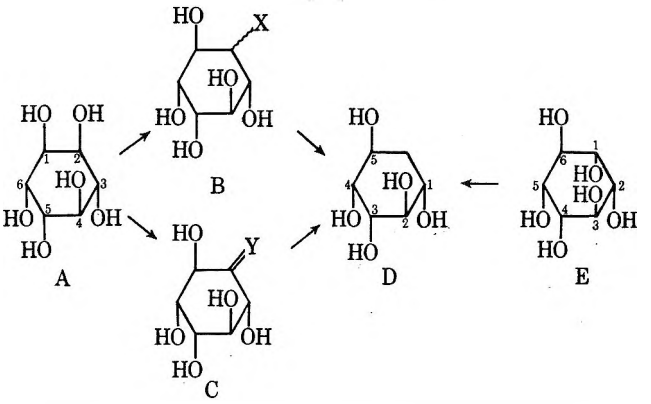
(19) F. A. Nelson and H. E. Weaver, *Science*, **146**, 223 (1964).

(20) We recommend that cyclitol diastereoisomers be designated by a modified Maquenne-type fractional notation, *e.g.*, (134/25). Accepted structural numbering and naming, *e.g.*, "1,2,3,4,5-cyclohexanepentol," is retained wherever feasible. Where accepted structural numbering is equivocal, *e.g.*, for cyclohexanehexol, the direction (*either* clockwise or counterclockwise), and if necessary, the starting point, for numbering are so chosen as to produce the set of numerator numbers with the lowest sum. For example, (−)-inositol is designated (124/356), *not* (235/416) or (356/124).

(21) To specify enantiomers, the *prenumbered* perspective formula, *e.g.*, **22**, is so oriented in three dimensions that numbering will proceed from right to left around the front. If the lowest numbered group is then oriented *down*, the prefix is D; if *up*, it is L. For further discussion, see G. E. McCasland, ref 12, pp 13–15, and further references cited therein.

(22) D. H. Whiffen, *Chem. Ind.* (London), 964 (1956).

tetrol, or suitable derivative and (2) removal of one hydroxyl group from a hexol (inositol), or suitable derivative. The latter approach seemed more promising, and the starting material thus might be either (−)-inositol A or *muco*-inositol E. The former inositol



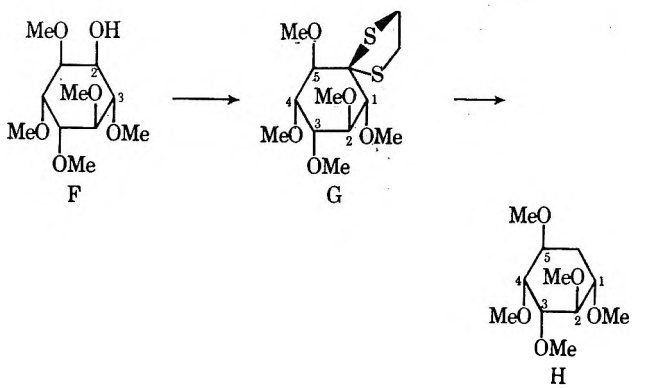
had the advantage of being optically active and readily available.

Since direct replacement of hydroxyl by hydrogen is not usually feasible, it was necessary to replace the position 2 hydroxyl group[23] in (−)-inositol A by some group easily removed by reduction. Suitable univalent groups would be chloro, bromo, iodo, or mercapto.[24] Suitable bivalent groups would be 2-keto, 2,2-di(alkylthio), 1,2-epoxy, or 2,3-epoxy.

Because the position 2 hydroxyl group in (−)-inositol is equatorial, there was little hope that it could be selectively displaced or oxidized so long as other, free hydroxyl groups were present in the molecule. Difficulties were also encountered in the preparation of a 1,2- or 2,3-epoxy derivative.

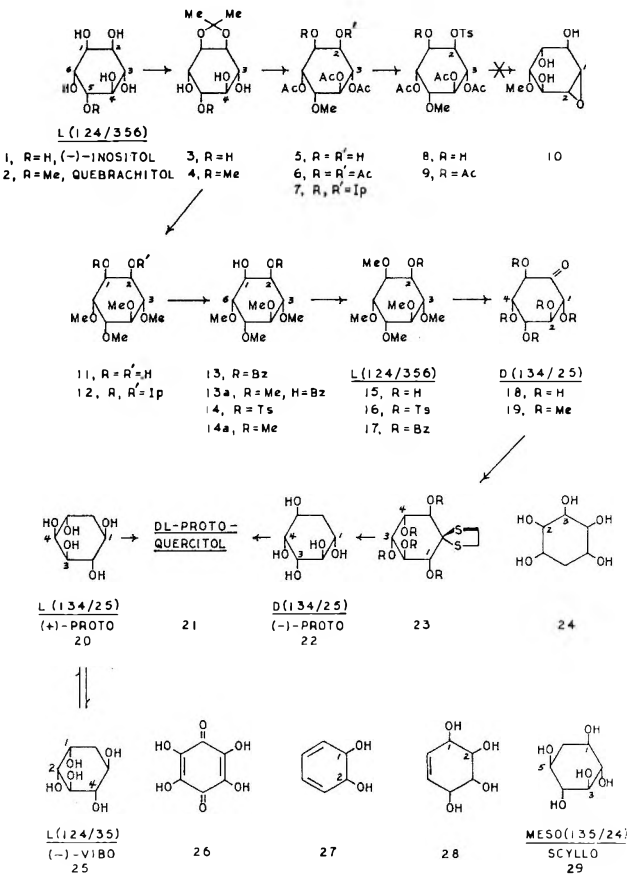
It was thus necessary to place protective groups on the remaining five hydroxyl groups before attempting to alter the group at position 2. Methyl ether groups were found best for this purpose. Although methyl protective groups are rarely used in syntheses of true sugars because of difficulty in removal, cyclitol methyl ethers are readily cleaved in high yield to the corresponding free cyclitols.

Attempted substitution by halogen of the free hydroxyl group in the pentamethyl ether F led to unexpected complications (see below); however, oxidation to carbonyl was readily accomplished. Attempts to reduce the ketone were unsuccessful, but its mercaptal derivative G on reduction did give the pentamethyl ether H of the desired cyclohexanepentol final product.



The synthetic steps may now be considered in greater detail. Direct conversion of (−)-inositol, **1** (see Chart I), into its pentamethyl ether, **15**, would scarcely be

Chart I



feasible. However, the previously reported[9] 1,2-O-isopropylidene derivative, **3**, was successfully converted into its tetramethyl ether, **12**, by reaction with methyl iodide in the presence of silver oxide. The ketal tetramethyl ether, obtained only as a syrup, was converted by mild acid hydrolysis into the hexol 3,4,5,-6-tetramethyl ether **11**, mp 92°. This tetramethyl ether was somewhat more conveniently obtained by methylation and subsequent deacetonation of the ketal monomethyl ether, **4**, a derivative of the well-known (−)-quebrachitol (**2**), derived from rubber latex.[25]

To methylate the axial (position 1) hydroxyl group in the tetramethyl ether **11**, we first had to protect the equatorial (position 2) hydroxyl group, which probably

(23) It should be noted that although (−)-inositol (formula 1) is dissymmetric, the molecule in its favored chair conformation does have a proper rotation axis of order 2 (symmetry C_2). For this reason, the 1-, 2-, and 4-monomethyl ethers are *identical* with the 6-, 5-, and 3-monomethyl ethers, respectively. Similar relationships apply to many other derivatives of (−)- or (+)-inositol. In this article, to avoid confusion, we have uniformly assigned the number 2 (not 5) to the ring position in (−)-inositol derivatives which was transformed into methylene in the final steps of our synthesis of *proto*-quercitol.

(24) For examples of preparations of various quercitols from the corresponding 6-chloro, 6-bromo, 6-iodo, or 6-mercapto derivatives, or from 1,2-anhydroinositols, see ref 12.

(25) The quebrachitol used was isolated from rubber latex and provided by the Plantation Division, U. S. Rubber Co. The preparation of highly pure (−)-quebrachitol and (−)-inositol (standard reference materials) is discussed by A. J. Fatiadi in National Bureau of Standards Technical Note 427, U. S. Government Printing Office, Washington, D. C., Oct 1967.

would be more reactive.[26,27] The needed equatorial monobenzoate, **13**, was readily obtained, but on attempted methylation, a (2 → 1) acyl migration occurred, so that the principal product was the 2,3,4,5,6-pentamethyl 1-benzoate (**13a**), and only a low yield of the desired 1,3,4,5,6-pentamethyl 2-benzoate, **17**, was obtained. The preparation and reactions of the "migrated" and nonmigrated benzoates provided some interesting and surprising results, which will be described in a subsequent article.[28]

Since sulfonate esters are not ordinarily subject to acyl migration, we next prepared the equatorial 2-*p*-toluenesulfonate tetramethyl ether **14**, mp 116°.[29] This derivative was successfully methylated to the corresponding pentamethyl ether, **16**, obtained only as a syrup; detosylation with sodium methoxide in ethanol gave the desired hexol 1,3,4,5,6-pentamethyl ether **15**. This ether has also been obtained only as a syrup; however, it was characterized by conversion into the crystalline pentamethyl monobenzoate **17**, mp 90°.

Reduction to methylene of the tosyloxy function (-CHOTs-) in the pentamethyl tosylate **16**, either directly or *via* a halogen substitution product, would have provided a short-cut to *proto*-quercitol pentamethyl ether, but unfortunately could not be accomplished. The substitution or reduction to methylene of alicyclic secondary tosyloxy groups is often difficult.

The hexol pentamethyl ether **15** on treatment with the new oxidant[30] ruthenium dioxide–sodium metaperiodate gave the desired *proto*-inosose pentamethyl ether **19** in the form of a syrup, which was characterized by conversion into the crystalline 2,4-dinitrophenylhydrazone, mp 203°. In some preparations, another convenient new oxidant,[31] dimethyl sulfoxide–acetic anhydride, was used (see Experimental Section), but the yield and purity of the product were not quite so good.

We now wished to convert the *proto*-inosose pentamethyl ether, **19**, into the (as yet unknown) free *proto*-inosose **18**. The latter, in all probability, would give a good yield of *proto*-quercitol when hydrogenated with a platinum catalyst in the presence of strong acid.[9] Unfortunately, all attempts to cleave the inosose pentamethyl ether with hydrohalic acids, or with boron trichloride,[29] were unsuccessful.[32] The unavailability of the *proto* isomer of inosose is one reason that the synthesis of *proto*-quercitol has never previously been accomplished.

Since the direct reduction of carbonyl to methylene[8] could not be accomplished, we next tried the conversion of the inosose pentamethyl ether, **19**, into a mercaptal derivative, which might more easily be reduced, using various alkanethiols, such as α-toluenethiol and 1,2-ethanedithiol. In no case could a crystalline mercaptal be obtained. However, when the crude syrupy mercaptal, **23**, from the ethanedithiol reaction was reduced with Raney nickel catalyst in boiling ethanol (without use of hydrogen gas), the desired pentol pentamethyl ether was successfully produced. This product, also, was a syrup, but on cleavage with hydrogen bromide in glacial acetic acid, it gave us the long sought crystalline final product, (−)-*proto*-quercitol.

The optical rotation of synthetic (−)-*proto*-quercitol was equal and opposite to that of natural (+)-*proto*-quercitol, and it had the same melting point, solubilities, ir spectrum, and pmr spectrum as an authentic sample of the dextro form. The properties of synthetic (−)-*proto*-quercitol were also in good agreement with those reported by Plouvier[11] for his natural levo form.

Since the dextro pentaacetate reportedly was amorphous, we prepared the pentabenzoate derivative of synthetic (−)-*proto*-quercitol. Its melting point, solubilities, and ir spectrum were identical with those of the dextro form,[33] and its optical rotation was equal and opposite. (Plouvier apparently did not prepare the levo pentabenzoate from his natural pentol.)

By recrystallization of a mixture of equal weights of natural (+)-*proto*-quercitols and synthetic (−)-*proto*-quercitols, we obtained racemic *proto*-quercitol. The only previous preparation of the racemic form was that of Plouvier,[11] who mixed the natural (+) and natural (−) enantiomers. Our racemic product had the expected zero optical rotation, within experimental error. Its melting point and (solid-state) ir spectrum were identical with those of (+)- or (−)-*proto*-quercitol, perhaps indicating that DL-*proto*-quercitol exists as a solid solution (not a racemate or conglomerate). The properties of our racemic form were in agreement with those reported by Plouvier.[11]

The racemic pentabenzoate was also prepared (apparently for the first time) by recrystallizing a mixture of equal weights of the (+)- and (−)-pentabenzoates. The product had the expected zero optical rotation. Its melting point (138–140°) was lower than that of the active form (155°), perhaps indicating that the racemic pentabenzoate exists as a conglomerate or racemate (not a solid solution; compare the properties of the racemic pentol). Although the solid-state ir spectra of the racemic and active pentabanzoates showed no significant differences, it is possible that differences would be apparent at very high resolution.

In an earlier attempt to synthesize (−)-*proto*-quercitol, we treated the hexol 2,3,4,5,6-pentamethyl ether (**14a**, R = Me) with phosphorus pentachloride.[28] The product on demethylation gave a chloropentol, which on dehalogenation surprisingly gave *meso*-scylloquercitol (**29**). Details will be given in a subsequent publication.[28]

(26) After experiments on the preparation of (−)-inositol benzyl ethers, Angyal and Steward [*Aust. J. Chem.*, **19**, 1683 (1966)] suggested that ". . . the reactivity of the axial hydroxyl groups in (−)-inositol is simliar to that of the equatorial hydroxyl groups." However, in our own synthesis now reported it appears that certain (−)-inositol equatorial hydroxyl groups *do* react preferentially at least in the formation of benzoate or *p*-toluenesulfonate esters.

(27) The etherification reaction transition state presumably contains five groups arranged around the halogen-bearing carbon in trigonal-bipyramid orientation (SN2 mechanism). The acylation (at least by benzoyl chloride) transition state presumably contains four groups arranged around the carbonyl carbon in tetrahedral orientation (nucleophilic substitution at an unsaturated carbon atom). *Both* the axial and equatorial forms of the etherification transition state seem to involve moderately strong steric repulsions by the cyclitol axial groups. In acylation, the axial form of the transition state is less hindered, and the equatorial form much less hindered, than in the etherification transition state.

(28) G. E. McCasland, M. O. Naumann, and L. J. Durham, manuscript in preparation.

(29) For an interesting preparation of 1-O-*p*-toluenesulfonyl-(−)-inositol by demethylation of the 1-O-tosyl-5-O-methyl derivative with boron trichloride, see S. D. Gero, *Tetrahedron Lett.*, 591 (1966).

(30) V. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, **43**, 3452 (1965).

(31) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).

(32) However, V. Prey and F. Stadler have reported a successful cleavage of an inosose tetramethyl ether, using hydrogen bromide in acetic acid; see *Ann.*, **660**, 155 (1962).

(33) K. H. Bauer and H. Moll, *Arch. Pharm.*, **280**, 37 (1942).

In still earlier experiments we sought to prepare *proto*-quercitol (dextro, levo, or DL) by a synthetic route involving hydrogenation of the active monomethyl ether, **10**, of 1,2-anhydro-*muco*-inositol. The quebrachitol tosylate tetraacetate **9** was prepared for use in this synthesis (see Experimental Section), but since efforts to convert it into the epoxide **10** were unsuccessful, this approach was abandoned.

Pmr Studies on the Synthetic Intermediates.—Proton magnetic resonance spectra at 60 and 100 MHz were recorded for most of the intermediates prepared, as described in detail in the Experimental Section. The intermediates so studied included (−)-quebrachitol, its 1,2-O-isopropylidene derivative, its 3,4,6-triacetate, its pentaacetate, its 3,4,6-triacetate 2-*p*-toluenesulfonate, and its 1,3,4,6-tetraacetate 2-*p*-toluenesulfonate. Even at 100 MHz, configurational interpretation of the pmr spectra of such cyclitols still is often difficult.

Double resonance and exchange with deuterium oxide were found helpful in the case of the (−)-quebrachitol 3,4,6-triacetate and the 3,4,6-triacetate 2-*p*-toluenesulfonate (see Experimental Section).

The spectra were also recorded for (−)-inositol 3,4,5,6-tetramethyl ether and its 2-*p*-toluenesulfonate, and for (−)-inositol 1,3,4,5,6-pentamethyl ether 2-monobenzoate.

The spectrum of (+)-*proto*-quercitol and its pentabenzoate were recorded at 60 and 100 MHz, and the former also at 220 MHz (see above). The spectrum of (−)-*proto*-quercitol was recorded at 100 MHz.

Experimental Section

All melting points have been corrected and were measured on a Nalge–Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were recorded on Perkin-Elmer Models 421 and 137 spectrometers. Solutions were concentrated at 30–40° under reduced pressure with a rotary evaporator. The petroleum ether used had a 60–80° boiling range.

Proton magnetic resonance spectra at 220 MHz (51.7 kG) were recorded with a Varian Model HRSC-IX or -220 spectrometer, using a superconducting niobium–zirconium solenoid in liquid helium (sample at room temperature in deuterium oxide).

Proton magnetic resonance spectra at 60 and 100 MHz were recorded on a Varian A-60 and a Varian HR-100 spectrometer. Spectra of free pentols were obtained from deuterium oxide solutions containing sodium 2,2-dimethyl-2-silapentanesulfonate (DSS) as internal standard. Unless otherwise noted, all other spectral were taken on chloroform-*d* solutions containing tetramethylsilane (TMS) as the internal reference. All chemical shifts are reported in parts per million relative to TMS (or DSS) taken as zero.

The (−)-quebrachitol **2** used was isolated from the latex of *Hevea Brasiliensis* by the Plantation Division, U. S. Rubber Co.; it was converted into (−)-inositol **1** by reaction with hydriodic acid in the usual manner.[25] The 1,2-O-isopropylidene derivative of (−)-inositol (**3**) and of (−)-quebrachitol (**4**) and the 3,4,6-tri-O-acetyl-1,2-O-isopropylidene (**7**), and 3.4,6-tri-O-acetyl (**5**) derivatives of (−)-quebrachitol were prepared by the procedures of Angyal and coworkers.[9]

Pmr Spectrum of L(124/356) Stereoisomer of 5-Methoxy-1,2,3,4,6-cyclohexanepentol [(−)-Quebrachitol] (2).—The spectrum at 100 MHz using deuterium oxide contained a sharp methoxyl proton singlet at 3.42 ppm. The two equatorial ring protons (H-1, H-6) at 4.03 and 4.23 ppm (not known which is which) each appeared as a pair of doublets, with splittings of about 3.8 and 2.5 Hz. The four axial ring protons produced signals in the region 3.3–3.8 ppm, which could not be interpreted because of overlapping, although some sharp lines were visible. When the frequency was changed to 60 MHz, extra lines appeared in the pair of doublets at 4.03 ppm, presumably due to increased virtual coupling.

Pmr Spectrum of 1,2-O-Isopropylidene-(−)-quebrachitol (4).—The spectrum at 100 MHz using deuterium oxide contained a methoxyl singlet at 3.44 ppm and ketal methyl singlets at 1.39 and 1.52 ppm. Ring proton signals were observed at 3.1–3.8 ppm (3–4 H, several sharp lines), 4.15 ppm (1 H, poorly resolved multiplet), and 4.32 ppm (2 H). The ring proton patterns could not be interpreted because of overlapping.

Pmr Spectrum of (−)-Quebrachitol 3,4,6-Triacetate (5).—The spectrum at 100 MHz using chloroform-*d* contained sharp three-proton singlets for the axial acetate methyl (2.12 ppm), the two equatorial acetate methyls (2.08 and 2.06 ppm), and the equatorial methoxyl methyl (3.38 ppm).

The equatorial AcO–CH ring proton H-6 produced a triplet at 5.48 ppm (spacing 3.5 Hz). The signals due to the axial AcO–CH ring protons H-3 and H-4 at 5.0–5.3 ppm resembled part of an A_2X_2 pattern (unchanged at 60 MHz). The remaining ring protons and the two hydroxyl protons appeared in the region 3.5–4.2 ppm.

The midfield spectrum was simplified by addition of a little deuterium oxide. The equatorial HO–CH proton (H-1) then appeared as a triplet at 4.05 ppm (spacing 3.5 Hz). Signals for the axial HO–CH proton (H-2) and and the axial MeO–CH proton (H-5) still overlapped, however.

Assignments for the protons H-2 (3.85 ppm) and H-5 (3.70 ppm) were confirmed by double resonance. The H-6 triplet was collapsed to a doublet by irradiation of H-5 (176 Hz upfield) and also by irradiation of H-1 (143 Hz upfield). The signal of H-2 was considerably simplified by irradiation of H-3 (130 Hz downfield), probably due in part to reduction of virtual coupling between H-2 and H-4. The signal for H-5 was considerably simplified by irradiation of H-6 (160 Hz downfield) or H-4 (143 Hz downfield); it was also affected by irradiation of H-3.

Pmr Spectrum of (−)-Quebrachitol Pentaacetate (6).—The spectrum at 100 MHz using chloroform-*d* contained sharp singlets for the three equatorial acetate methyls at 1.92, 2.01, and 2.05 ppm, and a six-proton singlet for the two axial acetate methyls at 2.15 ppm. The methoxyl methyl singlet was observed at 3.36 ppm. The equatorial MeO–CH proton (H-5) produced a complex multiplet at about 3.6 ppm. The remaining five ring protons produced complex overlapping multiplets in the region 5.0–5.2 ppm which could not be resolved at 100 MHz.

3,4,6-Tri-O-acetyl-5-O-methyl-2-O-*p*-toluenesulfonyl-(−)-inositol (Quebrachitol Tosylate Triacetate) (8).—To a solution of 0.5 g of the methyl ether triacetate (mp 130°) in 2.0 ml of pyridine was added at room temperature during 3 hr a solution of 0.40 g of *p*-toluenesulfonyl chloride in 3.0 ml of pyridine. The mixture was kept at room temperature for 6 days and then poured with stirring into 100 ml of water at 0°. After 1 hr the product was collected and recrystallized three times from 95% ethanol to give 0.40 g (54%) of the desired product, colorless needles, mp 135–136°.

Anal. Calcd for $C_{20}H_{26}O_{11}S$: C, 50.65; H, 5.49; S, 6.75. Found: C, 51.08; H, 5.71; S, 6.54.

The ir spectrum was recorded: ν_{max}^{Nujol} 3700, 1750, 1600, 1230, 840, 820, and 740 cm^{-1}.

Pmr Spectrum of (−)-Quebrachitol 2-*p*-Toluenesulfonate 3,4,6-Triacetate (8).—The spectrum at 100 MHz using chloroform-*d* contained sharp singlets for equatorial methoxyl methyl (3.55 ppm), for equatorial tosyl methyl (2.45 ppm) and for the three acetate methyls (2.13, 2.02, and 1.73 ppm). (The axial-equatorial assignments for the acetate methyl signals remain uncertain.) The hydroxyl proton produced a doublet at 3.28 ppm. The four tosyl aromatic protons produced an A_2B_2 pattern with components centered at 7.37 and 7.77 ppm.

Signals for the six ring protons (3.5–5.7 ppm) were sufficiently well separated to permit individual assignments, which were confirmed by double resonance. The quartetlike pattern of axial H-1 (4.23 ppm) was collapsed to a triplet (spacing 3.5 Hz, probably not J) by addition of a little deuterium oxide. The triplet was further collapsed to a doublet by irradiation of H-2 or H-6.

The axial proton H-2 (4.70 ppm) was observed as a pair of doublets (spacings 10 and 3 Hz), which was collapsed to a single small doublet by irradiation of H-3 or H-1. The axial proton H-3 produced a tripletlike signal (5.45 ppm, spacing 9.5–10 Hz). The axial proton H-4 appeared as a triplet (5.18 ppm, spacing 9.5–10 Hz). The axial proton H-5 produced a pair of doublets (3.70 ppm, spacings 9.5 and 3.5 Hz), which was collapsed to a

small doublet by irradiation of H-4 and to a large doublet by irradiation of H-6. The equatorial proton H-6 produced a small triplet at 5.53 ppm, with spacing about 4 Hz (probably not J). This sequence of double resonance experiments served to confirm that H-1 and H-6 are equatorial, while H-2, H-3, H-4, and H-5 are axial.

On reaction with acetic anhydride in pyridine, the product was converted into the previously reported[9] tetraacetate (9), mp 141–143° (lit.[9] mp 142–143°).

Pmr Spectrum of (−)-Quebrachitol 2-*p*-Toluenesulfonate 1,3,4,6-Tetraacetate (9).—The tosyl methyl and methoxy methyl groups produced sharp singlets at 2.42 and 3.33 ppm, respectively. The two axial and two equatorial acetate methyl groups produced sharp singlets at 1.88, 2.04, 2.08, and 2.15 ppm; the axial–equatorial assignments remain uncertain. The tosyl aromatic protons produced an A_2B_2 pattern with components centered at 7.37 and 7.73 ppm.

The axial ring protons H-2 and H-5 each produced a pair of doublets, centered at 4.88 and 3.53 ppm, respectively. In each case the spacings indicated the presence of one axial and one equatorial neighboring proton.

The four remaining ring protons appeared as complex overlapping multiplets in the region 5.2–5.5 ppm. By means of double resonance, the axial proton H-4 was estimated to be at 5.20 ppm, and the equatorial proton H-6 at approximately 5.40 ppm. The signals for protons H-1 and H-3 were not located.

Efforts to replace the tosyloxy group by hydrogen, either by direct reduction or by preliminary displacement of the *p*-toluenesulfonate group by an iodo or bromo group, were unsuccessful. Efforts to replace the 2-tosyloxy group and the neighboring *trans*-3-acetoxy group by a 2,3-epoxy group also gave no good result. Attempts to facilitate the SN2 reactions by use of a special solvent (such as dimethyl sulfoxide) were not helpful.

L(124/356) Stereoisomer of 3,4,5,6-Tetramethoxy-1,2-cyclohexanediol [Tetra-O-methyl-(−)-inositol] (11). A. From Isopropylidenequebrachitol (Silver Oxide Method).—To a 2.34-g portion of the finely powdered 1,2-O-isopropylidene derivative (mp 135°) of (−)-quebrachitol was added 12.0 g of silver oxide and 25 ml of methyl iodide, and the mixture was boiled under reflux with stirring for 30 hr. The mixture was filtered, and the residue was extracted with hot chloroform (four 20-ml portions). The combined filtrate was evaporated, giving a syrupy residue. The residue was remethylated with 5.0 g of silver oxide and 10 ml of methyl iodide in the same manner, giving **1,2-O-isopropylidene-3,4,5,6-tetra-O-methyl-(−)-inositol (12)**, in the form of a syrup, bp 128° (3.5 mm). The infrared spectrum was recorded ($\nu_{max}^{liq\ film}$ 2900, 1460, 1370, 1100, and 865 cm^{-1}.

To this syrup was added 20 ml of aqueous acetic acid (1:1), and the mixture was boiled for 2 hr under reflux. The residue, obtained on evaporation of the solvent, was crystallized from a mixture of benzene and petroleum ether (bp 60–80°), giving 1.1 g (47% based on isopropylidenequebrachitol) of the desired **tetramethyl ether 11** as colorless needles: mp 90–92°; $[\alpha]^{25}D$ −71.2° (*c* 3.3, water).

Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C 51.15; H, 8.66.

The ir spectrum was recorded (ν_{max}^{Nujol} 3640, 1150, 1100, and 1060 cm^{-1}).

The pmr spectrum was recorded at 60 MHz only, using chloroform-*d*. The four methoxyl groups produced sharp singlets at 3.48, 3.52, 3.61, and 3.64 ppm. A small triplet at 4.17 ppm was produced by one of the two equatorial ring protons. A broad unresolved multiplet centered at about 3.2 ppm was produced by two more of the ring protons. Signals for the three remaining ring protons were in the same region as the methoxyl signals.

B. From Isopropylidenequebrachitol (Potassium Hydroxide Method).—To a 10.0-g portion of the finely powdered 1,2-O-isopropylidene derivative (mp 135°) of (−)-quebrachitol was added 200 ml of benzene, 45 ml of methyl iodide, and 25.0 g of finely powdered potassium hydroxide, and the mixture was boiled under reflux with vigorous stirring for only 4 hr. After cooling, the supernatant solution was decanted, and the residue was washed by decantation with hot benzene. The combined decantate was evaporated giving **1,2-O-isopropylidene-3,4,5,6-tetra-O-methyl-(−)-inositol (12)** as a syrup. The ir spectrum was recorded and was identical with that of the product prepared by procedure A.

To this syrup was added 100 ml of aqueous acetic acid (1:1), and the mixture was boiled for 2 hr under reflux. The residue obtained on evaporation of the solvent was crystallized and recrystallized from ethyl acetate–petroleum ether, giving 7.0 g (70%) of the **tetramethyl ether 11** as colorless needles, mp 90–92°. A mixture melting point with the product from procedure A was not depressed, and the ir spectra were identical.

C. From Isopropylidene-(−)-inositol.—A 1.1-g portion of 1,2-O-isopropylidene-(−)-inositol (mp 157°), methylated and then hydrolyzed in the same manner as procedure A above, gave 0.40 g (35%) of the **tetramethyl ether 11** as colorless needles, mp 90–92°. A mixture melting point with the product from procedure A was not depressed, and the ir spectra were identical.

3,4,5,6-Tetra-O-methyl-2-O-*p*-toluenesulfonyl-(−)-inositol (14).—To a 10.0-g portion of the tetramethyl ether (mp 90–92°) in 30 ml of pyridine was added 10.0 g of *p*-toluenesulfonyl chloride, and the mixture was kept at room temperature for 48 hr. After addition of 5 ml of water, the mixture was evaporated to dryness. The syrupy residue was taken up in ethyl acetate, and the extract was washed with 1 *N* sulfuric acid, saturated sodium bicarbonate, and water. After drying, the ethyl acetate solution was evaporated, and the residue, a syrup, was crystallized from petroleum ether. After two recrystallizations from the same solvent the desired product (9.5 g, 58% yield) was obtained in the form of colorless needles: mp 116–117°; $[\alpha]^{25}D$ −89.3 (c 2.8, carbon tetrachloride).

Anal. Calcd for $C_{17}H_{26}O_8S$: C, 52.31; H, 6.67; S, 8.21. Found: C, 52.74; H, 6.58; S, 8.31.

The ir spectrum was recorded (ν_{max}^{Nujol} 3570, 1610, 1170, 1100, 850, and 820 cm^{-1}).

The pmr spectrum and integral were recorded at 60 and 100 MHz using chloroform-*d*. The four methoxyl groups produced signals at 3.21, 3.44, 3.48, and 3.54 ppm. The tosyl methyl group appeared at 2.46 ppm. The tosyl aromatic protons produced an A_2B_2 pattern with components centered at 7.35 and 7.82 ppm. A broad signal at 2.55 ppm presumably was produced by the hydroxyl proton. Three of the ring protons produced signals at 3.70 (H-6?, a pair of doublets, J = 3 and 5 Hz), at 4.30 (H-1?, triplet, spacing 4 Hz), and 4.50 ppm (H-2?, pattern resembling a pair of doublets with additional fine structure), respectively. Signals of the remaining three ring protons were partly obscured by the methoxyl signals.

2-O-Benzoyl-1,3,4,5,6-penta-O-methyl-(−)-inositol (Pentamethoxycyclohexyl Benzoate) (17). A. From the Tetramethyl Monobenzoate.—To a solution of 2.0 g of 2-O-benzoyl-3,4,5,6-tetramethyl-(−)-inositol[28] (mp 121°) in 15.0 ml of methyl iodide was added 12.0 g of freshly prepared silver oxide. The mixture was boiled for 48 hr under reflux with stirring, cooled, and filtered. The residue was extracted with chloroform (four 15-ml portions), and the combined filtrates were evaporated. The residual syrup was crystallized from *n*-heptane, giving 0.51 g (24%) of the product as colorless prisms: mp 88–90°; $[\alpha]^{26}D$ −95.4° (*c* 1.3, carbon tetrachloride). The low yield was due primarily to benzoyl migration.[28]

Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.40. Found: C, 60.67; H, 7.41.

The ir spectrum was recorded (ν_{max}^{Nujol} 1730, 1610, 1275, 1110, 980, and 715 cm^{-1}). The heptane mother liquors were reserved for preparation of the migrated pentamethyl ether monobenzoate.

The pmr spectrum was recorded at 60 MHz only, using chloroform-*d*. The five methoxyl groups produced sharp singlets at 3.42, 3.50 (six protons), 3.55, and 3.62 ppm. Aromatic proton signals were observed in the region 7.3–7.7 and 8.0–8.2 ppm. Two (or three) of the six ring protons produced poorly resolved multiplets centered at about 3.94 and 5.28 ppm; the remaining ring proton signals were partly obscured by the methoxyl signals.

By hydrolysis of the "nonmigrated" monobenzoate (1.0 g) with sodium hydroxide, there was obtained 0.55 g of **1,3,4,5,6-penta-O-methyl-(−)-inositol (15)** as a colorless syrup, whose ir spectrum was identical with that for the product prepared from the 5-tosyl pentamethyl ether (see below).

B. From the Tetramethyl Monotosylate.—To a solution of 10.0 g of the 3,4,5,6-tetramethyl ether 2-tosylate (mp 116–117°) in 75 ml of benzene was added 20 ml of methyl iodide and 10.0 g of finely powdered potassium hydroxide, and the mixture was boiled under reflux with vigorous stirring. After cooling, the supernatant solution was decanted, and the residue was washed by decantation with warm benzene. The combined decantate, after drying, was evaporated to give 9.5 g of **1,3,4,5,6-penta-O-methyl-2-O-*p*-toluenesulfonyl-(−)-inositol (16)** as a colorless syrup. The ir spectrum was recorded (ν_{max} 2900, 1600, 1460, 1370, 1100, 840, 815, and 740 cm^{-1}).

A mixture of 9.0 g of this syrup with 15 g of sodium methoxide and 80 ml of anhydrous ethanol was boiled under reflux for 14 hr. The solvent was evaporated, and to the residue was added 100 ml of water. The mixture was neutralized with 3 *M* hydrochloric acid. The aqueous mixture was extracted with chloroform, and the combined chloroform extract was washed successively with 3% sodium carbonate, 1 *M* hydrochloric acid, saturated sodium bicarbonate, and water. After drying, the chloroform solution was evaporated, giving 40 g of the **hexol 1,3,4,5,6-pentamethyl ether** (**15**) as a yellow syrup. The infrared spectrum was recorded ($\nu_{max}^{liq\ film}$ 3640, 2900, 1460, 1370, 1190, 1140, 1100, 1000, and 960 cm^{-1}).

A 0.70-g portion of this syrup was dissolved in 5 ml of pyridine, and 0.33 ml of benzoyl chloride was added. The mixture was heated at 100° for 20 min, then cooled. Chloroform (25 ml) was added, and the resulting mixture was washed with 1 *M* hydrochloric acid, saturated sodium bicarbonate, and water. After drying, the chloroform solution was evaporated, and the syrup residue was crystallized from *n*-heptane, giving 0.70 g (76%) of the **1,3,4,5,6-pentamethyl ether 2-monobenzoate** (**17**), colorless prisms, mp 88–90°. A mixture melting point with the product from procedure A was not depressed and the ir spectra were identical.

D(**134/25**) **Stereoisomer of 1,2,3,4,5-Pentamethoxy-6-cyclohexanone** (*proto*-**Inosose Pentamethyl Ether**) (**19**). **A. Ruthenium Dioxide Method.**—To a solution of 4.0 g of the syrupy hexol 1,3,4,5,6-pentamethyl ether (derived from the monobenzoate, mp 88–90°) in 80 ml of carbon tetrachloride containing a catalytic amount (100 mg) of ruthenium dioxide was added, at intervals with vigorous stirring, small quantities of 5% aqueous sodium metaperiodate solution. The pH of the mixture was maintained between 6 and 7 by the occasional addition of small amounts of dilute sodium bicarbonate solution, using a pH meter. The reaction was continued until a change in color occurred from black (ruthenium dioxide) to blackish yellow (ruthenium tetroxide). The aqueous layer was extracted with carbon tetrachloride (two 25-ml portions), and to the combined carbon tetrachloride extract was added a little 1-propanol to destroy any excess ruthenium tetroxide. The solution was filtered and washed with 1% aqueous sodium thiosulfate and with water. Evaporation of the solvent, after drying, gave 2.8 g of the product as a colorless syrup. The infrared spectrum was recorded ($\nu_{max}^{liq\ film}$ 2900, 1730, 1460, 1370, 1115, 1020, and 790 cm^{-1}).

Treatment of 50 mg of the above syrup with 2,4-dinitrophenylhydrazine in aqueous methanol containing sulfuric acid gave 63 mg (74%) of the **2,4-dinitrophenylhydrazone** as yellow needles, mp 198–201°. Recrystallization of the product from ethanol raised the melting point to 202–203°.

Anal. Calcd for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.64. Found: C, 47.34; H, 5.72.

The infrared spectrum was recorded (ν_{max}^{Nujol} 1640, 1610, 1530, 1110, and 1020 cm^{-1}).

B. Dimethyl Sulfoxide Method.—To a solution of 2.5 g of the syrupy hexol 1,3,4,5,6-pentamethyl ether (derived from the monobenzoate, mp 88–90°) in 30 ml of dimethyl sulfoxide was added 20 ml of acetic anhydride, and the mixture was kept at room temperature for 48 hr. Evaporation of the solvent under reduced pressure (0.5 mm) gave the product as a yellow syrup, whose ir spectrum was identical with that of the product from procedure A.

The syrup was dissolved in 6 ml of dimethyl sulfoxide, and a solution of 2.5 g of 2,4-dinitrophenylhydrazine in 20 ml of dimethyl sulfoxide and 4 drops of concentrated hydrochloric acid were added. After 5 hr at 0° the precipitated product was collected. A second crop was collected after an additional 12 hr at 0°. Recrystallization of the combined precipitates from 95% ethanol gave 2.2 g (51% based on hexol pentamethyl ether) of the **2,4-dinitrophenylhydrazone**, as yellow needles, mp 202–203°. A mixture melting point with the product from procedure A was not depressed, and the ir spectra were identical.

D(**134/25**) **Stereoisomer of Cyclohexanepentol** [(−)-*proto*-**Quercitol**] (**22**).—A mixture of 1.0 g of the syrupy *proto*-inosose pentamethyl ether (derivative of the 2,4-dinitrophenylhydrazone, mp 203°) and 1.5 ml of ethanedithiol was stirred with 1.0 ml of 12 *M* hydrochloric acid at room temperature for 24 hr. The mixture was poured into water (10 ml) and extracted with benzene (two 10-ml portions). The benzene extract was washed with ice-cold saturated sodium bicarbonate and with water. Evaporation of the benzene solution, after drying, gave 1.4 g of the dithioacetal **23** as a colorless syrup. The ir spectrum was recorded ($\nu_{max}^{liq\ film}$ 2950, 1460, 1370, 1115, and 1090 cm^{-1}).

A solution of 1.35 g of the syrupy dithioacetal in 30 ml of ethanol was boiled under reflux for 2 hr with 12 g (wet weight) of Raney nickel. After cooling, the supernatant solution was decanted, and the residue was washed by decantation with warm ethanol. The combined decantate was filtered. Evaporation of the solvent gave 0.55 g of *proto*-**quercitol pentamethyl ether** (**pentamethoxycyclohexane**) as a colorless syrup. The ir spectrum was recorded ($\nu_{max}^{liq\ film}$ 2950, 1460, 1370, 1100, and 1030 cm^{-1}).

A solution of 0.55 g of the above syrup dissolved in 5.0 ml of a commercial acetic acid solution containing 32% of hydrogen bromide (and probably a small amount of water) was boiled under reflux for 1 hr. Evaporation of the solvent gave a syrup, to which small amounts of ethanol were repeatedly added and evaporated. The residual syrup was dissolved in water (10 ml) and treated with decolorizing charcoal. After filtration and evaporation of the solvent, the syrupy residue was crystallized and recrystallized from 95% ethanol to give 120 mg of the desired (−)-*proto*-**quercitol** (**22**) as colorless needles: mp 238–239°; $[\alpha]^{25}D$ −25.1° (*c* 1, water).

Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.92; H, 7.34.

A mixture melting point with natural (+)-*proto*-quercitol [mp 238–239°; $[\alpha]^{25}D$ +25.3° (*c* 2, water)] was not depressed (see below), and the ir spectra were identical.

DL(**134/25**) **Diastereomer of Cyclohexanepentol** (**Racemic** *proto*-**Quercitol**) (**21**).—A mixture of 15.0 mg of natural (+)-*proto*-quercitol (mp 239°) and 15.0 mg of synthetic (−)-*proto*-quercitol (mp 239°) was recrystallized from 95% ethanol to give DL-*proto*-**quercitol** as colorless needles: mp 238–239° (lit.[11] mp 237°); optical rotation zero within experimental error.

(−)-*proto*-**Quercitol Pentabenzoate** (**22**, H = Bz).—A mixture of 20 mg of (−)-*proto*-quercitol (mp 239°), 1.0 ml of pyridine, and 150 mg of benzoyl chloride was heated at 100° for 10 min. After cooling, water (0.5 ml) was added, and after 10 min, the mixture was poured into ethyl acetate (15 ml). The ethyl acetate solution was washed with 2 *M* hydrochloric acid, saturated sodium bicarbonate solution, and water. Evaporation of the ethyl acetate, after drying, gave a syrup which was crystallized from 95% ethanol to give 55.0 mg of the pentabenzoate, as colorless needles: mp 154–155°; $[\alpha]^{25}D$ −62.8° (*c* 1, ethyl acetate).

Anal. Calcd for $C_{41}H_{32}O_{10}$: C, 71.71; H, 4.99. Found: C, 71.33; H, 4.69.

A mixture melting point with (+)-*proto*-**quercitol pentabenzoate** (mp 155°)[33] was depressed (see below). The pmr spectrum of (+)-*proto*-quercitol pentabenzoate was recorded. The methylene proton signals appeared at 2.5 (axial) and 2.75 ppm (equatorial), with appropriate splitting patterns. The ring proton H-2 appeared as a triplet at 6.2. The remaining ring proton signals (5.6–6.2) overlapped. Aromatic proton signals were observed in the regions 7.2–7.7 (*meta*, *para*), and 7.8–8.2 (*ortho*).

Racemic *proto*-**Quercitol Pentabenzoate.**—A mixture of 15 mg of (+)-*proto*-quercitol pentabenzoate (mp 155°) and 15 mg of (−)-*proto*-quercitol pentabenzoate (mp 155°) was recrystallized from 95% ethanol to give the racemic pentabenzoate as colorless needles: mp 138–140°; optical rotation zero within experimental error. No difference between the solid-state ir spectra of the racemic and active forms of the pentabenzoate could be observed with the Perkin-Elmer Model 421 spectrometer under the conditions used.

Registry No.—**2**, 3409-28-7; **4** 17230-37-4; **5**, 17230-38-5; **6**, 17230-39-6; **8**, 17230-40-9; **9**, 17230-41-0; **11**, 17230-42-1; **12**, 17278-10-3; **14**, 17230-43-2; **16**, 17230-44-3; **17**, 17278-11-4; **19**, 17230-45-4; 2,4-dinitrophenylhydrazone of **19**, 17230-46-5; **22**, 17278-12-5; **22** (H = Bz), 17230-47-6; **23**, 17230-48-7.

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Anomeric 2-Amino-2-deoxy-D-glucofuranosyl Nucleosides of Adenine and 2-Amino-2-deoxy-β-D-glucopyranosyl Nucleosides of Thymine and 5-Methylcytosine

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Fusion of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**1**) with bis(trimethylsilyl)-thymine gave a relatively low yield of 1-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)thymine (**2**) which on controlled acidic hydrolysis gave either 1-(2-acetamido-2-deoxy-β-D-glucopyranosyl)thymine or the previously reported 1-(2-amino-2-deoxy-D-glucopyranosyl)thymine hydrochloride, herein established as the β-D anomer. Treatment of **2** with phosphorus pentasulfide and subsequent heating with methanolic ammonia at 100° gave 1-(2-amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine dihydrochloride (**6**). In selected cases, therefore, the *N*-acetyl group can serve as an amino-protective group in these reactions. The previously reported ethyl tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-α-D-glucofuranoside (**7**) was completely deacetylated by successive treatment with phosphorus pentasulfide and methanolic ammonia. After introduction of the *N*-(2,4-dinitrophenyl) group and acetylation, ethylthio replacement by chlorine yielded a glycosyl chloride derivative **12** which was brought into reaction with *N*-acetylchloromercuriadenine to yield, after removal of the acetyl and 2,4-dinitrophenyl groups, a crystalline anomeric mixture of 9-(2-amino-2-deoxy-D-glucofuranosyl)adenine nucleosides which, by separation on a column of ion-exchange resin, yielded the pure, crystalline components in a ratio of three parts of the β-D to two parts of the α-D form. Anomeric assignments were made on the basis of nmr and polarimetric data.

In continuation of our program in establishing methods for the synthesis of nucleosides of 2-amino-2-deoxyglycoses, we report herein work done in a pyranose structure with the *N*-acetyl group as the amino-protective agent and the glycosyl chloride as the reagent. The condensation yield, by the trimethylsilylpyrimidine fusion method, was low. With an aldose in which the 2-acetamido group is in a trans position to a hydroxyl group, the acetamido group has been removed by base only with great difficulty. However, the de-*N*-acetylation procedure of Fox, *et al.*,[1] obviates this difficulty.

Fusion of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride[2] (**1**) and bis(trimethylsilyl)-thymine[3,4] gave a blocked nucleoside (**2**) in 14% yield (Figure 1). The nuclear magnetic resonance spectrum of **2**, measured in deuteriochloroform, revealed a long doublet at δ 5.97 ppm with a first-order coupling constant, $J_{1',2'}$ = 9 cps, characteristic of an axial–axial relationship of the 1′ and 2′ protons. Since the *C1* D conformation for **2** is highly probable, these data establish the β-D configuration of **2**. Hydrolysis of **2** with hydrochloric acid[5] yielded the nucleoside 1-(2-amino-2-deoxy-β-D-glucopyranosyl)thymine hydrochloride (**5**) whose synthesis had been reported by Wolfrom and Bhat[6] by another method and in much higher yield. Pyrimidine, but not purine, nucleosides are stable to such acid treatment. The β-D configuration is, therefore, established for the compound which Wolfrom and Bhat isolated. Treatment of **2** with methanolic hydrogen chloride[4] yielded 1-(2-acetamido-2-deoxy-β-D-glucopyranosyl)thymine, hitherto unreported.

Following the general de-*N*-acetylation procedure of Fox and associates,[1] **2** was brought into reaction with phosphorus pentasulfide in pyridine to give the syrupy intermediate **3**. Compound **3** was purified by preparative thin layer chromatography and, without further characterization, was treated with methanolic ammonia[1] at 100° to give 1-(2-amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine, isolated as the dihydrochloride (**6**).

Thus, although the *N*-acetyl is not the amino-protective group of choice in these reactions, this group can nevertheless be utilized, in certain cases, under properly selected conditions. Other workers[5,7,8] have utilized the *N*-acetyl blocking group with amino sugars containing the pyranose ring, although the *N*-acetyl was not always removed from the reaction product. When applied to the more reactive furanose structure, we have encountered oxazoline formation.[9]

The anomeric forms of 9-(2-amino-2-deoxy-D-glucopyranosyl)adenine have been synthesized[10] through the use of the *N*-(2,4-dinitrophenyl) group in the chloromercuri procedure of Davoll and Lowy.[11] We have described[9] the synthesis, in low yield, of a nucleoside derivative of 2-amino-2-deoxy-D-glucofuranose through

(1) K. A. Watanabe, J. Beránek, H. A. Friedman, and J. J. Fox, *J. Org. Chem.*, **30**, 2735 (1965).

(2) D. Horton and M. L. Wolfrom, *ibid.*, **27**, 1794 (1962).

(3) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).

(4) T. Nishimura and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 352, 357 (1964).

(5) C. L. Stevens and K. Nagarajan, *J. Med. Pharm. Chem.*, **5**, 1124 (1962).

(6) M. L. Wolfrom and H. B. Bhat, *Chem. Commun.*, 146 (1966); *J. Org. Chem.*, **32**, 1821 (1967).

(7) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. Williams, *ibid.*, **19**, 1786 (1954); F. J. McEvoy, M. J. Weiss, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 205 (1960); F. J. McEvoy, B. R. Baker, and M. J. Weiss, *ibid.*, **82**, 209 (1960).

(8) T. Sato and Y. Ishido, Japanese Patent 6695; *Chem. Abstr.*, **61**, 14772 (1964).

(9) M. L. Wolfrom and M. W. Winkley, *J. Org. Chem.*, **31**, 3711 (1966).

(10) M. L. Wolfrom, H. G. Garg, and D. Horton, *ibid.*, **30**, 1556 (1965).

(11) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **73**, 1650 (1951).

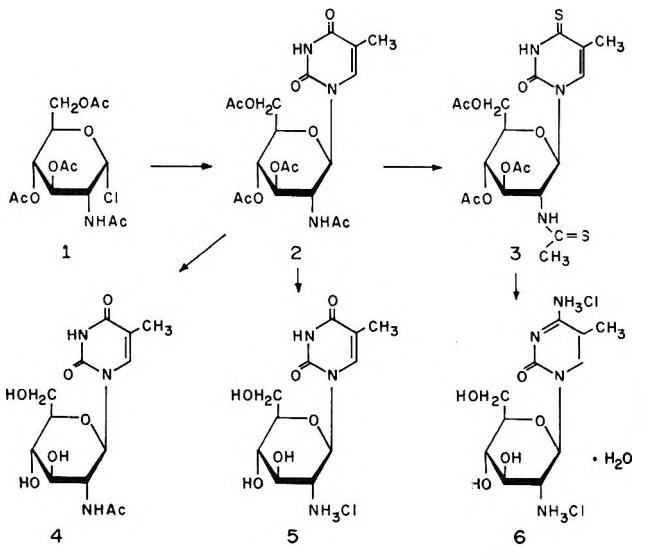

Figure 1.—**3** was not obtained crystalline.

the use of an oxazoline formed when the ethylthio group of 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside[12,13] (**7**) was replaced by chlorine (Figure 2). We describe herein[14] the crystalline anomeric forms of 9-(2-amino-2-deoxy-D-glucofuranosyl)adenine prepared by utilization of the essentially nonparticipating *N*-(2,4-dinitrophenyl) group introduced in the sugar series by Lloyd and Stacey.[15]

In order to place the 2,4-dinitrophenyl group in the previously isolated[12,13] 1-thio-α-D-glucofuranosyl derivative of the amino sugar, the *N*-acetyl and *O*-acetyl groups were removed by the method of Fox and coworkers,[1] and the 2,4-dinitrophenyl group was directly introduced on the nitrogen atom of **9**. In this procedure, the fully acetylated ethyl 1-thio-α-D-glycoside (**7**) was converted into ethyl tri-*O*-acetyl-2-deoxy-2-(thioacetamido)-1-thio-α-D-glucofuranoside (**8**) by treatment with phosphorus pentasulfide in pyridine.[1] The syrupy product (**9**) which was obtained on treating **8** with methanolic ammonia[1] at 100° was characterized by the crystalline derivatives ethyl 2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside (and its triacetate) and ethyl 2-deoxy-2-(2,4-dinitroanilino)-1-thio-α-D-glucofuranoside (**10**). Acetylation of **10** gave a syrupy triacetate (**11**) which in turn was converted by chlorine[16] into the syrupy glycosyl chloride **12**.

Use was then made of the chloromercuri procedure[11] to obtain a nucleoside of adenine. The reaction product from the condensation of the glycosyl chloride **12** with 6-*N*-acetyl-9-chloromercuriadenine was de-*N*-acetylated (on the purine) with picric acid[17] to yield a crystalline picrate (anomeric mixture) which was deblocked with a basic ion-exchange resin to give the crystalline anomeric mixture **13**. The nmr spectrum, in deuterium oxide, of **13** revealed a pair of isolated doublets at δ 6.00 ($J_{1',2'}$ = 2.5 cps) and 6.50 ppm ($J_{1',2'}$ = 5 cps). The protons at H-2 and H-8 of the purine ring appeared as two distinct singlets at δ 8.33 and 8.37 ppm and two overlapping singlets at δ 8.18 ppm as might be expected from a pair of anomers. The two singlets at lower magnetic field were somewhat diminished, by deuteration, on prolonged standing or on heating.[18]

An elegant separation of the two anomers was achieved by the method of Dekker.[19] Aqueous methanol elution from a column of basic ion-exchange resin separated the components very well. Assignment of anomeric form was made on the basis of nmr data[20] and was in agreement with the polarimetric values found. For the α-D anomer the presence of the doublet at δ 6.50 ($J_{1',2'}$ = 5 cps) and the absence of the one at 6.00 ppm ($J_{1',2'}$ = 2.5 cps) indicates a clear separation from the β-D anomer. The reverse held true for the β-D form. The X-ray powder diffraction data of the nucleoside anomeric mixture, in comparison with those of the separated components, clearly indicate a mechanical mixture of crystals and not a molecular compound. The latter was favored for an analogous but 1:1 anomeric mixture of adenine nucleosides of 2-amino-2-deoxy-D-ribofuranose.[21] The optical rotatory data of the isolated mixture would indicate a 63:37% (β-D:α-D) admixture, and indeed 63% β-D anomer was actually isolated in comparison with 31% α-D form.

Experimental Section[22]

1-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-thymine (2).—A mixture of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[2] (**1**, 20 g) and bis(trimethylsilyl)thymine[3,4] (30 g) was fused at 125–135° under a slightly reduced pressure. After the vigorous effervescence had ceased, the mixture was cooled and 50% aqueous methanol was added, after which the mixture was boiled for a few minutes and evaporated to small volume. More aqueous methanol was added and again partially removed by evaporation to a small volume. This was followed by repeated evaporations to dryness with absolute ethanol. The residue was extracted with dichloromethane and the extract was washed with saturated, aqueous sodium hydrogen carbonate, and water. The dried (magnesium sulfate) solution was evaporated to a syrup which was crystallized from methanol–ether to yield 5.0 g of crude **2**, mp 177–185°. This product was extracted with chloroform, and the extract was evaporated to a syrup which was crystallized from methanol–ether to yield 3.55 g (14%): mp 208–209°; $[\alpha]^{22}D$ −20 ± 1° (c 2.13, methanol); λ_{max}^{KBr} 3.07 (NH), 5.72 (OAc), 5.90 (C=O of thymine), and 6.05, 6.48 (NHAc) μm; λ_{max}^{MeOH} 265 nm (ε 9800); nmr (deuteriochloro-

(12) M. L. Wolfrom, S. M. Olin, and W. J. Polglase, *J. Amer. Chem. Soc.*, **72**, 1724 (1950).

(13) M. L. Wolfrom and M. W. Winkley, *J. Org. Chem.*, **31**, 1169 (1966).

(14) Preliminary communication: M. L. Wolfrom and M. W. Winkley, *Chem. Commun.*, 533 (1966).

(15) P. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 116 (1960).

(16) M. L. Wolfrom and W. Groebke, *J. Org. Chem.*, **28**, 2896 (1963).

(17) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Amer. Chem. Soc.*, **79**, 2778 (1957).

(18) M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. P. Ts'O, *ibid.*, **86**, 696 (1964).

(19) C. A. Dekker, *ibid.*, **87**, 4027 (1965).

(20) T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 803 (1965); K. Imai, A. Nohara, and M. Honjo, *ibid.*, **14**, 1377 (1966).

(21) M. L. Wolfrom and M. W. Winkley, *J. Org. Chem.*, **32**, 1823 (1967).

(22) Melting points were determined with a Hershberg-type apparatus [A. Thompson and M. L. Wolfrom, *Methods Carbohyd. Chem.*, **1**, 517 (1962)]. Specific rotations were determined in a 2-dm polarimeter rube. Infrared spectra were measured with a Perkin–Elmer Infracord spectrometer. Ultraviolet spectra were measured with a Bausch and Lomb Spectronic 505 spectrometer. Nmr data were recorded by J. D. Wander and J. B. Hughes with a Varian A-60 nmr spectrometer and were taken in deuterium oxide (freshly prepared solutions) or deuteriochloroform with an internal standard of sodium 4,4-dimethyl-4-silapentane 1-sulfonate or tetramethylsilane, respectively. Microanalytical determinations were made by W. N. Rond. X-Ray powder diffraction data give interplanar spacings in angstroms, for Cu Kα radiation, λ 1.539 Å, nickel filter, camera diameter of 114.6 mm, and photographic recording. Relative intensities were estimated visually: s, strong; m, medium; w, weak; v, very. The strongest lines are numbered (1, strongest); multiple numbers indicate approximately equal intensities. Thin layer (0.25-mm thickness unless otherwise noted) chromatography was performed by the ascending method with Desaga equipment using silica gel G (E. Merck, Darmstadt, Germany) activated at 110° with detection by sulfuric acid for colorless materials. Indicated amounts of developer are by volume. Unless otherwise noted, evaporations were performed under diminished pressure.

form) δ 1.92 (3 H, singlet, methyl at C-5), 2.07, 2.10 (12 H, NHAc and OAc), 3.87–5.67 (6 H, sugar ring), 5.97 (1 H, doublet, $J_{1',2'}$ = 9 cps, H-1'), 7.13 (1 H, broad doublet, NH at C-2'), 7.37 (1 H, singlet, H-6), and 10.25 ppm (1 H, broad singlet, H-3); X-ray powder diffraction 9.82 s (1, 1), 8.42 vw, 5.75 s (1, 1), 4.98 m, 4.87 s (2), 4.62 m, 4.23 vw, 4.07 vw, 3.97 s (3), 3.81 m, 3.66 m, 3.47 m, 3.40 m, 3.23 vw, 3.13 vw, and 3.02 w.

Anal. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.11; H, 5.53; N, 9.23. Found: C, 49.92; H, 5.46; N, 9.41.

This compound was homogeneous by thin layer chromatography with ethyl acetate–methanol (9:1) developer (R_f 0.74).

1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)thymine (4).—The above-described compound (**2**, 0.83 g) was dissolved in anhydrous methanol (30 ml), and the solution was almost saturated at 0° with hydrogen chloride. After standing at room temperature for 24 hr, the solution was evaporated to dryness. A filterable solid was obtained on trituration of the residue with ether: yield 0.67 g; mp 170–180°. Pure material was obtained on crystallization from ethanol–1-propanol: yield 0.44 g (73%): mp 262–263° dec; $[\alpha]^{20}D$ +19 ± 1° (*c* 2.25, methanol); λ_{max}^{KBr} 2.90–3.10 (NH, OH), 5.8–6.1 (C=O of thymine, NHAc), and 6.50 (NHAc) μm; $\lambda_{max}^{H_2O}$ 265 nm (ε 9450); X-ray powder diffraction 10.16 m, 9.21 vw, 7.37 m, 6.51 s (2), 5.21 m, 4.79 w, 4.56 s (1), 4.29 w, 4.07 s (3), 3.96 w, 3.83 vw, 3.69 m, 3.57 w, 3.47 w, 3.31 m, 3.13 m, 2.94 w, 2.83 w, 2.73 m, and 2.61 w.

Anal. Calcd for $C_{13}H_{19}N_3O_7$: C, 47.41; H, 5.81; N, 12.76. Found: C, 47.13; H, 5.55; N, 12.74.

This compound was homogeneous by thin layer chromatography with ethyl acetate–methanol (7:3) developer (R_f 0.37).

1-(2-Amino-2-deoxy-β-D-glucopyranosyl)thymine Hydrochloride (5).—Compound **2** (0.28 g) in 6 *N* hydrochloric acid[5] (6 ml) was heated for 10 hr at 95° under reflux, after which the residue obtained on solvent removal was triturated with ether to obtain a filterable solid in a yield of 0.22 g. Pure material was obtained on recrystallization from water–ethanol–1-propanol in a yield of 141 mg (71%): mp 304–307° dec (with darkening at 294°); $[\alpha]^{25}D$ +27 ± 2° (c 1.00, water). The X-ray powder diffraction pattern was identical with that obtained by Wolfrom and Bhat[6] who also reported mp 301–304° and $[\alpha]^{22}D$ +35° (c 2.34, water).

1-(2-Amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine Dihydrochloride (6).—Following the general procedure of Fox and coworkers,[1] compound **2** (3.36 g) and phosphorus pentasulfide (13.1 g) in reagent grade pyridine (300 ml) was heated under reflux, with stirring, for 6 hr. The dark red solution was concentrated to small volume and extracted with chloroform. The extract was washed with water, 1 *N* hydrochloric acid, water, aqueous sodium hydrogen carbonate, and again with water. The dried (magnesium sulfate) solution was concentrated to a syrup which, on thin layer chromatography, exhibited a major yellow spot of R_f ~0.8. The product was then subjected to preparative thin layer chromatography on 200 × 200 × 1 mm plates (100 mg per plate). The principal yellow zone was excised and extracted with acetone. The residue obtained on acetone removal was extracted with dichloromethane to yield 1.57 g (44%) of a yellow syrup (**3**).

The syrup was dissolved in anhydrous methanol (20 ml), and to this was added a solution of methanol (80 ml) previously almost saturated at 0° with ammonia. The mixture was sealed in a steel cylinder and heated for 18 hr at 100°. The yellow solution so obtained was filtered; the residue obtained on solvent removal was treated with water; and a small quantity of Dowex 1X2 (OH^-, 50–100 mesh) was added to it. The mixture was filtered and washed with 60% aqueous methanol. The filtrate was evaporated to dryness, and the residue was subjected to an oil pump vacuum at 60°. The syrupy residue was dissolved in aqueous methanol, treated with decolorizing carbon, and filtered. The filtrate was evaporated to a syrup which was dissolved in aqueous ethanol and made acid to pH 3 by the dropwise addition of concentrated hydrochloric acid. 1-Propanol was added, and the solution was concentrated. Crystallization occurred to yield 0.79 g (73%), mp 209–211° dec. Recrystallization from concentrated hydrochloric acid by the addition of 1-propanol gave pure material: mp 219–221° dec (darkening at 210°); $[\alpha]^{24}D$ +43 ± 2° (c 1.34, water); λ_{max}^{KBr} 2.9–3.1 (NH, OH), 5.78, 5.90, 6.22, and 6.45 (NH_3R^+, pyrimidine) μm; $\lambda_{max}^{H_2O}$ 279 nm (ε 8320); X-ray powder diffraction 9.82 s (1, 1, 1), 8.19 vw, 7.49 w, 6.23 m, 5.18 m, 4.87 vw, 4.59 s (3, 3), 4.17 w, 4.05 s (3, 3), 3.75 s (2), 3.53 m, 3.35 s (1, 1, 1), 3.13 m, 2.99 s (1, 1, 1), 2.89 vw, 2.84 vw, 2.77 w, 2.65 w, 2.56 m, and 2.48 w.

Anal. Calcd for $C_{11}H_{20}N_4O_5Cl_2 \cdot H_2O$: C, 35.02; H, 5.88; N, 14.86; Cl, 18.79. Found: C, 35.00; H, 5.63; N, 15.09; Cl, 18.59.

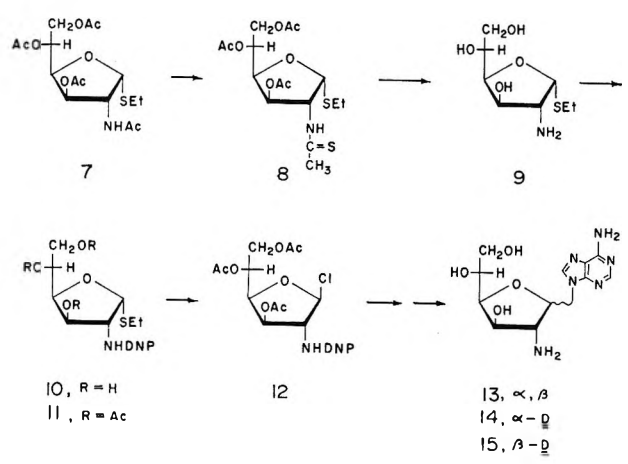

Figure 2.—9, 11, and 12 were not obtained crystalline.

Ethyl 3,5,6-Tri-*O*-acetyl-2-deoxy-2-(thioacetamido)-1-thio-α-D-glucofuranoside (8).—Ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside[12,13] (**7**, 19.54 g) was treated with phosphorus pentasulfide (11.26 g) in pyridine (500 ml) as described above for the synthesis of **3**, except that the washing of the chloroform extract with 1 *N* hydrochloric acid was omitted. The final, dried chloroform solution was evaporated to a slightly yellow syrup by several coevaporations with toluene. This syrup was crystallized from ethyl acetate–ether to yield 14.06 g (69%) of a slighly yellow solid, mp 111–112°. This solid was treated with decolorizing carbon in methanol solution. Carbon and solvent removal and crystallization from ethyl acetate–ether afforded a pure material as white crystals: mp 111–112°; $[\alpha]^{21}D$ +125 ± 1° (*c* 3.72, chloroform); λ_{max}^{KBr} 3.05 (NH), 5.71, 5.81 (OAc), and 6.50 μm (NH, amide); X-ray powder diffraction 10.91 s, 8.93 s, 7.56 s (2), 6.15 vw, 5.43 vw, 4.95 s (1), 4.69 w, 4.52 w, 4.35 w, 4.05 m, 3.60 s (3), 3.33 w, 3.14 m, 2.96 w, 2.90 vw, 2.71 w, and 2.54 w.

Anal. Calcd for $C_{16}H_{25}NO_7S_2$: C, 47.17; H, 6.18; N, 3.44; S, 15.74. Found: C, 47.20; H, 6.50; N, 3.80; S, 15.84.

This compound was homogeneous by thin layer chromatography with chloroform–ethyl acetate (1:1) developer.

Ethyl 2-Deoxy-2-(2,4-dinitroanilino)-1-thio-α-D-glucofuranoside (10).—The above-described compound **8** (5.0 g) was heated with ammoniacal methanol (100 ml) as described above for the synthesis of compound **6**. To the final, dried syrup (obtained just before the previously described conversion into the dihydrochloride **6**) was added sodium hydrogen carbonate (0.71 g) in water (50 ml) and 1-fluoro-2,4-dinitrobenzene (1.58 g) in ethanol (50 ml), and the mixture was shaken overnight. The resultant solution was concentrated to a small volume, whereupon a yellow solid separated. The mixture was diluted with water, and the solid was removed by filtration, washed with water, dried by suction, and washed with benzene to yield 3.06 g (63% from **8**), mp 135–136°. Recrystallization from ethyl acetate afforded pure **10**: mp 136–137°; $[\alpha]^{24}D$ −43 ± 2° (*c* 1.75, methanol); λ_{max}^{KBr} 2.8–3.1 (OH, NH), 6.13, 6.22, 6.64 (aryl C=C), 6.58 (NH, NO_2), 7.46 (NO_2), 12.18 and 13.40 μm (substituted phenyl); X-ray powder diffraction 8.75 s, 8.04 m, 7.13 vw, 5.47 s (1, 1), 5.09 w, 4.84 s (3), 4.71 s, 4.19 vw, 3.95 s (1, 1), 3.73 w, 3.50 s (2), 2.99 w, 2.94 w, 2.83 vw, 2.75 vw, 2.69 w, 2.65 m, and 2.58 w.

Anal. Calcd for $C_{14}H_{19}N_3O_9S$: C, 43.19; H, 4.92; N, 10.79; S, 8.23. Found: C, 43.00; H, 4.76; N, 10.00; S, 8.30.

This compound was homogeneous by thin layer chromatography with ethyl acetate developer.

Ethyl 2-(Benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside.—To crude **9** (6.10 g) prepared from **8** (6.45 g) in water (30 ml) was added sodium hydrogen carbonate (1.3 g) and benzyloxycarbonyl chloride (2.4 ml). The mixture was stirred vigorously for 15 min. Upon addition of a small piece of ice, precipitation occurred. The solid was removed by filtration and washed consecutively with an aqueous solution of potassium hydrogen carbonate and with water to yield 3.20 g (57% from **8**), mp 126–130°. Recrystallization from ethyl acetate afforded pure material in a yield of 2.02 g (35% from **8**):

mp 139–140°; $[\alpha]^{24}D$ +122 ± 2° (c 1.93, methanol); λ_{max}^{KBr} 2.80–3.10 (OH, NH), 5.93, 6.51 ($NHCO_2R$), 6.05 (aryl C=C), 13.70, and 4.40 μm (substituted benzene); X-ray powder diffraction 8.93 s (1), 7.76 s (3, 3), 5.86 s (3, 3), 5.18 m, 4.84 s (2), 4.62 m, 4.46 m, 4.31 w, and 3.95 w.

Anal. Calcd for $C_{16}H_{23}NO_6S$: C, 53.76; H, 6.48; N, 3.91; S, 8.97. Found: C, 53.34; H, 6.23; N, 3.88; S, 8.88.

This substance was homogeneous by thin layer chromatography using ethyl acetate–methanol (9:1) developer.

Ethyl Tri-*O*-acetyl-2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside.—Ethyl 2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside (1.78 g) was acetylated overnight at room temperature with acetic anhydride (20 ml) and pyridine (20 ml). The precipitate that formed on pouring the mixture into ice and water was removed by filtration to yield 2.59 g. The solid was dissolved in dichloromethane, and the solution was washed consecutively with water, saturated aqueous sodium hydrogen carbonate, and water. The syrup obtained on solvent removal from the dried (magnesium sulfate) dichloromethane solution was crystallized from dichloromethane–hexane to yield 2.29 g (95%): mp 121–122°; $[\alpha]^{25}D$ +125 ± 2° (c 2.48, methanol); λ_{max}^{KBr} 3.01 (NH), 5.75 (OAc), 5.90, 6.47 ($NHCO_2R$), 5.95 (aryl C=C), 13.17, and 14.23 μm (substituted benzene); X-ray powder diffraction 13.39 w, 10.65 s (3, 3), 8.42 s (2), 7.19 vw, 6.65 vw, 5.24 w, 4.90 s (1), 4.71 m, 4.37 w, 4.21 m, 4.00 m, 3.72 s (3, 3), 3.56 w, 3.40 m, 3.18 m, and 2.94 w.

Anal. Calcd for $C_{22}H_{29}NO_9S$: C, 54.66; H, 6.04; N, 2.89; S, 6.63. Found: C, 54.20; H, 6.00; N, 2.92; S, 6.93.

9-[3,5,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α,β-D-glucofuranosyl]adenine Picrate.—Acetic anhydride (50 ml) was added to a solution of 10 (4.87 g) in pyridine (50 ml), and the mixture was kept overnight at room temperature. The solution was poured into ice and water, and the precipitated syrup was separated by decantation and washed with water in the same manner. The washed syrup was dissolved in dichloromethane, and the solution was washed consecutively with cold, aqueous sodium hydrogen carbonate and with water. The dried (magnesium sulfate) solution was evaporated to dryness. Repeated evaporation with toluene removed the last traces of pyridine. The syrup was then dried in an oil pump vacuum overnight to yield 6.36 g (99%) of 11. This syrup was homogeneous by thin layer chromatography with chloroform–ethyl acetate (9:1) developer.

Dry chlorine was passed for 10 min into an ice-cold solution of 11 (6.36 g) in dried (Drierite) dichloromethane (50 ml). The solution was evaporated to dryness, and the resultant syrup was transferred with 50 ml of dichloromethane to a stirred, azeotropically dried suspension of 6-*N*-acetyl-9-chloromercuriadenine[23] (12 g), cadmium carbonate (6 g), and Celite (6 g) in hot toluene (300 ml). The dichloromethane was removed by distillation, and the mixture was heated for 6.5 hr under reflux with vigorous stirring and under protection from moisture. The cooled mixture was filtered, and the filter cake was washed with a large volume of dichloromethane. The filtrate was evaporated to dryness, and the residue was extracted with dichloromethane. The extract was washed consecutively with 30% aqueous potassium iodide, cold, saturated, aqueous sodium hydrogen carbonate, and water. The dried (magnesium sulfate) extract was evaporated to dryness to yield 7.43 g. The residue was applied to 200 × 200 × 1 mm plates of silica gel (~100 mg per plate), and the plates were developed with ethyl acetate. The main yellow zone, R_f 0.25, was excised and eluted with acetone. The residue obtained on acetone removal was extracted with dichloromethane, and the solvent was removed by evaporation to yield 3.90 g (50% from 11) of crude syrup.

To the above syrup (3.90 g) in ethyl acetate (40 ml) and methanol (160 ml) was added picric acid (4.5 g), and the mixture was heated for 30 min under reflux. The yellow, crystalline product which separated on cooling was removed by filtration and washed with methanol to yield 4.92 g (97%): mp 187–192° dec; $[\alpha]^{25}D$ +37 ± 2° (c 0.96, acetone); λ_{max}^{KBr} 5.70 (OAc), 5.88, 6.19, 6.37, 6.65 (picrate, aryl C=C, purine), 6.58, 7.58 (NO_2), and 13.43 μm. This crystalline picrate anomeric mixture exhibited a distinct X-ray powder diffraction diagram.

Anal. Calcd for $C_{29}H_{27}N_{11}O_{18}$: C, 42.61; H, 3.33; N, 18.85. Found: C, 42.97; H, 3.93; N, 18.93.

9-(2-Amino-2-deoxy-α,β-D-glucofuranosyl)adenine (13).—To a stirred solution of the above anomeric mixture of picrates (4.92 g) in acetone (320 ml) and water (80 ml) at 45–50° was added, portionwise, an excess of Dowex 1-X2 (OH^- resin, 50–100 mesh), and the mixture was stirred until it became colorless. The resin was removed by filtration and washed with a large volume of hot methanol. The filtrate and washings were evaporated to dryness, and the residue was triturated with methanol–dichloromethane until a filterable solid (1.46 g) was obtained. This material was decolorized by treating its aqueous methanol solution with activated carbon. The residue obtained on solvent removal was crystallized from aqueous ethanol to yield 0.88 g (49%): mp 214–222°; $[\alpha]^{25}D$ −41° (c 1.12, water); λ_{max}^{KBr} 2.90–3.10 (OH, NH), 6.01, 6.23, 6.40, and 6.82 μm (NH, purine); $\lambda_{max}^{H_2O}$ 262 nm (ε 14,400); nmr (deuterium oxide) δ 3.8–5.1 (solvent and sugar ring protons), 6.00 (0.6 H, isolated doublet, $J_{1',2'}$ = 2.5 cps, H-1'), 6.50 (0.4 H, isolated doublet, $J_{1',2'}$ = 5 cps, H-1'), 8.18 (2 overlapping singlets), and 8.33 and 8.37 ppm (distinct singlets, all 3 ascribed to H-2 and H-8); X-ray powder diffraction 8.58 m, 7.37 m, 5.68 s (2), 5.34 w, 4.92 s (3, 3), 4.71 w, 4.48 w, 4.31 s (3, 3), 4.02 s (1, 1), 3.78 vw, 3.63 vw, 3.40 s (1, 1), 3.09 wv, 3.01 vw, and 2.85 m.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.85; H, 5.85; N, 28.78.

Thin layer chromatography on silica gel with ethyl acetate–methanol (1:1) developer revealed two ninhydrin-positive components with R_f values 0.27 and 0.35. Paper chromatography with 1-butanol–ethanol–water (40:11:19) developer revealed two uv-absorbing and ninhydrin-positive components with $R_{adenine}$ 0.40 and 0.48.

Separation of the Anomeric 2-Amino-2-deoxy-D-glucofuranosyl Nucleosides 14 and 15.—Following the general procedure of Dekker,[19] the anomeric mixture of nucleosides (**13**, 500 mg) in methanol–water (3:7) (20 ml) was siphoned onto a column (31 × 3.1 cm) of Bio Rad AG1-X2 (OH^-, 200–400 mesh) resin, previously saturated with the same solvent mixture. Elution was effected with the same solvent mixture. The effluent was monitored by a uv analyzer, and 10-ml fractions were collected. At tube 79 a uv-absorbing component appeared and was completely removed at tube 118. At tube 137 the eluent was changed to 50% methanol, and a second uv-absorbing component appeared between tubes 165 and 206. The contents of tubes 79–118 (fraction 1) and tubes 165–206 (fraction 2) were separately pooled and evaporated to dryness. The residue from fraction 1 was crystallized from aqueous ethanol to yield 314 mg (63%) of **9-(2-amino-2-deoxy-β-D-glucofuranosyl)adenine (15)**: mp 225–226° dec; $[\alpha]^{22}D$ −57 ± 2° (c 1.23, water); λ_{max}^{KBr} 3.00–3.10 (NH, OH), 5.95, 6.23, 6.35, and 6.77 μm (NH, purine); $\lambda_{max}^{H_2O}$ 262 nm (ε 14,400); nmr (deuterium oxide) δ 3.8–5.1 (solvent and sugar ring), 6.00 (1 H, isolated doublet, $J_{1',2'}$ = 2.5 cps, H-1') and 8.18 and 8.37 ppm (2 H, singlets, H-2, H-8); X-ray powder diffraction 7.31 s (3), 5.68 w, 5.30 s (2, 2), 5.09 w, 4.74 w, 4.46 s (1, 1), 4.17 s (1, 1), 3.96 w, 3.76 w, 3.63 w, 3.40 s (2, 2), 3.11 w, 2.94 w, 2.80 s, 2.68 w, and 2.54 vw.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.66; H, 5.73; N, 28.37.

The residue from fraction 2 was crystallized from aqueous ethanol to give 153 mg (31%) of **9-(2-amino-2-deoxy-α-D-glucofuranosyl)adenine (14)**: mp 223–224° dec; $[\alpha]^{22}D$ −3 ± 1° (c 1.00, water); λ_{max}^{KBr} 2.90–3.10 (NH, OH), 5.95, 6.20, 6.38, and 6.80 μm (NH, purine); $\lambda_{max}^{H_2O}$ 262 nm (ε 14,500); nmr (deuterium oxide) δ 3.8–5.1 (solvent and sugar ring), 6.50 (1 H, isolated doublet, $J_{1',2'}$ = 5 cps, H-1'), and 8.18 and 8.33 ppm (2 H, singlets, H-2 and H-8); X-ray powder diffraction 11.48 m, 7.25 s (3), 6.60 w, 6.23 m, 5.86 vw, 5.40 w, 5.01 m, 4.82 w, 4.64 w, 4.41 s (2), 4.19 vw, 3.98 s, 3.72 vw, 3.56 s (1), 3.35 w, 3.27 w, 3.04 vw, and 2.95 vw.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.68; H, 5.58; N, 28.37.

Thin layer chromatography with ethyl acetate–methanol (1:1) developer showed that each of the components was homogeneous with the faster moving being the α-D anomer. The ir spectra of the two anomers were very similar except in the 10.3–12.4-μm spectral region.

Registry No.—**2**, 17478-49-8; **4**, 17478-50-1; **5**, 17478-51-2; **6**, 17478-52-3; **8**, 13190-62-0; **10**, 13190-63-1; **13**, 17519-22-1; **14**, 13190-59-5; **15**, 14402-55-2; ethyl 2-(benzyloxycarboxylamino)-2-deoxy-1-thio-α-D-glucofuranoside, 17478-57-8; ethyl tri-*O*-acetyl-2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofu-

(23) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

ranoside, 17478-58-9; 9-[3,5,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α,β-D-glucofuranosyl]adenine picrate, 17519-23-2.

Acknowledgment.—This work was supported by Grants No. CA-03232-09 and CA-03232-10 from the Department of Health, Education and Welfare, U. S. Public Health Service, National Institutes of Health, Bethesda, Md (The Ohio State University Research Foundation Projects 759H and 759I). Preliminary work on a portion of this problem was performed by P. McWain.

The Baeyer–Villiger Reaction of Alkyl Aryl Ketones[1]

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The Baeyer–Villiger reaction of nitroacetophenones with trifluoroperoxyacetic acid was studied. The normal preferential aryl migration was observed with the *meta* and *para* isomers, whereas a reversal of migration aptitudes of the nitrophenyl and methyl groups was observed with the *ortho* isomer (Ar/Me ratio, 0.06–0.10). A unique participation of the protonated "Criegee intermediate" has been suggested to account for the unusually active methyl migration. The study was extended to other nuclear substituted aromatic ketones. The electronic effects and possible participation of the substituents are discussed. The relative migration aptitudes of the substituents investigated were determined by product distributions.

In the course of degradation studies of tryptophan, it was necessary to study the oxidation of 2′-aminoacetophenone. The oxidizing agent, trifluoroperoxyacetic acid, which is effective for the oxidation of anilines to the corresponding nitro compounds, was employed.[3] It was found that the amino ketone was oxidized initially to the nitro ketone, 2′-nitroacetophenone (**1**), which then underwent the Baeyer–Villiger reaction to yield a mixture of methyl *o*-nitrobenzoate and *o*-nitrophenyl acetate. Pure 2′-nitroacetophenone was treated with excess peroxy acid under similar conditions, and the products were isolated and hydrolyzed to *o*-nitrobenzoic acid and *o*-nitrophenol. The ratio of phenol to the benzoic acid was found to be 0.06 by isolation procedure and 0.10 by a titration method (Table I). These values may be taken as a reflection of the ratio of methyl and aryl migration and unambiguously indicate that, in 2′-nitroacetophenone, the methyl group migration is about ten times the nitrophenyl migration.

For comparison the *meta* and *para* isomers, 3′- and 4′-nitroacetophenone (**2** and **3**), were treated in the same manner, and the products were analyzed by titration (Table I). The phenol/benzoic acid ratios with these two isomers were greater than unity, indicating that the normal preferential aryl migration had occurred even in the presence of the electron-withdrawing effect of the nitro group.

The unusual reversed order of preference for migration observed with the *ortho*-nitro compound **1** was considered to be of significance. The change in migration aptitude observed with this compound indicates that the nitro group in the *ortho* position participates in such a manner as to create a net effect which either retards the aryl migration, facilitates the methyl migration, or is involved in both of these effects.

Of the three nitroacetophenones, only the *meta* and *para* isomers (**2** and **3**) have been studied previously.[4–7] Conducting rate studies by following the consumption of peroxybenzoic acid in the oxidation of **2** and **3**, Friess and Soloway[7] were unable to isolate the expected ester products. Hawthorne and Emmons[5] gave only the rate constants for the reaction of 3′-nitroacetophenone (**2**) and other substituted acetophenones including 4′-bromo- and 4′-methylacetophenones. The 4′-chloroacetophenone was found to give 2.9% of methyl migration.[6] The product distribution in the reaction of **3** with trifluoroperoxyacetic acid is given in Table I.

When oxidized by peroxybenzoic acid in chloroform, all acetophenones which were studied gave no detectable amount of the corresponding methyl benzoate.[7] In other words, in no case was there evidence for methyl migration. Similarly, only phenols were obtained from peroxyacetic acid oxidation of 4′-nitro- and 4′-methoxyacetophenone.[4,8]

The order of preference for migration among alkyl groups in this rearrangement has been reported to be tertiary > secondary > primary > methyl.[4,6,9] Phenyl approximates isopropyl, cyclopentyl, and benzyl in migratory aptitude.[6] Thus, it can be generalized that methyl ketones will give mostly, if not entirely, acetate esters.[10] Furthermore, electron-releasing substituents enhance, whereas electron-attracting substituents decrease, the migratory aptitude of aryl groups.[6,11]

One could postulate the participation of the nitro group in the decomposition of the protonated Criegee intermediate **4**. The nucleophilic attack of the oxygen atom of the nitro group at one of the oxygen atoms of the peroxy ester linkage aids the leaving of the trifluoroacetic acid molecule, leading to the formation of a six-membered cyclic intermediate **5**.

(1) Presented at the 1st Annual Midwest Regional American Chemical Society Meeting, Kansas City, Mo., Nov 1965.

(2) Taken in part from the Ph.D. Dissertation presented by J. P. Li, to the Graduate School of the University of Kansas, Jan 1966.

(3) W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3470 (1954).

(4) Y. Yukawa and T. Yokoyama, *Nippon Kagaku Zasshi*, **73**, 371 (1952); *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **9**, 180 (1952).

(5) M. F. Hawthorne and W. D. Emmons, *J. Amer. Chem. Soc.*, **80**, 6398 (1958).

(6) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *ibid.*, **80**, 6393 (1958).

(7) S. L. Friess and A. H. Soloway, *ibid.*, **73**, 3968 (1951).

(8) A. V. Wacek and A. V. Bezard, *Chem. Ber.*, **74**, 845 (1941).

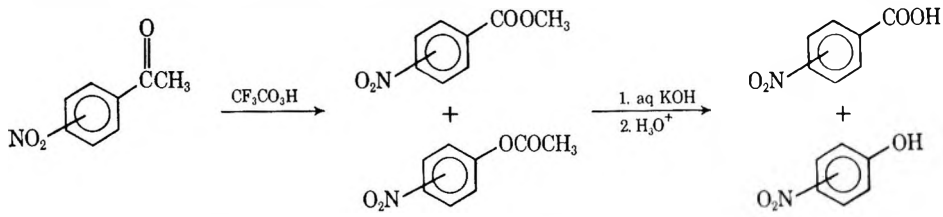
(9) S. L. Friess, *J. Amer. Chem. Soc.*, **71**, 2571 (1949).

(10) P. A. S. Smith, in "Molecular Rearrangements," part 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 577–589.

(11) W. von E. Doering and L. Speers, *J. Amer. Chem. Soc.*, **72**, 5515 (1950).

TABLE I

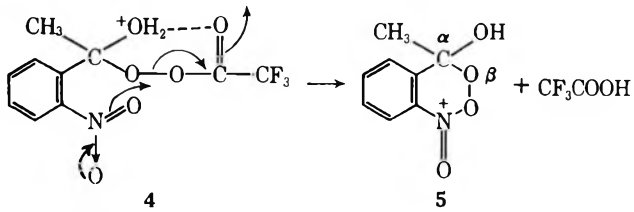
PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF NUCLEAR-SUBSTITUTED ACETOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid, %	Substituted phenol, %	Ar/Me	Method
1	2′-NO_2	38[a]	94	6	0.06	Isolation
		68.4	90.7	9.3	0.10	Titration
2	3′-NO_2	100.0	37	63	1.70	Titration
3	4′-NO_2	90.6	31	69	2.22	Titration
		93	31.5	68.5	2.17	Titration
		(70	13	87	6.7	Uv)[b]
	H	48.8	0	100	Very large	Uv
		(90	0	100	Very large	Ir)[b]

[a] Recovery of starting nitro ketone, 23.6%. [b] Reference 6.

In the phenonium ion involved in a phenyl 1,2 shift, the migrating phenyl ring is presumably perpendicular to the bond between the migration origin and the migration terminus.[12] In the intermediate **5**, the plane

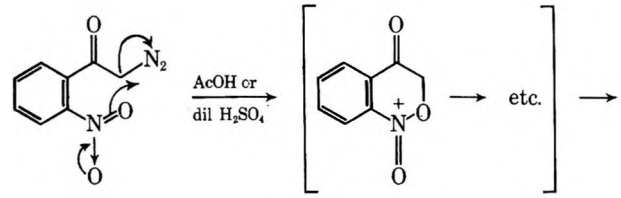


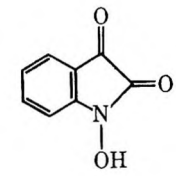
of the benzene ring and the C_α–O_β bond form a dihedral angle of *ca.* 15–20°. To migrate, the benzene ring must twist 70–75° more before its π electrons can approach the terminus oxygen atom (O_β). In a bicyclic system such as **5**, a twist of the aromatic ring in this manner is extremely difficult. Furthermore, the positive charge at the nitrogen atom may exert a strong negative inductive effect on the benzene ring, and further separation of charges may also occur.

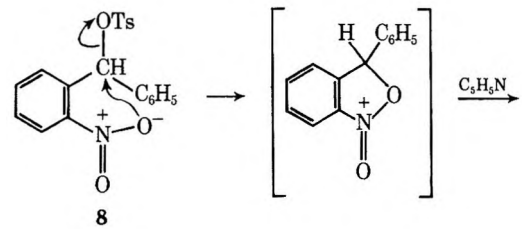
All of these effects could act in retarding the aryl migration with the net result being a predominating shift of the methyl group.

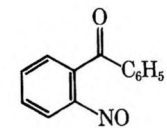
This type of *ortho*-nitro-group participation has been suggested to account for the acid-catalyzed conversion of *o*-nitrobenzoyldiazomethane (**6**) into N-hydroxyisatin (**7**),[13,14] and the base-catalyzed formation of 2-nitrosobenzophenone (**9**) from nitrobenzhydryl *p*-toluenesulfonate (**8**).[15]

The results obtained from the three isomeric nitroacetophenones indicated that the Ar/Me ratios decreased in the order *para* > *meta* ≫ *ortho*. This order is parallel to the increasing distances between the nitro group and the migrating center. If no *ortho* effect existed in this system, the resonance effect of the electron-withdrawing nitro group would be expected to









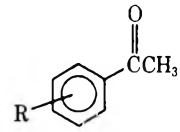
give Ar/Me ratios in the order *meta* > *para* ≅ *ortho*. Since the observed order was *para* > *meta* ≫ *ortho*, it may be tentatively concluded that the inductive effect plays a partial role in limiting the aryl migration. This same order, *para* > *meta* > *ortho* was observed for the aryl migration in the trifluoromethylacetophenones (**10**–**12**) which would have the influence of only a strong inductive effect.

In hope of deducing any possible electronic and anchimeric effects of the nitro group, a series of isomeric acetophenones with various substituents on the ring have been selected and studied. They were the trifluoromethylacetophenones (**10**–**12**), acetylbenzoic

(12) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 575.
(13) J. A. Moore and D. H. Ahlstrom, *J. Org. Chem.*, **26**, 5254 (1961).
(14) E. C. Taylor and D. R. Eckroth, *Tetrahedron*, **20**, 2059 (1964).
(15) W. B. Dickinson, *J. Amer. Chem. Soc.*, **86**, 3580 (1964).

TABLE II

PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF SUBSTITUTED ACETOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid, %	Substituted phenol, %	Ar/Me	Method
10	2′-CF_3	...	Minor	Major	>1	Isolation
		25.7	29.97	70.03	2.33	Titration
		27.4	33.33	66.66	2.00	Titration
11	3′-CF_3	53.9	19.11	80.89	4.25	Titration
		65.3	8.39	91.61	10.92	Titration
12	4′-CF_3	72.7	12.79	87.21	6.98	Titration
		25.0	21.25	78.75	3.71	Titration
13	2′-COOH	42.0	5.66	94.34	16.6	Isolation
		53.4	0	100	*a*	Isolation + uv
		50.0	0	100	*a*	Isolation + uv
14	4′-COOH	85.7	3.45	96.55	28.0	Isolation
		85.0	0	100	*a*	Isolation + uv
		99.0	0	100	*a*	Isolation + uv
15	2′-$COOCH_3$	72.7	11.64	88.36	7.7	Isolation
		92.1	7.39	92.61	12.46	Titration
		88.7	9.49	90.51	9.54	Titration
		66.0	0	100	*a*	Isolation + uv
		94.8[b]	24.0	76.0	3.17	Glpc
16	4′-$COOCH_3$	76.5	3.55	96.45	27.2	Isolation
		79.0	0	100	*a*	Isolation + uv
		94.0[b]	2.04	97.96	48	Glpc
17	2′-OCH_3	73.1	10.13	89.87	8.87	Titration
		81.8	13.18	86.82	6.59	Titration
18	3′-OCH_3	54.8	24.27	75.73	3.12	Titration
		47.9	37.29	62.71	1.68	Titration
19	4′-OCH_3	75.1	12.12	87.88	7.25	Titration
		79.5	16.46	83.54	5.07	Titration

[a] Very large. [b] Analyzed as the unhydrolyzed esters.

acids (**13**, **14**), methyl acetylbenzoates (**15**, **16**), and methoxyacetophenones (**17**–**19**) (Table II). The above ketones were oxidized with trifluoroperoxyacetic acid under identical conditions.

The potentiometric titration with tetrabutylammonium hydroxide in nonaqueous media, described by Cundiff and Markunas,[16] was adopted as a general analysis procedure and supplemented by other methods, such as ultraviolet spectrometry and gas chromatography, wherever suitable for the particular mixture of products. Preliminary experiments on some of these ketones enabled the isolation and identification of the expected products. The purified products were compared with the authentic compounds by infrared spectra, melting points, and thin layer chromatographic techniques.

Acetylsalicylic acid, methyl acetylsalicylate, and *p*-hydroxybenzoic acid acetate were refluxed separately with trifluoroacetic acid in chloroform or dichloromethane. The substances were quantitatively recovered, unchanged in each case. These experiments showed that these compounds, being primary products of the Baeyer–Villiger reaction, did not undergo Fries rearrangement or any other chemical transformation under the reaction conditions used.

The results obtained from these ketones are listed in Table II. The Ar/Me ratios obtained with these acetophenones were considerably larger than unity in comparison with the nitroacetophenones. Although the Ar/Me ratio varied considerably from one run to another for a given ketone, it is apparent that the normal preferential aryl migration was observed consistently in all compounds investigated, including all *ortho* isomers.

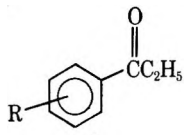
That the Ar/Me ratio dropped from 48 for the *para* isomer **16** to 3.17 for the *ortho* isomer **15** by gas–liquid partition chromatographic analysis is worthy of consideration. This large change suggests a large amount of methyl migration occurring in the oxidation of **15**. It appears that the carboxyl group indeed participated in a manner similar to that proposed for the nitro group, so as to aid the methyl migration, but not to the extent that caused reversal of migration aptitudes. No neighboring-group participation by the trifluoromethyl and methoxy groups occurred.

It is well known that an ethyl group migrates more readily than a methyl group owing to its greater ability to sustain a positive charge. Taking this into consideration, the Ar/Et ratios obtained from the nitropropiophenones would be expected to be smaller than, but parallel to, the Ar/Me ratios of the nitroacetophenones. Therefore, the oxidation reaction was extended to the isomeric nitropropiophenones (Table III).

The unsubstituted propiophenone (**20**) exhibited the normal preferential phenyl migration over alkyl migration, as expected. The oxidation of 3′-nitropropiophenone (**22**) afforded a high percentage of ethyl *m*-

(16) R. H. Cundiff and P. C. Markunas, *Anal. Chem.*, **28**, 792 (1956).

TABLE III
PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF SUBSTITUTED PROPIOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid, %	Substituted phenol, %	Ar/Et	Method
20	H	72.2	39.05	60.95	1.56	Titration
		...	Minor	Major	>1	Isolation
21	2′-NO_2	39.8	62.76	37.24	0.59	Titration
		26.5	98.11	1.89	0.02	Isolation
22	3′-NO_2	48.0	82.06	17.95	0.22	Titration
		90.0	100	0	0	Isolation
23	4′-NO_2	29.7	55.77	44.23	0.82	Titration
		100	100	0	0	Isolation

nitrobenzoate but no *m*-nitrophenylpropionate. The ethyl *m*-nitrobenzoate thus obtained was hydrolyzed with aqueous potassium hydroxide, giving *m*-nitrobenzoic acid in quantitative yield. In another experiment, the oxidation products were hydrolyzed without isolation, and *m*-nitrobenzoic acid was obtained in 90% yield.

Analysis of the acidic products by titration established a ratio of 0.22.

With the *ortho* and *para* isomers, **21** and **23**, no attempt to isolate the benzoates and propionates was made. These esters were hydrolyzed without separation or purification. Both *o*-nitrobenzoic acid and *o*-nitrophenol were obtained in pure form from 2′-nitropropiophenone (**21**). 4′-Nitropropiophenone (**23**) afforded only *p*-nitrobenzoic acid by isolation procedure. No *p*-nitrophenol could be detected in the crude product by uv spectroscopy. Analysis by titration, however, indicated the formation of definite amounts of nitrophenols from **21** and **23**.

The results in Table III indicate that (1) the Ar/Et ratios associated with all three nitropropiophenones are smaller than unity and (2) these ratios are of about the same order.

Contrary to the corresponding homologs (the nitroacetophenones) and like 2′-nitropropiophenone (**21**), 3′- and 4′-nitropropiophenones (**22** and **23**) gave reversed migration preference of the aryl and alkyl groups. This may suggest that in the Baeyer–Villiger reaction the migration aptitudes decrease in the order phenyl > ethyl > nitrophenyl > methyl.

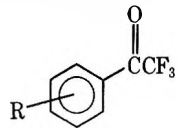
The Ar/Et ratios, being of the same order in magnitude, failed to indicate the importance of the inductive effect or of the resonance effect exerted by the nitro group in the oxidation of these aromatic ketones. Since participation by the nitro group is impossible in the *meta* and *para* isomers, **22** and **23**, and yet ethyl migration occurred to about the same extent as in the *ortho* isomer **21**, the role of nitro group participation in the oxidation of **21** cannot be assigned.

In summary, it can be postulated that, in the decomposition of the Criegee intermediate, there are three competing reactions: (a) nucleophilic displacement at the oxygen by aryl, (b) nucleophilic displacement at the oxygen by alkyl, and (c) nucleophilic displacement at the oxygen by an *ortho* substituent.

No report of the migration of a trifluoromethyl group could be found in the literature. It was speculated that peroxy acid oxidation of 2,2,2-trifluoroacetophenones would be a good reaction for the study of the migration of CF_3. Owing to the influence of the fluorine atoms, the carbon atom of a trifluoromethyl group is considerably more electronegative in comparison to that of a methyl group. Accordingly, the trifluoromethyl group would be expected to have a smaller migration ability than a methyl group and, in turn, than a phenyl group.

Preliminary experiments showed that 2,2,2-trifluoroacetophenone (**24**) gave good yields of benzoic acid upon the treatment of the ketone under Baeyer–Villiger conditions, followed by base-catalyzed hydrolysis (Table IV). Some phenol was also formed in the reaction, as the residue obtained from the extracts of the acidified hydrolysate had a phenollike odor, gave a positive ferric chloride test (violet color), and exhibited a sharp band at 2.78 μ in the ir spectrum in chloroform. The formation of phenol indicated that at least some phenyl migration occurred. As for the benzoic acid produced, there was no indication whether it arose from the Baeyer–Villiger product, trifluoromethyl benzoate, or directly from the unchanged starting material as a result of a haloform-type reaction. It is known that trifluoroacetophenone is decomposed by alkali through the haloform-type reaction to fluoroform and benzoate. When trifluoroacetophenone was refluxed with trifluoroacetic anhydride in chloroform in the presence of a few drops of trifluoroacetic acid for 4 hr, the reaction mixture showed no change in the uv spectrum, and 90% of the starting ketone could be recovered. Therefore, the ketone did not produce benzoic acid under the Baeyer–Villiger reaction conditions when per acid was absent. An attempt was made to isolate the Baeyer–Villiger products, trifluoromethyl benzoate and phenyl trifluoroacetate; however, the products or the corresponding hydrolytic products could not be isolated readily in a quantitative or semiquantitative manner. Unreacted ketone decomposed readily and thus gave spurious results. Thus in the data reported for compound **24** the phenol percentage is apparently small owing to the isolation of a large amount of benzoic acid, at least part of which arises from a haloform reaction.

TABLE IV
PRODUCT DISTRIBUTION OF THE BAEYER–VILLIGER REACTION OF SUBSTITUTED 1,1,1-TRIFLUOROACETOPHENONES



Compound	R	Total yield of products, %	Substituted benzoic acid,[a] %	Substituted phenol, %	Method
24	H	71.9	92.62	7.38	Isolation
		37.2	72.58	27.42	Titration
25	2′-NO_2	38.3	56.73	43.27	Titration
26	3′-NO_2	48.6	78.01	21.99	Titration

[a] Ar/CF_3 ratios could be not calculated owing to the uncertain route of formation of the benzoic acids.

Nonaqueous titration of the reaction products of the three trifluoroacetophenones, **24–26**, gave consistent results; however, further investigation is required before the conclusion that the trifluoromethyl group has preferential migration over the phenyl or substituted phenyl group.

In the oxidation studies of the aromatic ketones described above, two phenomena were generally observed: (1) for a given substituted ketone, the *ortho* isomer usually gave inferior yields of products to the other two isomers; and (2) the rate of oxidation was influenced by the nature of the substituent. Electron-withdrawing ring substituents (NO_2, CF_3, COOR) retarded and electron-releasing substituents (OCH_3) increased the rate of the reaction. The effects of the substituents on the reaction rates have been studied and discussed by Hawthorne and Emmons.[5]

Experimental Section[17]

Materials.—The alkyl aryl ketones, which were obtained from commercial sources, were purified by redistillation or recrystallization, and their physical constants and nmr spectra were measured to check the identity and purity. Other were prepared according to reported methods or standard procedures. The chloroform used as solvent in the Baeyer–Villiger reactions was analytical reagent grade obtained from Mallinckrodt Chemical Works and was freshly passed through a neutral alumina column (Woelm, grade I) immediately before use. Hydrogen peroxide (90%) was purchased from FMC Corp., New York, N. Y., and trifluoroacetic anhydride, from Eastman Kodak Co., which was used without further purification.

Methyl *o*-Acetylbenzoate (15).—To a solution of *o*-acetylbenzoic acid [Aldrich; recrystallized from *n*-hexane–benzene, mp 114.5–115.2° (lit.[18] mp 115°); 1.64 g, 10 mmol] in diethyl ether (50 ml), an ethereal solution of diazomethane was added slowly with stirring until the yellow color of diazomethane persisted. The reaction mixture was allowed to stand at room temperature for several hours. Concentration of the reaction solution *in vacuo* afforded a pale oily residue. The pure product **15** was obtained as an almost colorless liquid by distillation: bp 94–95° (2 mm) [lit.[19] bp 137–139° (14 mm)]; $n^{20}D$ 1.5252; nmr (CCl_4) δ 2.49 (singlet, 3 H), 3.93 (singlet, 3 H), 7.43–8.15 (multiplet, 4 H).

Methyl *p*-Acetylbenzoate (16).—The ester **16** was prepared by the procedure described above utilizing *p*-acetylbenzoic acid [Sapon Laboratories, Oceanside, N. Y.; recrystallized from methanol–*n*-hexane–benzene, mp 209.0–209.9° (lit.[20] mp 208°); 10 mmol] and diazomethane generated from N-methyl-N′-nitro-N-nitrosoguanidine (17.7 mmol). The ester **25** was recrystallized from *n*-hexane–benzene to give white, silky needles: mp 95.0–95.5° (lit.[21] mp 95.2–95.4°); nmr ($CDCl_3$) δ 2.69 (singlet, 3 H), 4.06 (singlet, 3 H), 8.25 (symmetrical doublet with satellites, base spreading over 8.05–8.49, 4 H).

2′-Nitropropiophenone (21) and 3′-Nitropropiophenone (22).—These compounds were prepared by the procedure of Zenitz and Hartung[22] involving the nitration of propiophenone.

A. 2′-Nitropropiophenone (21).—The oily residue (32.4 g, 0.18 mol, 36% yield) was distilled to yield a yellow liquid: bp 97–99° (0.15–0.2 mm) [lit.[22] bp 152–155° (2–3 mm)]; $n^{20}D$ 1.5446; λ_{max}^{EtOH} 258 mμ (ϵ 7260); λ_{max}^{neat} 5.88 (C=O), 6.55 and 7.41 μ (NO_2); nmr (CCl_4) δ 1.17 (triplet, J = 7–8 cps, 3 H), 7.24 (quartet, J = 7–8 cps, 2 H), 1.8–2.73 (multiplet, 4 H).

B. 3′-Nitropropiophenone (22).—The crystalline product obtained in the nitration of propiophenone was recrystallized from 95% EtOH to yield almost white or faintly yellow prismatic granules: 37 g (0.21 mol, 41% yield); mp 99.0–100.0° (lit.[22] mp 98–99°); λ_{infl}^{EtOH} 255 mμ (ϵ 8500); λ_{max}^{KBr} 5.92 (C=O), 6.58, and 7.46 μ (NO_2); nmr (CH_2Cl_2) δ 1.23 (triplet, J = 7.3 cps, 3 H), 3.11 (quartet, J = 7.3 cps, 2 H), 7.73 (triplet, J = 7.6 cps, 1H), 8.23–8.56 (multiplet, 2 H), 8.76 (triplet, J = 2 cps, 1 H).

4′-Nitropropiophenone (23).—It was prepared according to Sugimoto.[23] The compound was recrystallized twice from EtOH to yield orange prisms: mp 87.0–88.0° (lit.[23] mp 90°); 2.82 g (15.7 mmol, 23.4% yield); λ_{max}^{EtOH} 262.6 mμ (ϵ 8000); $\lambda_{max}^{CCl_4}$ 5.89 (C=O), 6.54 and 7.45 μ (NO_2); nmr ($CDCl_3$) δ 1.27 (triplet, J = 7.2 cps, 3 H), 3.08 (quartet, J = 7.2 cps, 2 H), 8.15 and 8.38 (a pair of distorted doublets, J = 9 cps, 4 H).

Nitration of 2,2,2-Trifluoroacetophenone (24).—In a two-necked, 1-l. round-bottomed flask equipped with a thermometer and a pressure-equalizing dropping funnel, fuming HNO_3 (Fisher Certified reagent, 90%, d 1.50; 430 ml) was placed, stirred, and cooled in an ice–salt bath. 2,2,2-Trifluoroacetophenone (K and K Laboratories, Inc., $n^{20}D$ 1.4635; 87 g, 0.5 mol) was added dropwise at a rate so that the temperature of the reaction mixture was maintained at −3 to −8°. The addition required 40 min. The reddish orange reaction solution was stirred at −2 to −5° for 15 min, poured into 2 l. of ice and H_2O, and stirred. The water phase was decanted from the pale mixture of solid and oily liquid that separated at the bottom and was extracted with C_6H_6 (five 150-ml portions). The resulting C_6H_6 solution was washed with a small amount of H_2O, filtered, dried ($MgSO_4$), and concentrated *in vacuo*. The brown residue was distilled. The unreacted starting material was collected at 65–66° (29 mm), 23.35 g (0.134 mol; 26.8% recovery). Later fractions collected at 139–142° (29 mm) gave a mixture of 2′- and 3′-nitro-2,2,2-trifluoroacetophenones, 43.2 g (0.197 mol, 29.4% total yield based on 0.5 mol of the starting ketone **24** or 53.8% yield based on the consumed amount of **24**).

3′-Nitro-2,2,2-trifluoroacetophenone (26).—The mixture of 2′- and 3′-nitro-2,2,2-trifluoroacetophenones obtained above was stored in a refrigerator. Crystals formed and were collected by filtration. The process was repeated on the filtrate until no more crystals were obtained. The crystals were combined and recrystallized three times from benzene–petroleum ether (bp 36–40°) to yield pale prisms, mp 55.0–55.8°. The product **26** distilled at 140–141° (28 mm): $\lambda_{max}^{CCl_4}$ 5.77 (C=O), 6.5 (doublet), 7.4 (NO_2), 8.24, 8.4, 8.68 μ (CF_3); λ_{max}^{KBr} 5.79 (C=O), 6.5, 7.4 (NO_2), 8.2, 8.4, 8.7 μ (CF_3); λ_{max}^{EtOH} 257 mμ (ϵ 7435); nmr (CCl_4) δ 8.87 (broad, half band width, 4.5 cps, 1 H), 8.53 (triplet, J = 8 cps, further split 2 H), 2.13 (triplet, J = 8 cps, 1 H).

Anal. Calcd for $C_8H_4F_3NO_3$: C, 43.85; H, 1.84; N, 6.39. Found: C, 43.89; H, 1.73; N, 6.30.

2′-Nitro-2,2,2-trifluroracetophenone (25).—The liquid phases and mother liquors obtained above were combined, and purified by column chromatography. The distillates and the residue in the pot were combined (*ca.* 6 g), dissolved in a small amount of CH_2Cl_2, and introduced into a silicic acid column (Mallinckrodt, 100 mesh; 150 g in 3 × 43 cm). Elution of the components with CH_2Cl_2–petroleum ether (bp 30–60°) afforded 2.81 g of **25** and 2.11 g of **26**.

2′-Nitro-2,2,2-trifluoroacetophenone (**25**), eluted from the column, was a gas chromatographically pure, pale liquid: $n^{20}D$ 1.4850; $\lambda_{max}^{CCl_4}$ 3.24, 3.46, 5.70 (C=O), 6.51, 7.41 (NO_2), 8.22, 8.41, 8.7 μ (CF_3); λ_{max}^{EtOH} 261.8 mμ (ϵ 2200); $\lambda_{max}^{cyclohexane}$ 255 mμ (ϵ 7370); nmr (CCl_4) three groups of multiplets at 446–508 cps.

Anal. Calcd for $C_8H_4F_3NO_3$: C, 43.85; H, 1.84; N, 6.39. Found: C, 44.10; H, 1.84; N, 6.26.

The Baeyer–Villiger Reaction. General Procedure.—Hydrogen peroxide (90%) (0.6 g, 16 mmol) was suspended by stirring

(17) Melting points were determined on a calibrated Thomas–Hoover capillary melting point apparatus and were corrected. Refractive indices were determined on a Carl Zeiss refractometer. Ir spectra were recorded on Beckman IR-8 and IR-10 infrared spectrophotometers. Uv data were obtained on a Cary recording spectrophotometer Model 14. Nmr spectra were measured on a Varian A-60 spectrometer, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (δ). Gas–liquid partition chromatography was conducted on an F & M Model 810-19 analytical gas chromatograph, using a flame detector and columns (1/8 in. × 4 ft) packed with 5% w/w diethylene glycol adipate (LAC-446, F & M Scientific Corp.) on Gas Chrom P (70–80 mesh, Applied Science Laboratories, Inc.) at 170°. Helium carrier gas flow was approximately 75 ml/min at 40 psi. Microanalyses were performed on an F & M carbon, hydrogen, and nitrogen analyzer Model 185 in this department. Removal of solvent by evaporation *in vacuo* was accomplished by using a Calab Model C rotary evaporator, normally at temperatures below 25°.

(18) R. Riemschneider and H. G. Kassahn, *Chem. Ber.*, **92**, 1705 (1959).

(19) R. Riemschneider, H. G. Kaahn, and L. Hörner, *Monatsh. Chem.*, **91**, 1034 (1960).

(20) R. Meyer, *Ann. Chem.*, **219**, 234 (1883).

(21) Monsanto Chemical Co., British Patent 636,196 (1950); *Chem. Abstr.*, **44**, 8951d (1950).

(22) B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 444 (1946).

(23) N. Sugimoto, *Chem. Abstr.*, **49**, 11707b (1955).

in $CHCl_3$ (10 ml) in an ice bath. Trifluoroacetic anhydride (5.9 g, 28 mmol) was added, and the mixture was stirred in the cold for 15 min. To the resulting peroxy acid solution, the ketone (10 mmol) in $CHCl_3$ (10 ml) was added, and the mixture was refluxed in an oil bath at *ca.* 70° for 5 hr. After cooling, the reaction mixture was concentrated to dryness *in vacuo* to remove $CHCl_3$, excess trifluoroacetic anhydride, and the trifluoroacetic acid produced. The residue was stored over KOH pellets under reduced pressure overnight.

For the oxidation of 5 mmol of ketone, half quantities of the peroxide and acid anhydride were used, and the amount of the solvent was reduced proportionately.

Base Hydrolysis of the Baeyer–Villiger Reaction Products.—The residue obtained from the Baeyer–Villiger reaction mixture (from 10 mmol of the ketone) was mixed with 2 *N* aqueous KOH (10 ml), and sufficient absolute EtOH was added to secure solution, if necessary. The mixture was stirred at 25° overnight, extracted with CH_2Cl_2, cooled in an ice bath, acidified with concentrated HCl (to congo red paper), and extracted with EtOEt (or CH_2Cl_2). The EtOEt extracts were washed with a small quantity of H_2O, filtered, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was analyzed by the appropriate method.

Isolation of the Substituted Benzoic Acid and Phenol.—The acidic substances obtained from the hydrolysate were chromatographed on a silicic acid column (Mallinckrodt, 100 mesh, 1 × 13 cm), using CH_2Cl_2 as the eluting solvent. The residues obtained from the fractions were weighed and identified by ir and uv spectroscopy and/or melting point. The yields and ratio of the phenol and the benzoic acid were calculated.

Titration of the Product Mixtures.—Titrations were conducted on a Sargent Model D recording titrator. The delivery rate was 0.7 ml/min with a 10-ml buret.

The Baeyer–Villiger products of the nitroacetophenones were titrated in dilute EtOH with 0.1 *N* NaOH, using a Beckman standard combination electrode.

For nonaqueous titrations, a Beckman general purpose glass electrode (silver–silver chloride internal) and a modified Beckman sleeve junction calomel electrode were used. The calomel electrode was modified by replacing the saturated aqueous KCl solution with a saturated KCl solution in anhydrous MeOH.[16] Benzene (Fisher Certified reagent), pyridine (Fisher Certified reagent or Mallinckrodt Analytical Reagent), and CH_3CN (Baker Analyzed reagent) were used without further treatment. Anhydrous MeOH was prepared according to Vogel.[24] The tetrabutylammonium hydroxide titrant was prepared according to Cundiff and Markunas[16] from tetrabutylammonium iodide (polarographic grade, The G. Frederick Smith Chemical Co., Columbus, Ohio) and silver oxide (Mallinckrodt, purified powder), and standardized by titrating against benzoic acid (National Bureau of Standards). The reservoir for the titrant was connected to an ascarite tube and $MgClO_4$ tube.

The residue obtained from the acidified hydolysate was dissolved in pyridine, transferred quantitatively to a 25-ml volumetric flask, and diluted to the mark. Aliquots (1.00 ml) of this solution were diluted with pyridine or acetonitrile (25 ml) and titrated potentiometrically with 0.1 *N* tetrabutylammonium hydroxide solution. In separate titrations, the corresponding, authentic benzoic acid and phenol were added separately to the samples to confirm their presence. Mixtures of known composition were titrated as controls for the procedure, and the results were within the confidence limits. The yields and ratio of the phenol and the benzoic acid were calculated.

The Baeyer–Villiger Reaction of Methyl *o*-Acetylbenzoate (15) and Analysis of Products by Gas Chromatography.—To the peroxy acid, generated from 90% H_2O_2 (4 drops) and trifluoroacetic anhydride (1 g) in $CHCl_3$ (10 ml), a $CHCl_3$ solution of **15** (173 mg, 0.97 mmol, in 5 ml) was added, and the mixture was refluxed at 70° for 5 hr. The yellow reaction solution was evaporated *in vacuo*. The residue thus obtained was dissolved in EtOAc (Fisher Certified reagent), washed with H_2O (three 5-ml portions), filtered, and dried ($MgSO_4$). Evaporation of the solution afforded an oil, 178.6 mg (0.92 mmol as $C_9H_{10}O_4$, 94.8% total yield of both products). Analysis by glpc (at 150°, helium flow rate, 60 ml/min) indicated it to contain methyl acetylsalicylate, dimethyl phthalate, and traces of impurities. The relative peak areas 3.17:1.

The Baeyer–Villiger Reaction of Methyl *p*-Acetylbenzoate (16) and Analysis of Products by Gas Chromatagraphy.—The reaction was performed as with the *ortho* isomer, employing the same amount of peroxy acid and identical conditions. Methyl *p*-acetylbenzoate (199 mg, 1.117 mmol) afforded an oil (265.4 mg). Glpc analysis indicated that both methyl *p*-acetoxybenzoate and dimethyl terephthalate were obtained and represented 94% total yield. The relative peak areas 48:1. The ir spectrum of the oily residue closely resembled that of authentic methyl *p*-acetylbenzoate.

Registry No.—**1,** 577-59-3; **2,** 121-89-1; **3,** 100-19-6; **10,** 17408-14-9; **11,** 349-76-8; **12,** 709-63-7; **13,** 577-56-0; **14,** 586-89-0; **15,** 1077-79-8; **16,** 3609-53-8; **17,** 4079-52-1; **18,** 586-37-8; **19,** 100-06-1; **20,** 93-55-0; **21,** 17408-15-0; **22,** 17408-16-1; **23,** 3758-70-1; **24,** 434-45-7; **25,** 17408-17-2; **26,** 657-15-8.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grant GM-07444.

(24) A. I. Vogel, "A Text-Book of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co. Ltd., London, 1956, p 169.

Reactions of Nitropolymethylbiphenyls

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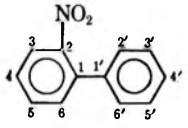
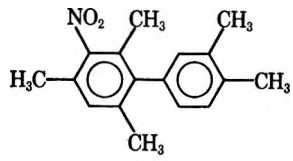
The nitropolymethylbiphenyls most readily obtained by nitrative coupling of methylated benzenes were converted into carbazoles by the Cadogan reaction, to amines by hydrogenation, and to phenols and fluorenes *via* the diazonium salts. These phenols are weak acids on the basis of their solubility; nmr data are given for the carbazoles and fluorenes. A mechanism is proposed for the formation of fluorenes from diazotized *o*-amino-*o'*-methylbiphenyls.

Nitrative coupling of methylated benzenes[1-3] made available several new nitropolymethylbiphenyls. To study their behavior and to confirm some of the structures, we have converted the more readily accessible into amines by hydrogenation, into phenols *via* the diazonium salts, and, when structural features were suitable, into carbazoles by the Cadogan reaction and into fluorenes by the Mascarelli reaction.

The starting compounds are listed below. With one exception, the structures originally proposed[1,2] were confirmed.





VII

No.	Methylated positions
I	3′, 4, 4′, 5
II	2′, 4, 4′, 5
III	2′, 4, 4′, 5, 5′
IV	3, 3′, 4, 4′, 6
V	2′, 3, 3′, 4, 4′, 5
VI	3, 3′, 4, 4′, 5, 6

Polymethylcarbazoles by the Cadogan Reaction.—Reductive cyclization of *o*-nitrobiphenyls by triethyl phosphite gives a high yield of carbazoles if at least one *ortho'* position of the biphenyl is unsubstituted.[4] This reaction gives valuable information concerning the structure of the starting nitrobiphenyl. It confirms not only the *ortho* position of the nitro group, but also helps in locating the substituents in the unnitrated benzene ring. We obtained carbazoles from I, II, and III at the reflux temperature of the triethyl phosphite solution (160–170°) but at a slower rate than indicated by the experimental conditions of Cadogan, *et al.*[4] This may be due to the presence of methyl groups which create a higher electron density on the nitro group, thus hindering nucleophilic attack by triethyl phosphite.[4,5] Compounds IV, V, and VI underwent reaction with triethyl phosphite only at 195–205°, probably because of steric hindrance by the 3-methyl groups. Even then, the rate of carbazole formation was very slow. Attempts to accelerate the reaction by raising the temperature failed because of decomposition of the triethyl phosphite. Under the forcing conditions, N-ethylation of the carbazole by the phosphorus ester also complicated the reaction. For these reasons, triphenyl phosphine[4] might be a better reagent for the reductive cyclization of IV, V, and VI.

The minor by-products of the reaction were diethylaminobiphenyls, ethylaminobiphenyls, and the N-ethylcarbazoles already mentioned.

Compounds II, III, and V gave only one, but I, IV, and VI gave two carbazole isomers. Originally IV, from the cross-coupling of *o*-xylene and pseudocumene, was pictured as 2-nitro-2′,3,4,4′,5′-pentamethylbiphenyl.[2] However, since it forms two isomeric carbazoles, that assignment must have been wrong; formula IV agrees both with the results of the Cadogan reaction and also with the spectroscopic data.[2] A third possibility based on spectroscopic data, 2-nitro-3,3′,4′,5,6-pentamethylbiphenyl, is ruled out by the identity of one of the isomeric carbazoles from IV with the carbazole prepared from III. Analogously, the formation of two isomeric carbazoles from VI rules out the alternative 2-nitro-2′,3,3′,4,4′,5′-hexamethylbiphenyl assignment which could not be eliminated by spectroscopy.[2]

The melting points and elemental analyses of the new polymethylcarbazoles are given in Table I. Table II gives the nmr absorptions. If located at the 4 or 5 position, the methyl protons are deshielded by approximately 0.4 ppm and the aromatic protons by approximately 0.9 ppm. The deshielding can be attributed to the ring current of those rings to which these substituents are not attached. The effect of ring current on the aromatic protons in other polycyclic aromatic hydrocarbons is well documented,[6] and recently the deshielding of aromatic and methylene protons at the 4 and 5 positions of carbazole was also demonstrated.[7]

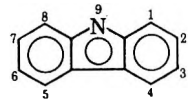
The symmetrical structure of VIII is shown by its high melting point and nmr spectrum; its isomer must have structure IX. From IV, the minor isomer was identical with compound XI prepared from III; the structure XII is left for the other isomer. The structure XVII was assigned to the higher melting isomer from VI on the basis of the nmr coupling pattern of the aromatic protons. For the compounds XIV and XVI nmr and ir spectra clearly indicated that N-ethylation had occurred.

Aminopolymethylbiphenyls.—The reduction of I to the corresponding amine with tin and hydrochloric acid was reported in 1911.[8] Compounds I–VII were readily reduced to the corresponding amines without side reaction with ethanolic hydrazine and Raney Ni.[9]

(1) I. Puskas and E. K. Fields, *J. Org. Chem.*, **31**, 4204 (1966).
(2) I. Puskas and E. K. Fields, *ibid.*, **32**, 589 (1967).
(3) I. Puskas and E. K. Fields, *ibid.*, **32**, 3924 (1967).
(4) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965).
(5) G. Smolinsky and B. I. Feuer, *J. Org. Chem.*, **31**, 3882 (1966).
(6) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., Toronto, 1959, pp 247–254. (b) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, New York, 1965, pp 141–145.
(7) R. E. Moore and H. Rapoport, *J. Org. Chem.*, **32**, 3335 (1967).
(8) A. W. Crossley and C. H. Hampshire, *J. Chem. Soc.*, 721 (1911).
(9) D. Balcom and A. Furst, *J. Amer. Chem. Soc.*, **75**, 4334 (1953).

TABLE I

MELTING POINTS AND ELEMENTAL ANALYSES OF THE NEW POLYMETHYLCARBAZOLES



Starting nitro compd	Compd, indicated by the positions of the methyl groups	Formula no.	Mp, °C[a]	Formula[b]	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
I	2,3,6,7	VIII	244–246	$C_{16}H_{17}N$	86.1	7.7	6.3	85.9	7.7	6.5
I	1,2,6,7	IX	202–205	$C_{16}H_{17}N$	86.1	7.7	6.3	86.4	7.6	6.3
II	2,3,5,7	X	185–186	$C_{16}H_{17}N$	86.1	7.7	6.3	85.8	7.6	6.1
III or IV	1,2,4,6,7	XI	147–148	$C_{17}H_{19}N$	86.0	8.1	5.9	85.7	8.1	6.0
IV	1,2,4,7,8	XII	189.5–191	$C_{17}H_{19}N$	86.0	8.1	5.9	85.9	7.9	5.8
V	1,2,3,5,6,7	XIII	192–193	$C_{18}H_{21}N$	86.0	8.4	5.6	85.6	8.3	5.5
V	1,2,3,5,6,7; 9-ethyl	XIV	169–171	$C_{20}H_{25}N$	86.0	9.0	5.0			5.0
VI	1,2,3,4,6,7	XV[c]	193–195	$C_{18}H_{21}N$	86.0	8.4	5.6	86.8	8.3	
VI	1,2,3,4,6,7; 9-ethyl	XVI	137.5–138	$C_{20}H_{25}N$	86.0	9.0	5.0			4.8
VI	1,2,3,4,7,8	XVII	203–205	$C_{18}H_{21}N$	86.0	8.4	5.6	85.6	8.1	

[a] Corrected. [b] Confirmed by mass spectrometry. [c] Lack of material prevented the repetition of the elemental analyses. Spectroscopic and gas chromatographic data, however, leave no doubt, that we had the compound at hand in high purity.

TABLE II

NMR ABSORPTIONS OF THE POLYMETHYLCARBAZOLES

Compd	Nmr τ values[a] Deuteriochloroform Aromatic protons	Deuteriochloroform Methyl protons	Deuteriopyridine or pyridine,[b] methyl protons
VIII	*c*	7.61 (12)	7.64 (6)[b]
			7.70 (F)[b]
IX	*c*	7.55 (12)	7.60 (3)[b]
			7.66 (6)[b]
			7.72 (3)[b]
X	2.25 (1)	7.25 (3)	7.18 (3)
	3.26 (2)	7.60 (6)	7.62 (6)
	3.40 (1)	7.64 (3)	7.71 (3)
XI	2.27 (1)	7.27 (3)	7.15 (3)
	3.11 (1)	7.68 (6)	7.63 (12)
	3.30 (1)	7.69 (3)	
		7.82 (3)	
XII	2.16 (1)[d]	7.21 (3)	7.20 (3)
	2.97 (1)[d]	7.57 (12)	7.64 (12)
	3.18 (1)		
XIII	2.18 (1)	7.25 (3)	7.15 (3)
	3.07 (1)	7.58 (3)	7.55 (6)
		7.62 (3)	7.70 (3)
		7.72 (9)	7.79 (6)
XIV	2.14 (1)	7.25 (3)	
	3.02 (1)	7.41 (3)	
		7.58 (6)	
		7.73 (6)	
XVI	2.03 (1)	7.20 (3)	
	2.91 (1)	7.33 (3)	
		7.57 (6)	
		7.73 (6)	
XVII	2.08 (1)[d]	7.22 (3)	
	3.00 (1)[d]	7.57 (9)	
		7.64 (6)	

[a] Numbers in brackets indicate the number of protons. [b] Indicates pyridine. [c] Owing to poor solubility, signals were hardly distinguishable from the noise level. [d] Center of doublet with coupling constants 8.1 (XII) and 7.5 (XVII) cps.

Characterization of the new aminopolymethylbiphenyls is shown in Table III.

Catalytic hydrogenation of I–VII was only moderately successful. Thus, on Raney Ni in ethanolic solution I was easily reduced, but VII, II, and III were reduced sluggishly, and required relatively large quantities of catalyst. The severe conditions required for completion of the reaction resulted in the formation of several by-products; mass spectrometry indicated that, in addition to alkylation by the solvent,[10] dimerizations, trimerizations, and reductive cleavage to benzene derivatives took place. With *o*-nitrobiphenyls, some carbazole also formed.

Palladium-on-charcoal and Adams catalysts did not give better results. At room temperature in dimethoxyethane palladium on charcoal caused hydrogenolysis of the solvent and alkylation of the amine. Hydrogenation of IV, V, and VI was extremely slow.

Diazotization of Aminopolymethylbiphenyls in Aqueous Sulfuric Acid. Phenol Formation and the Mascarelli Reaction.—Mascarelli has shown that thermal decomposition of diazotized 2-amino-2′-methylbiphenyls gives fluorenes.[11–14] As this reaction has received little attention, we studied it with our diazotized amines.

Thermal decomposition of diazotized XVIII, XIX, and XXI in approximately 2.5% aqueous H_2SO_4 gave the expected fluorenes; hydrolysis to phenols always occurred as well. In accord with the structural assignments, 2-amino-3′,4,4′,5-tetramethylbiphenyl[8] and compounds XX, XXII, and XXIII gave phenols and by-products but no fluorene derivatives. Tables IV and V list the new polymethylfluorenes and the hydroxypolymethylbiphenyls, respectively.

To improve the yield of fluorene, we diazotized XIX and decomposed it in 80% H_2SO_4 as well as in dilute HCl, alone and with cuprous chloride. The yield did not increase. Decomposition of the diazonium fluoroborate gave mainly the fluorinated biphenyl (65%) and only 25% fluorene.

In contrast to *o*-hydroxybiphenyl, the phenols of Table V were not extracted by 10% NaOH; their solubility was extremely low even in Claisen's alkali.[15] This behavior is similar to that exhibited by sterically

(10) M. Freifelder, *Engelhard Ind. Tech. Bull.*, **2**, No. 3, 93 (1961); D. H. Johnson, *J. Chem. Soc., C*, 1284 (1967).

(11) L. Mascarelli, *Gazz. Chim. Ital.*, **66**, 843 (1936); *Chem. Abstr.*, **31**, 6222 (1937).

(12) L. Mascarelli and D. Gatti, *Atti Congr. Nazl. Chim. Pura Appl., Milan, 1932*, 503 (1933); *Chem. Abstr.*, **29**, 4351 (1935).

(13) L. Mascarelli and B. Longo, *Gazz. Chim. Ital.*, **67**, 812 (1937); *Chem. Abstr.*, **32**, 4564 (1938).

(14) L. Mascarelli and A. Angeletti, *Gazz. Chim. Ital.*, **68**, 29 (1938); *Chem. Abstr.*, **32**, 4565 (1938).

(15) L. Claisen, *Ann.*, **418**, 96 (1919); **442**, 210 (1925).

TABLE III

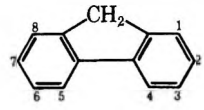
MELTING POINTS AND ELEMENTAL ANALYSES OF THE NEW AMINOPOLYMETHYLBIPHENYLS

Starting nitro compd	Amine	Mp, °C, or $[n]^{19.6}D$	Formula[a]	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
II	XVIII	1.5986	$C_{16}H_{19}N$	85.3	8.5	6.2	85.3	8.5	6.3
III	XIX	1.5950	$C_{17}H_{21}N$	85.3	8.8	5.9	85.0	8.8	5.8
IV	XX	80–81	$C_{17}H_{21}N$	85.3	8.8	5.9	85.5	9.0	
V	XXI	122–123	$C_{18}H_{23}N$	85.3	9.2	5.5	85.6	9.0	
VI	XXII	110.5–1115	$C_{18}H_{23}N$	95.3	9.2	5.5	85.8	9.2	
VII	XXIII	63.5–64.5	$C_{17}H_{21}N$	85.3	8.8	5.9	84.9	8.8	6.0

[a] Confirmed by mass spectrometry.

TABLE IV

YIELDS AND PHYSICAL CONSTANTS OF THE NEW POLYMETHYLFLUORENES



Starting nitro compd	Position of methyl groups	Formula no.	Yield,[a] %	Mp, °C[b]	Formula[c]	Anal, % Calcd C	Calcd H	Found C	Found H
II	2,3,7	XXIV	36	110–111	$C_{16}H_{16}$	92.3	7.7	92.0	7.6
III	2,3,6,7	XXV	40	171	$C_{17}H_{18}$	91.8	8.2	91.7	8.2
V	1,2,3,7,8	XXVI	36	177.5–178.0	$C_{15}H_{20}$	91.5	8.5	91.2	8.5

[a] Isolated yields. Total yields were in the 50–57% range according to gas chromatographic analyses. Compound XXV crystallized most readily owing to its symmetrical structure. [b] Corrected. [c] Confirmed by mass spectrometry.

TABLE V

MELTING POINTS AND ELEMENTAL ANALYSES OF THE NEW HYDROXYPOLYMETHYLBIPHENYLS

Starting nitro compd	Phenol[a,b]	Mp, °C, or $[n]^{20}D$	Formula[c]	Anal, % Calcd C	Calcd H	Found C	Found H
I	XXVII	72–73	$C_{16}H_{18}O$	84.9	8.0	85.0	7.8
II	XXVIII	1.5853	$C_{16}H_{18}O$	84.9	8.0	84.3	8.0
III	XXIX	1.5820	$C_{17}H_{20}O$	85.0	8.4	85.2	8.2
IV	XXX	1.5803	$C_{17}H_{20}O$	85.0	8.4	84.1	8.5
V	XXXI	102–102.5	$C_{18}H_{22}O$	85.0	8.7	85.0	8.6
VI	XXXII	78–79	$C_{18}H_{22}O$	85.0	8.7	85.0	8.5
VII	XXXIII	66.5–68.0	$C_{17}H_{20}O$	85.0	8.4	84.7	8.3

[a] Purification of these compounds was difficult. However, purities were higher than 99% with the exception of compounds XXIX (97.6%), XXX (93.0%), and XXXI (94.5%) based on gas chromatographic analyses. [b] Nmr spectra confirmed the hydroxypolymethylbiphenyl structures and eliminated the possibility of isomericbenzyl alcohols. [c] Confirmed by mass spectrometry.

TABLE VI

NMR ABSORPTIONS OF THE POLYMETHYLFLUORENES

Compd	Nmr τ values in deuteriochloroform[a] Aromatic protons[b]	Methylene protons	Methyl protons
XXIV	2.49 (1)[c]	6.36 (2)	7.66 (3)
	2.54 (1)		7.76 (6)
	2.85 (2)		
	2.94 (1)[c]		
XXV	2.52 (2)	6.31 (2)	7.69 (12)
	2.76 (2)		
XXVI	2.58 (1)[c]	6.52 (2)	7.69 (3)
	2.64 (1)		7.73 (3)
	2.88 (1)[c]		7.80 (6)
			7.85 (3)

[a] Numbers in parentheses indicate the numbers of protons. [b] When coupling was observed the peak positions were calculated based on the interpretation of the coupling pattern. [c] Centers of doublets with coupling constants of 7.8 (XXIV) and 7.5 (XXVI) cps.

hindered phenols.[16] Recently ionic dissociations of substituted phenols have been extensively studied.[17–19] The change of the Hammett reaction constants for *o,o'*-disubstituted phenols has been interpreted as a consequence of steric inhibition of solvation in the hindered phenoxide anions.[17–19] The phenols of Table V appear to be weak acids on the basis of their solubility; their p*K*'s could not be calculated because the substituent constants for polymethylphenyl groups are unknown. However, electron donation by methyl substituents cannot adequately account for their weak acidity. Severe steric hindrance to hydration cannot be invoked either; many of these phenols have one unsubstituted *ortho* position. Clearly, a quantitative study of the ionic dissociation of these phenols would be desirable.

Table VI shows the nmr absorptions of the polymethylfluorenes. According to the most reasonable interpretation of the data, the aromatic proton signals at the lower field must be due to the protons located in the 4 or 5 positions, where deshielding by the ring current would be expected as in the carbazoles. Comparison of the data in Tables VI and II indicate that in the carbazoles the aromatic protons in the 1, 2, 3, 6, 7, and 8 positions resonate at higher field and in the 4 and 5 positions at lower field than in the fluorenes. This could be explained by assuming that in the fully aromatic carbazoles the 14 π electrons circulate in three loops, whereas in fluorenes the 12 π electrons circulate only in two loops around the two six-membered rings under the influence of magnetic field. Consequently, the π-electron density and the intensity of the ring current in the six-membered rings of fluorene will be higher, and therefore the aromatic deshielding mechanism will be more pronounced. In the 4 and 5 positions, however, the substituents are exposed to the ring current of only one additional loop in fluorene and of two additional loops in carbazole. As a result, additional

(16) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Amer. Chem. Soc.*, **67**, 303 (1945); also G. H. Stillson, *ibid.*, **68**, 722 (1946).
(17) L. A. Cohen and W. M. Jones, *ibid.*, **85**, 3397 (1963).
(18) A. Fischer, G. J. Leary, R. D. Topsom, and J. Vaughan, *J. Chem. Soc., B*, **686**, 846 (1967).
(19) C. H. Rochester and B. Rossall, *ibid.*, 743 (1967).

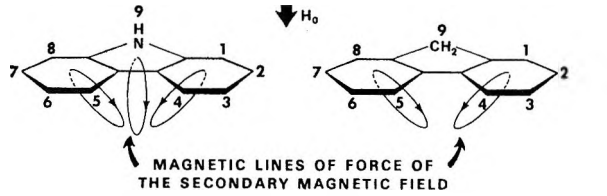
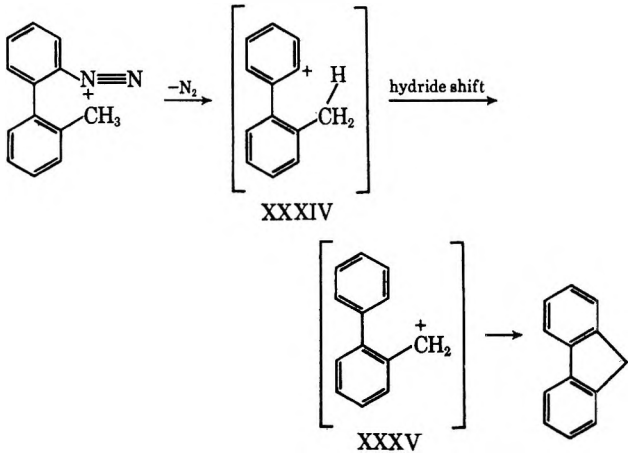


Figure 1.—Schematic representation of the deshielding mechanism at the 4 and 5 positions of carbazoles and fluorenes.

deshielding in these positions should be approximately twice as much in carbazole as in fluorene. This is illustrated in Figure 1. An alternative explanation, that fluorene is nonplanar, is untenable on the basis of the X-ray crystallographic investigations by Burns and Iball.[20]

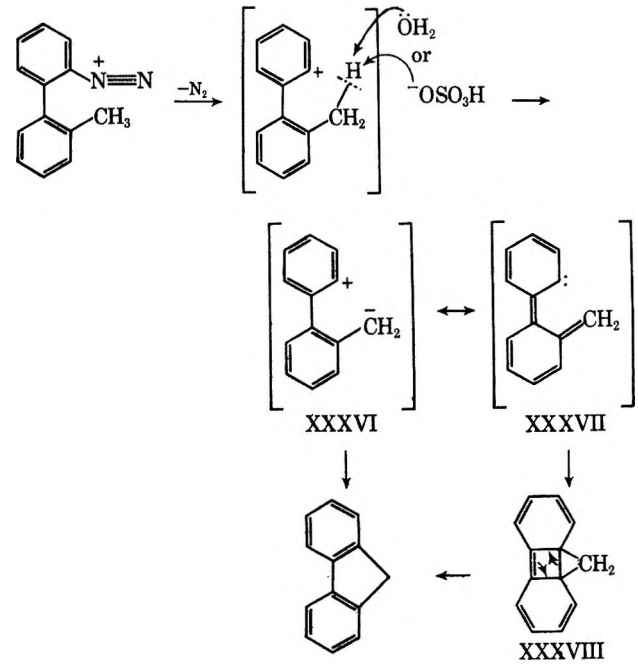
A mechanism involving an intramolecular 1,5-hydride shift has been proposed by Cohen, *et al.*,[21] for the Mascarelli reaction, shown in Scheme I. Their suggestion is based on the observation[22] that intramolecular 1,5-hydride shifts occur during the decomposition of diazotized N,N-disubstituted *o*-aminobenzamides. Whereas their evidence appears to be convincing for benzamides, it does not necessarily apply to biphenyls. Furthermore, it is known from the work of Gies and Pfeil[23] that, during diazotization of aromatic amines, hydrocarbon by-products are formed unless the diazotization is carried out in cold, very dilute acid. Although the exact mechanism of these reactions is not known, it must involve intermolecular reactions. In this light the evidence for the intramolecular 1,5-hydride shifts in the benzamide case would be much stronger had it been shown that the hydride ion transfer is independent of the substrate concentration and also occurs in high dilution. A 1,5-hydride shift does not appear to explain the Mascarelli reaction. Had the benzylic cation XXXV been formed, it would have produced benzyl alcohol by-product, just as phenol is formed from the phenyl cation XXXIV. We observed only fluorene and phenol, although we looked for a benzyl alcohol. The possibility cannot be excluded that the rate of intramolecular cyclization of XXXV is much faster than its rate of hydrolysis, but this did not apply for benzamides where the analogous hydrolysis was much more pronounced than the intramolecular cyclization. That any benzyl alcohol formed was converted into fluorene by the dilute aqueous acid is also unlikely, especially with our polymethyl compounds when the benzyl alcohol would be expected to precipitate from the solution. No fluorene was reported from *o*-phenylbenzyl alcohol in refluxing hydrobromic acid.[24]

SCHEME I



The mechanism in Scheme II appears more reasonable for the Mascarelli reaction. The phenyl cation XXXIV generated by the loss of nitrogen could polarize the benzylic C–H bond located nearby; a benzylic proton is then lost to yield the bipolar ion XXXVI, which goes to fluorene simultaneously with the loss of the proton. Theoretically, XXXVI could give a resonance hybrid

SCHEME II



carbene (XXXVII) which might give XXXVIII by the addition to the double bond. Since a compound like XXXVIII would hardly survive the experimental conditions, an extensive search for such a product was not made. If the proton abstraction from XXXIV is important in fluorene formation it should be helped by electron-withdrawing and hindered by electron-releasing substituents unless the substituents are in *ortho* positions.[11] The yields of fluorene from diazotized 2-amino-2′-methylbiphenyl[12] and 2-amino-2′,4′-dimethylbiphenyl are nearly 100%[13]; the fluorene yield decreases with increasing number of methyl substituents (Table IV). This agrees qualitatively with our mechanism. Indazole formation from diazotized *o*-toluidines probably involves a similar mechanism. Only nitro- and chloro-substituted diazotized *o*-toluidines give good yields of indazoles;[25] in these cases the abstraction of a benzylic proton would be facilitated by the electron-withdrawing substituent without decomposition to nitrogen and a phenyl cation. A similar mechanism

(20) D. M. Burns and J. Iball, *Proc. Roy. Soc.*, **A227**, 200 (1955).
(21) T. Cohen and J. Lipowitz, *J. Amer. Chem. Soc.*, **86**, 2514 (1964), and references cited therein.
(22) T. Cohen and J. Lipowitz, *ibid.*, **86**, 2515 (1964).
(23) H. Gies and E. Pfeil, *Ann.*, **578**, 11 (1952).
(24) G. H. Cookson and F. G. Mann, *J. Chem. Soc.*, 2888 (1949).
(25) E. H. Rodd, Ed., "Chemistry of Carbon Compounds," Vol. IV, part A, Elsevier Publishing Co., Amsterdam, 1957, pp 279–280.

might also be involved for the synthesis of 4-hydroxycinnoline from diazotized *o*-aminoacetophenones.[26] Proton abstraction in acid may indeed occur if it is concerted with the next reaction step.

Experimental Section

Nmr spectra were measured on a Varian Associates HR-60 spectrometer at 52 Mc with tetramethylsilane as an internal standard. Mass spectra were taken on a modified CEC Model 21-103 mass spectrometer. Gas chromatographic analyses were carried out on a Varian Aerograph, Model 202, with 4.5 ft × 0.25 in. SE-30 silicone-gum rubber column.

Carbazole Formation.—A 5-g sample of I, II, or III, was refluxed in 15 ml of triethyl phosphite for 20–24 hr. After the phosphorus esters were distilled at 0.2 Torr, the residues crystallized. From I the isomeric carbazole mixture was separated by fractional crystallization from benzene–dioxane. Compound VIII was isolated in 27% and IX was isolated in 42% yield. From II and III, X and XI were obtained after recrystallization from benzene–methanol in 71 and 58% yields, respectively.

A 3-g sample of IV, V, or VI, and 25 ml of triethyl phosphite were shaken in a pressure vessel, evacuated to 2 Torr at 205° for 63 hr. This treatment was too short for V and VI, and 44 and 33% starting material, respectively, did not react. Under these conditions N-ethylation was not significant. However, in some cases, decomposition of the phosphorus ester was shown by development of pressure. When compound V was treated with triethyl phosphite at 205° for 156 hr, the N-ethylcarbazole XIV was the major and the only isolated product. Treatment of VI with triethyl phosphite at 192° for 12 days resulted to a great extent in N-ethylation of the carbazoles; compounds XVI and XVII could be isolated from this mixture by fractional crystallization from benzene–methanol.

Compound XI was isolated both from III, as the only product, and from IV, as one of the isomeric products; mixture melting point and infrared spectra confirmed the identity.

Balcom Reduction of the Nitropolymethylbiphenyls.—A mixture of 5 g of nitroarene, 75 ml of ethanol, 15 ml of 65% hydrazine, and 0.2–0.8 g of wet Raney nickel was refluxed for 3–5 hr. Removal of the solvent from filtered solutions gave the amines in quantitative yield. For analyses the solid products were recrystallized from hexane; the liquid amines were analyzed without further purification.

Hydrogenations of Nitropolymethylbiphenyls over Raney Nickel. A 5–10-g sample I, II, III, or VII, ethanol (50–100 ml), and wet Raney nickel (0.5–1.0 g) were charged into a 300-ml pressure vessel. The cylinder was evacuated, filled with hydrogen at 500 psig, and heated on a rocker with automatic temperature control at 100–105° for 1, 14, 40, and 8 hr, respectively. Removal of the solvent from filtered solutions gave crystalline amine only from I; after recrystallization from methanol it melted at 73–76° (lit.[6] mp 80°). The amine XXIII from VII crystallized after a few weeks, mp 53–59° (less pure than that obtained by the Balcom method). The syrupy amine XIX from III was 93% pure according to gas chromatography.

Hydrogenation of 2-Nitro-2′,4,4′,5,5′-pentamethylbiphenyl (III) over Pd/C in Dimethoxyethane.—Compound III (19 g) was hydrogenated in 100 ml of dimethoxyethane with 4 g of 5% Pd/C for 10 hr at 25° (500 psig of hydrogen pressure). Removal of the catalyst by filtration and of the solvent by evaporation *in vacuo* left a syrup (17 g) which gave the following mass spectrometric analysis at low ionizing voltage: mass (relative intensity), 225 (1.6), 239 (100), 253 (5.2), 267 (0.8), 281 (10.3), 297 (4.9), 311 (0.1), 312 (0.1). Products with masses 253, 281, and 297 very likely correspond to methylated, methylethylated, and methoxyethylated amine, resulting from hydrogenolysis of the solvent.

Rate Studies of Hydrogenations over Palladized Charcoal in Acetone.—Because of difficulties involving solubilities and solvent interactions, we used acetone instead of alcohols or ethers. This would be expected to give isopropylamines[27] with consumption of one extra mole of hydrogen per mole of nitro compound.

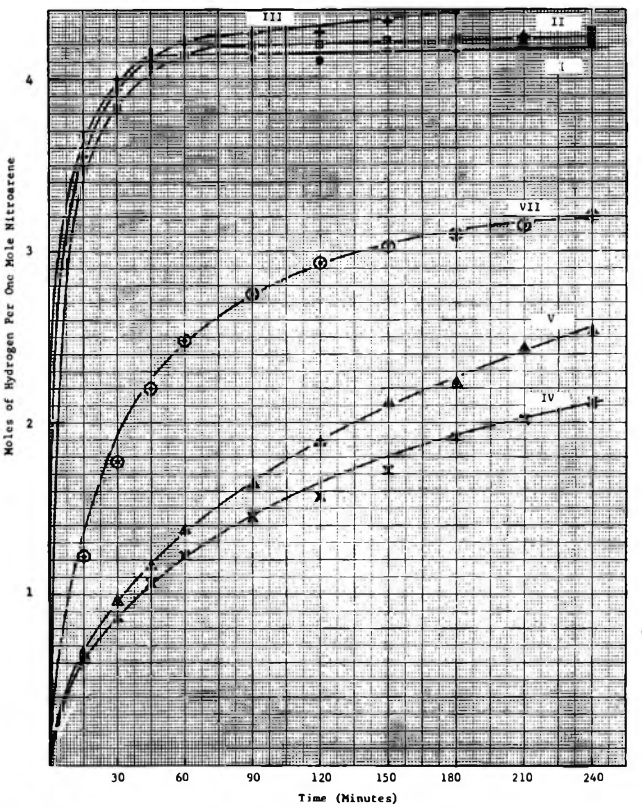


Figure 2.—Hydrogenation of nitropolymethylbiphenyls over palladium–charcoal in acetone solution.

A suspension of 1 g of 5% palladium on charcoal in 105 ml of acetone was saturated with hydrogen in a magnetically stirred microhydrogenator. Samples of I, II, III, IV, V, or VII (0.200 g in 5 ml of acetone) were injected with a syringe through a serum cap. The hydrogen uptake at atmospheric pressure and room temperature (corrected for solvent absorption) is recorded in Figure 2.

Diazotization of Aminopolymethylbiphenyls and Decomposition in Aqueous Sulfuric Acid.—A mixture of 0.02 mol of amine and 250 ml of 3% sulfuric acid was stirred and warmed to form a fine suspension of the amine salt. The suspension was rapidly cooled, and, if the crystals were large, they were finely ground. Then the mixture was diazotized at −2 to 0° with a solution of 1.7–2.0 g of sodium nitrite in 12 ml of water and stirred for one additional hour at 0°. Solutions of the diazonium salts from 2-amino-3′,4,4′,5-tetramethylbiphenyl, XVIII, XIX, XX, and XXIII were filtered, and decomposed at 70–75° after addition of a spatula tip of urea. The diazonium salts from XXI and XXII precipitated; these were decomposed in a stirred suspension after addition of urea.

The product that precipitated from the cooled solution was extracted with ether, and the ether solution was washed, dried, and evaporated *in vacuo*. From XVIII, XIX, and XXI the corresponding fluorenes XXIV, XXV, and XXVI were readily obtained by recrystallization from methanol or benzene–methanol. Purification of the phenols XXVII–XXXIII from 2-amino-3′,4,4′,5-tetramethylbiphenyl and the amines XVIII–XXIII was more difficult, primarily because of their high solubility in organic solvents. These phenols could not be extracted into 10% aqueous sodium hydroxide; even Claisen's solution prepared from 300 g of potassium hydroxide, 200 ml of water, and 800 ml of methanol had unfavorable distribution constants (*e.g.*, the ether solution of the fluorene–phenol mixture from VIII was extracted 16 times with Claisen's solution). This treatment removed only 94% of the phenol from the ether layer.

In the absence of fluorene formation, the phenols were obtained by fractionation at 0.1 Torr, followed by recrystallization from hexane when applicable. In case of fluorene formation, the mother liquors of the fluorenes were taken down to dryness. Residues were crystallized from aqueous methanol to remove fluorenes as completely as possible. From their mother liquors the phenols were recovered in 93–97% purity. Removal of the residual fluorene by chromatography was successful only for

(26) For review of previous mechanistic suggestions, see R. C. Elderfield, Ed., "Heterocyclic Compounds," Vol. 6, Chapman & Hall, Ltd., New York, N. Y., 1957, pp 136–155.

(27) W. S. Emerson and H. W. Mohrman, *J. Amer. Chem. Soc.*, **62**, 69 (1940).

XXVIII. From basic alumina (Brockmann grade I) hexane eluted the fluorene only; the phenol was eluted with hexane-chloroform.

Attempts to Improve the Yield of Fluorene Formation from XIX. A.—Compound XIX (2.4 g) was diazotized in 200 ml of 1.5% hydrochloric acid and the diazonium salt decomposed at 70°. Yields of the corresponding fluorene, phenol, and chlorobiphenyl were 52, 39, and 2%, respectively, according to mass spectrometric analysis of the product mixture at low voltage (7.5 V uncor). This method may be favored over the diazotization in dilute sulfuric acid for solubility reasons, if isolation of the phenol is not required.

B.—Compound XIX was diazotized as in method A and decomposed at room temperature after a solution of 1.6 g of cuprous chloride in 56 ml of 8% hydrochloric acid was added. Mass spectrometric analysis of the product mixture showed 43% fluorene, 43% phenol, and 5.5% chlorinated biphenyl.

C.—Compound XIX (2.4 g) was stirred with 80% sulfuric acid and diazotized at 0° by adding finely powdered sodium nitrite (0.8 g). The solution was cloudy. After 1 hr, the mixture was decomposed at 45°. Mass spectrometric analysis indicated 49% fluorene, 9% phenol, 26% dimeric hydrocarbons, and 7% dimeric ether or phenol in the product mixture.

D.—Boric acid (1.2 g) was stirred in concentrated hydrochloric acid (8 ml) and sodium fluoride (3.4 g) was slowly added in a fume hood. After standing 1 hr, the sodium chloride precipitate was suction filtered on a fiber-glass filter. The diazonium solution prepared from 2.4 g of compound XIX in 40 ml of 2.5% hydrochloric acid was added to the filtrate. The pale yellow diazonium fluoroborate precipitate was filtered, washed with distilled water, and vacuum dried over phosphorus pentoxide at 55°. The ir spectrum of the dried salt indicated the presence of crystal water (3320 cm^{-1}); its decomposition point was 95°. During overnight drying at 55° the salt decomposed. The product mixture, according to mass spectrometric and gas chromatographic analyses, was 65% fluorinated biphenyl and 25% fluorene. Decomposition of the diazonium fluoroborate at 100° gave 70% fluorinated biphenyl and 18% fluorene.

Registry No.—VIII, 17447-85-7; IX, 17449-10-4; X, 17477-84-8; XI, 17449-11-5; XII, 17449-12-6; XIII, 17477-85-9; XIV, 17416-89-6; XV, 17416-90-9; XVI, 17416-91-0; XVII, 17447-86-8; XVIII, 17416-92-1; XIX, 17447-87-9; XX, 17447-97-1; XXI, 17416-93-2; XXII, 17447-88-0; XXIII, 17447-89-1; XXIV, 17416-94-3; XXV, 17447-90-4; XXVI, 17447-98-2; XXVII, 17416-95-4; XXVIII, 17447-91-5; XXIX, 17447-92-6; XXX, 17447-93-7; XXXI, 17447-94-8; XXXII, 17447-95-9; XXXIII, 17447-96-0.

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Resolution of Trifluoromethylcarbinols[1,2]

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(±)-Phenyltrifluoromethylcarbinol and (±)-*t*-butyltrifluoromethylcarbinol have been resolved *via* the 3β-acetoxy-Δ⁵-etienate esters, but (±)-methyltrifluoromethylcarbinol could not be resolved by this method. The completeness of the resolution of the first compound was confirmed by a gas chromatographic study of its O-methylmandelate ester, and the enantiomeric purity of a partially active sample of the methyltrifluoromethylcarbinol was determined by the same method. This glpc method was not applicable to the determination of enantiomeric purity of *t*-butyltrifluoromethylcarbinol.

As part of a continuing investigation[4,5] of asymmetric reductions of the corresponding ketones, it became necessary to know the absolute configuration and maximum rotation of phenyl-, *t*-butyl-, and methyltrifluoromethylcarbinols (IA, IB, and IC). The present paper describes the resolutions of two of these, and the subsequent paper[6] describes the experiments upon which the absolute configurations are based.

(±)-Phenyltrifluoromethylcarbinol (IA) was converted into the diastereomeric 3β-acetoxy-Δ⁵-etienate esters[7] which were carried through an extensive systematic fractional crystallization using 2-propanol as solvent.[3] Both the less soluble and more soluble diastereomers were obtained, from which were regenerated by lithium aluminum hydride reduction, respectively, the (−)-carbinol, $[\alpha]^{25}D$ −31.85° (neat), and the (+)-carbinol, $[\alpha]^{26}D$ +31.82° (neat). The absolute enantiomeric purities of these samples were established by gas–liquid partition chromatographic (glpc) studies as described in the following section.

(±)-*t*-Butyltrifluoromethylcarbinol (IB) was also resolved *via* the 3β-acetoxy-Δ⁵-etienate ester, but only the less soluble diastereomer could be obtained in purified form after exhaustive fractional crystallization from 2-propanol. The (+)-carbinol, $[\alpha]^{23}D$ +5.55° (neat, *d* 1.12), was regenerated by lithium aluminum hydride reduction. We presume this (+)-*t*-butyltrifluoromethylcarbinol to be enantiomerically pure; however there is no direct evidence for this beyond the normal recrystallization behavior of the etienate ester and the reasonable magnitude of its rotation since the glpc method and nmr method[8] were inapplicable as described in the following section.

Previous attempts to resolve methyltrifluoromethylcarbinol (IC) *via* the brucine salt of the acid phthalate failed for reasons similar to those reported in the earlier attempted resolution of phenyltrifluoromethylcarbinol.[4] The 3β-acetoxy-Δ⁵-etienate was prepared but failed to crystallize; we, therefore, resorted to glpc methods for

(1) We acknowledge with gratitude support for these studies from the National Science Foundation (GP 6738) and the National Institutes of Health (GM 05248).

(2) A preliminary report of some of these results has been published: D. M. Feigl and H. S. Mosher, *Chem. Commun.*, 615 (1965).

(3) Taken from the Ph.D. Thesis of D. M. Feigl, Stanford University, 1965.

(4) H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *J. Amer. Chem. Soc.*, **78**, 4374 (1956).

(5) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964).

(6) H. M. Peters, D. M. Feigl, and H. S. Mosher, *ibid.*, **33**, 4245 (1968).

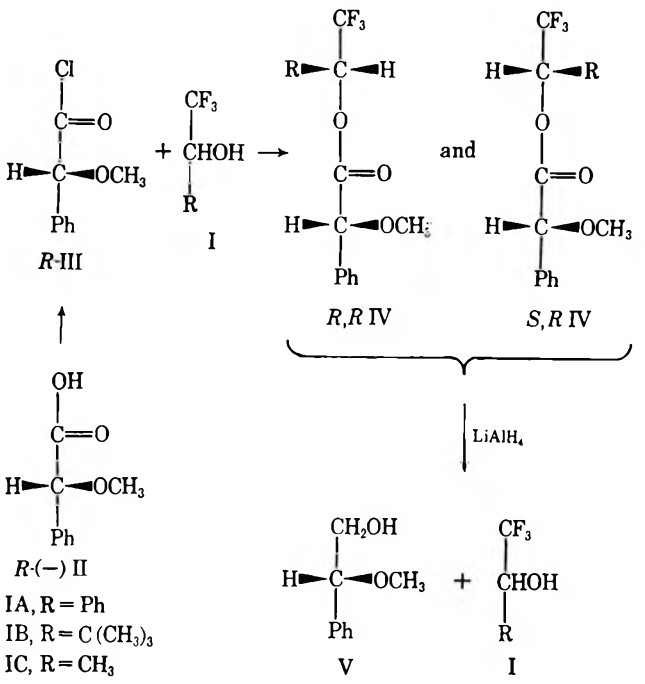
(7) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(8) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968).

determining the enantiomeric purity[9] of a partially active sample obtained by asymmetric reduction.[3]

The general use of glpc for determining enantiomeric purity has been reviewed,[9] but it seems worthwhile to comment on its specific application to the compounds under consideration. The O-methylmandelate esters (IV) of the three carbinols (IA, IB, and IC) were prepared as indicated in the Scheme I.

SCHEME I



When an enantiomerically pure reagent[10] (*R* III) is allowed to react with a carbinol (I) consisting of a mixture of enantiomers, a mixture of epimers (*R,R* IV and *S,R* IV) will result. If there is no racemization of carbinol (I), reagent (III), or products (IV), and if there is no kinetic resolution during this process, then the mixture of epimers (*R,R* IV and *S,R* IV) will be formed in exactly the same ratio as the enantiomers initially present. Therefore, any suitable method for determining the epimer composition (*R,R* IV and *S,R* IV) will constitute a valid method for determining the enantiomeric purity of the original carbinol (I). We have employed this method to establish the enantiomeric purity of phenyltrifluoromethylcarbinol (IA) using O-methylmandeloyl chloride[2,11] (III) as the chiral reagent. The epimeric phenyltrifluoromethylcarbinyl O-methylmandelates (*R,R* IVA and *S,R* IVA) resulting from the reaction of resolved IA with *R*-(−) II were readily separable by glpc (Carbowax 20M, 20 ft × 1/4 in. column, 250°, helium flow rate 86 ml/min, retention times 61 and 64 min, respectively). The acid chloride, prepared[12] from acid which was 96% enantiomerically pure[13] was treated with resolved IA in benzene–pyridine solution at 25° for 3 hr. The esters gave a gas chromatogram showing two peaks, the first and lesser one with an area of 3 ± 1% of the major peak. Based upon the known presence of 2% of the (+)-O-methylmandelic acid in reagent II, this result is within experimental error of that expected of enantiomerically pure IA and confirms the completeness of the resolution of the etienate ester.[14] An aliquot of this same reaction mixture which was stirred for 7 hr instead of three gave a product with identical composition as determined by glpc. When this reaction was first carried out however, the benzene–pyridine solution of mandeloyl chloride and resolved alcohol was heated for 8 hr under reflux in an oil bath at 90°. The isolated diastereomeric ester mixture gave a gas chromatogram indicating relative areas of approximately 33:67. On the basis of this experiment alone we might have concluded that the etienate-resolved carbinol was only 67% enantiomerically pure. This mixture of esters was reduced with lithium aluminum hydride to regenerate carbinol IA and to give 2-methoxy-2-phenylethanol (V) which had a rotation $[\alpha]^{28}D$ −73° (*c* 5.2, ethanol) compared with $[\alpha]^{29}D$ −127° (*c* 2.6, ethanol) for the product obtained by direct lithium aluminum hydride reduction of the starting O-methylmandelic acid (I → V). This indicated approximately 40% racemization at the mandelate moiety during the reaction when carried out at reflux. It is therefore essential in applying this glpc method (or the nmr method[8]) to the determination of enantiomeric purity that the necessary control experiments be done to ensure that no racemization or kinetic resolution has taken place under the reaction conditions employed.

The diastereomeric O-methylmandelate esters of (±)-*t*-butyltrifluoromethylcarbinol were obtained in excellent yield, but we were unable to find glpc conditions which would separate them. Furthermore, nmr studies[8] on the esters made from this resolved carbinol showed that extensive racemization had taken place. The same was true for the atrolactate ester of this carbinol. N-Trifluoroacetylleucine and N-trifluoroacetylproline gave diastereomers from (±) IB which were nicely separated by glpc, but the yields were so low under a variety of conditions that these derivatives were precluded from study for the purpose of determining enantiomeric purity. The completeness of the resolution of this carbinol is therefore not proven and only presumed on the basis of the constant melting point and rotation of the etienate ester and the reasonable magnitude of its rotation.

Application of glpc to the determination of the enantiomeric purity of a partially active sample of methyltrifluoromethylcarbinol *via* the O-methylmandelate es-

(9) The theory and details of this method have now been reviewed by M. Raban and K. Mislow in "Topics in Stereochemistry," Vol. II, E. L. Eliel and N. L. Allinger, Ed., Interscience Publishers, New York, N. Y., 1967, p 230.

(10) It is not absolutely necessary to use enantiomerically pure III since a correction can be made for the known amount of the diastereomeric products *R,S* IV and *S,S* IV which will have the same retention times as their enantiomers *S,R* IV and *R,R* IV but the results will be in error to the extent that kinetic resolution is involved in the reaction.

(11) M. Raban and K. Mislow, *Tetrahedron Lett.*, 3961 (1966).

(12) The acid chloride was prepared by allowing the acid to stand at room temperature with excess thionyl chloride in a benzene–thionyl chloride solution for 8 hr, prolonged refluxing with thionyl chloride, or attempted purification by distillation caused partial racemization.

(13) Per cent enantiomeric purity is defined as the excess of one enantiomer over the racemate; *i.e.*, this sample of acid was a mixture of 98% (−) isomer and 2% (+) isomer as measured by optical rotation.

(14) W. H. Pirkle [*J. Amer. Chem. Soc.*, **88**, 1837 (1966)] has calculated a value of [α] 36.5 ± 7.5° (neat) for the rotation of enantiomerically pure IA based upon the nmr analysis of the (−)-α-phenethylamine solution of a partially active sample of phenyltrifluoromethylcarbinol. This value within its broad limits of error agrees with the value of [α]D 31.8 obtained by resolution and confirmed by glpc in the present study and by nmr on the O-methylmandelate.[8]

ters has already been published.[2] The value of $[\alpha]^{27}D$ +5.6° (neat)[15] obtained in this way corresponds to the value of $[\alpha]^{27}D$ −5.65 which has now been obtained by Crawford[16] by resolution. We have also confirmed the glpc-determined enantiomeric purity of the partially active sample by use of nmr on the O-methylmandelate.[8] We also attempted to use (−)-hydratropic acid as the chiral reagent for diastereomer analysis of methyltrifluoromethylcarbinol. During the sequence of acid chloride formation, treatment with IC in benzene–pyridine *at room temperature*, and reduction with lithium aluminum hydride to give 2-phenylpropanol, racemization to the extent of approximately 10% took place in the hydratropate moiety. This again emphasizes the necessity for control experiments before this general method can be applied with safety in any particular system.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected; elemental analyses were performed by Mr. E. Meier of the Stanford University Microanalytical Laboratories; and the gas chromatography was done with a Varian Aerograph A-90 instrument. All products showed ir and nmr spectra compatible with the assigned structures.

3β-Acetoxy-Δ⁵-etienic Acid.—This acid (354 g) was prepared in 78% yield by hypobromite oxidation of pregnenolone acetate[17,18] followed by acetylation[19] with acetic anhydride in dry pyridine.

Phenyltrifluoromethylcarbinyl 3β-Acetoxy-Δ⁵-etienate.—3β-Acetoxy-Δ⁵-etienic acid (40 g) was treated with oxalyl chloride (100 g) in benzene (500 ml) for 10 hr at room temperature and isolated as described by Djerassi, *et al.*[19] The resulting yellow oil was stirred with a solution of 18 g of phenyltrifluoromethylcarbinol[4] in 500 ml of anhydrous pyridine at room temperatue for 65 hr. The reaction mixture was poured into 4 l. of cold 2.4 *N* hydrochloric acid, and the ester was extracted with ether to give, after drying ($MgSO_4$) and concentration, an orange-colored glass which was dissolved in 200 ml of warm hexane and cooled slowly to 5° to give, after concentration of the mother liquors, a total of 44.4 g of a tan solid: 86% crude yield; $[\alpha]^{25}D$ −13.9 ± 0.2°. A total of 90 g of the mixture of esters was subjected to a 14-stage systematic fractional crystallization using about 6–10 ml of 2-propanol/gram of solid,[20] to give about 12 g of the more insoluble ester, mp 125–126.5°, $[\alpha]^{20}D$ 0.0° (*c* ~1, acetone), and about 7 g of more soluble ester, mp 153–155°, $[\alpha]^{25}D$ −21° (*c* 1, acetone).

Anal. Calcd for $C_{30}H_{37}O_4F_3$: C, 69.50; H, 7.14. Found: C, 69.64, 69.33; H, 7.19, 7.28.

(−)-Phenyltrifluoromethylcarbinol.—The less soluble ester (11.11 g) was reduced with lithium aluminum hydride, (1.65 g) in ether solvent (120 ml). The reaction mixture was refluxed for 30 min and decomposed with saturated ammonium chloride solution. The ether layer was dried ($MgSO_4$); the ether was removed under vacuum; and the residue was distilled at 17-mm pressure to give (−)-phenyltrifluoromethylcarbinol, bp 99–105°, 3.1 g (82% yield), which was further purified by preparative glpc (silicone rubber column 20 ft × 3/8 in., 153°, helium flow rate 52 ml/min) to give a product with $\alpha^{25}D$ −20.59° (neat, *l* = 0.5); $[\alpha]^{26}D$ −31.85° (neat); $n^{24}D$ 1.4602.

(+)-Phenyltrifluoromethylcarbinol was regenerated in the same way to yield material with $\alpha^{26}D$ +41.14° (neat, *l* = 1), $[\alpha]^{26}D$ +31.82 (neat).

t-Butyl Trifluoromethyl Ketone.—We found the literature methods using *t*-butylmagnesium chloride on trifluoroacetic acid[21,22] or trifluoroacetic anhydride[23] to be unsatisfactory. Trifluoroacetonitrile (68 g) was dissolved in ether in a flask cooled in Dry Ice and equipped with a Dry Ice condenser. Cuprous chloride (1 g) was added, followed by *t*-butylmagnesium chloride (595 ml of a 1.15 *N* solution). After the reaction mixture had been stirred overnight at room temperature, it was cooled and decomposed by the addition of hydrochloric acid (250 ml of 6 *N*). The mixture was warmed to room temperature with stirring, and, after 30 min, the ether layer was separated, dried ($MgSO_4$), and distilled to give a 54% crude yield of material boiling between 57 and 78°. Gas chromatographic purification of this material and several other samples made by alternate procedures[21,23] gave material with $n^{23}D$ 1.3383 which differed considerably from the literature value[22] of $n^{20}D$ 1.3515. A higher boiling material was traced to an impurity in the trifluoroacetonitrile.

When this same procedure was followed, except that the mixture was hydrolyzed with ammonium chloride at room temperature, an 82% yield of *t*-butyltrifluoromethylketimine was obtained (bp 76–80°; $n^{20}D$ 1.3617).

Anal. Calcd for $C_6H_{10}F_3N$: C, 47.06; H, 6.54; N, 9.15. Found: C, 47.45; H, 6.71; N, 8.91.

(+)-t-Butyltrifluoromethylcarbinol.—This was prepared by lithium aluminum hydride reduction of the ketone in 88% yield: bp 107–113°; $n^{24}D$ 1.3668 (lit.[24] bp 110.5°; $n^{20}D$ 1.3670).

(+)-t-Butyltrifluoromethylcarbinol.—Using the procedure described for the 3β-acetoxy-Δ⁵-etienate of phenyltrifluoromethylcarbinol, *t*-butyltrifluoromethylcarbinyl 3β-acetoxy-Δ⁵-etienate (113 g) was prepared in 86% crude yield, and the mixture of diastereomers was subjected to a 12-stage systematic fractional crystallization from 2-propanol. Two types of crystals were encountered, needles and plates. The plates required many recrystallizations before a portion was obtained as needles, but once the needles were obtained they yielded the pure disastereomer in about four recrystallizations: mp 142–144°; $[\alpha]^{25}D$ −24° (*c* 1, acetone).

Anal. Calcd for $C_{28}H_{41}O_4F_3$: C, 67.47; H, 8.23. Found: C, 67.29; H, 8.21.

The more soluble diastereomer could not be obtained from the mother liquors. The resolved etienate (8 g) was subjected to lithium aluminum hydride reduction as described for the phenyl analog to give 1.9 g of carbinol, which was further purified by preparative glpc (PDEAS column, 10 ft × 3/8 in., 115°, helium flow rate 48 ml/min) to give a product with $\alpha^{23}D$ +6.20° (neat, *l* = 1); $n^{25}D$ 1.3664.

Methyltrifluoromethylcarbinyl 3β-Acetoxy-Δ⁶-etienate.—By the procedure described for the phenyl analog this compound was only obtained as a glass.

(−)-Phenyltrifluoromethylcarbinyl O-Methylmandelate.—O-Methylmandelic acid[25] {1.0 g, 6 mmol; $[\alpha]^{25}D$ −144° (ethanol); 96% enantiomerically pure based on the highest literature value of $[\alpha]^{17}D$ −150° (ethanol)[26]} was converted into the acid chloride by stirring with 10 g of thionyl chloride at room temperature overnight. The excess thionyl chloride was removed under vacuum; 3 ml of anhydrous benzene was added to the residue; and the solution concentrated to dryness; this latter process was repeated to remove the last traces of thionyl chloride. The acid chloride was dissolved in benzene (3 ml) and combined with (−)-phenyltrifluoromethylcarbinol (0.29 g, 1.5 mmol) in 3 ml of anhydrous pyridine. After the mixture had stood 3 hr at room temperature, one-half was diluted with water, stirred, and extracted with ether; the ether solution was washed with cold dilute hydrochloric acid, bicarbonate solution, and water, and dried ($MgSO_4$), and the volatile materials were removed under vacuum, leaving 0.13 g of yellow oil. After the second half of the mixture had stood 7 hr at room temperature, it was processed in the same manner to give the ester which gave an identical gas chromatogram.

This same experiment was originally conducted with the variation that the mixture of mandeloyl chloride, (−)-phenyltrifluoromethylcarbinol, pyridine, and benzene was heated under reflux in an oil bath at 90° overnight and then worked up in the

(15) In ref 2, a typesetting error placed brackets around the observed rotation of $\alpha^{26}D$ −2.20 ± 0.02° (neat, *l* = 0.5), $\alpha^{27}D$ −4.40° (neat, *l* = 1), and $\alpha^{27}D$ max − 7.1° (neat, *l* = 1).

(16) J. W. C. Crawford, *J. Chem. Soc.*, 4280 (1965); 2332 (1967).

(17) We wish to thank the Syntex Corp. for a generous gift of this starting material.

(18) J. Staunton and E. J. Eisenbraun, *Org. Syn.*, **42**, 4 (1962).

(19) C. Djerassi, J. Burakevich, J. W. Chamberlin, D. Elad, T. Toda, and G. Stork, *J. Amer. Chem. Soc.*, **86**, 465 (1964).

(20) Reference 3 must be consulted for the details of this lengthy process.

(21) K. T. Dishart and R. Levine, *J. Amer. Chem. Soc.*, **78**, 2268 (1956).

(22) A. Sykes, J. C. Tatlow, and C. R. Thomas, *J. Chem. Soc.*, 835 (1956).

(23) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(24) E. T. McBee, O. R. Pierce, and O. D. Meyer, *J. Amer. Chem. Soc.*, **77**, 83 (1955).

(25) W. A. Bonner, *ibid.*, **73**, 3126 (1951).

(26) A. McKenzie and H. Wren, *J. Chem. Soc.*, **115**, 611 (1919).

same way. An analytical gas chromatogram of the resulting ester mixture showed relative peak areas of about 33 to 67. The mixture of diastereomeric esters was spearated from extraneous impurities by preparative glpc (SF-96 silicone column, 6 ft × 1/4 in. 190°, helium flow rate 100 ml/min, retention time 10 min, one peak) to give 0.37 g which was reduced with lithium aluminum hydride, hydrolyzed, and distilled to give 0.29 g of a carbinol mixture which was separated by glpc (SE-30 silicone column, 20 ft × 3/8 in. 200°, helium flow rate 75 ml/min) to give phenyltrifluoromethylcarbinol {retention time 16 min; 10 mg; $\alpha^{28}D$ −0.26 ± 0.02° (c 2.0, chloroform, l = 0.5); $[\alpha]^{28}D$ −25 ± 2° (c 2, chloroform)} and 2-methoxy-2-phenylethanol {retention time 36 min; 26 mg; $\alpha^{28}D$ −1.89 ± 0.01° (c 5.15, ethanol, l = 0.5); $[\alpha]^{28}D$ −73° (c 5.15, ethanol)}. The rotation of the volatile phenyltrifluoromethylcarbinol was determined on a very small amount of material, and the indicated racemization of 15 ± 6% may not be significant, but the latter compound is clearly racemized to the extent of approximately 35% as shown by the following experiment.

(−)-2-Methoxy-2-phenylethanol.—O-Methylmandelic acid {1.0 g; $[\alpha]^{25}D$ −144° (c 1.2, ethanol); 96% enantiomerically pure} was reduced with lithium aluminum hydride, and the (−)-2-methoxy-2-phenylethanol was isolated and purified as above to give a product with $\alpha^{27}D$ −134.78° (neat, l = 1); $\alpha^{29}D$ −8.17 ± 0.02° (c 6.425, ethanol, l = 1); $[\alpha]^{29}D$ −127.0 ± 0.4° (c 6.4, ethanol).

Partially Active (+)-Methyltrifluoromethylcarbinol.—Methyl trifluoromethyl ketone (7 g) was treated with 65 ml of a 0.93 *N* solution of the Grignard reagent from (+)-1-chloro-2-phenylbutane[5] [$\alpha^{27}D$ +5.68° (neat); 96% enantiomerically pure] in ether at 35°. The reaction mixture was processed in the usual way and distilled to give a 63% yield of (−)-methyltrifluoromethylcarbinol which upon purification by gas chromatography had $\alpha^{26}D$ −2.20° (neat, l = 0.5). A second experiment using twice these amounts gave material after purification of $\alpha^{24}D$ −2.03° (neat, l = 0.5).

Esters from (+)-, (−)-, and (±)-Methyltrifluoromethylcarbinol and (−)-O-Methylmandelic Acid.—The preparation and gas chromatography of these have been previously described.[2]

Registry No.—Phenyltrifluoromethylcarbinyl 3β-acetoxy-Δ⁵-etienate, 17628-68-1; (−)-IA, 10531-50-7; (+)-IA, 340-06-7; *t*-butyltrifluoromethylketimine, 17629-00-4; (+)-IB, 17628-71-6; (−)-2-methoxy-2-phenylethanol, 17628-72-7; (+)-IC, 17628-73-8.

Absolute Configuration of Substituted Trifluoromethylcarbinols[1,2]

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By application of Freudenberg's rule of rotational shifts as applied to a series of acetate, benzoate, and acid phthalate esters, the absolute *S* configuration was assigned to (+)-phenyltrifluoromethylcarbinol, (−)-methyltrifluoromethylcarbinol, and (−)-*t*-butyltrifluoromethylcarbinol. However, these correlations were not ideal, and thus the absolute configurations of the phenyl and methyl compounds were verified by synthesis of their O-methyl and O-ethyl ethers by the action of sulfur tetrafluoride on (*S*)-O-methylmandelic acid and (*S*)-O-ethyllactic acid, respectively. This process is one which does not affect the chiral center of known configuration. The absolute configurations of these trifluoromethyl compounds and their several derivatives are now established with certainty.

In order to gain additional information concerning the relative importance of steric *vs.* electronic effects in the Grignard asymmetric reduction reaction[4-8] we have been studying the asymmetric reduction of several substituted trifluoromethyl ketones. The previous paper in this series[9] describes the resolution of three such compounds: phenyltrifluoromethylcarbinol, methyltrifluoromethylcarbinol, and *t*-butyltrifluoromethylcarbinol. The present paper describes studies which establish the absolute configuration of these compounds.

We initially investigated[5] the application of Freudenberg's rule of rotational shifts[10] to a series of derivatives of these carbinols and compared the results with those from the corresponding nonfluorinated carbinols of known configuration. The results for the phenylalkylcarbinols are summarized in Table I, for the methylalkylcarbinols in Table II, and for the *t*-butylalkylcarbinols in Table III.[11]

The derivatives of (+)-phenyltrifluoromethylcarbinol exhibit rotational shifts comparable with those for the corresponding (+)-phenylalkylcarbinols if one excludes the acid phthalate of phenylmethylcarbinol from consideration.[12,13]

It is *not* possible to make a logical arrangement of the data based upon the opposite assumption that (−)-phenyltrifluoromethylcarbinol is related to the other (+)-phenylalkylcarbinols. Therefore, it seems reasonably certain, based upon these data, that (+)-phenyltrifluoromethylcarbinol is configurationally related to the (+)-phenylalkylcarbinols as represented

(1) Presented in part before the Division of Organic Chemistry at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) We acknowledge with gratitude support for these studies from the National Science Foundation (GP 6738) and the National Institutes of Health (GM 05248).

(3) (a) Taken in part from the Ph.D. Theses of H. M. Peters, Stanford University, Oct 1966, and D. M. Feigl, Stanford University, Oct 1965. (b) Parke, Davis & Co Fellow, 1965–1966.

(4) H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *J. Amer. Chem. Soc.*, **78**, 4374 (1956).

(5) D. M. Feigl, Ph.D. Thesis, Stanford University, Oct 1965.

(6) D. L. Dull, Ph.D. Thesis, Stanford University, June 1967.

(7) B. J. G. McFarland, Ph.D. Thesis, Stanford University, Nov 1965.

(8) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964), and references therein.

(9) D. M. Feigl and H. S. Mosher, *ibid.*, **33**, 4242 (1968).

(10) K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1933, p 677.

(11) These data are presented in modified form. Derivatives actually may have been prepared from either enantiomer, but the results reported in Tables I–III have been adjusted as if compounds of only one of the two enantiomers had been used. Enantiomerically impure samples were often used in the preparation of derivatives. However, great care was taken to prevent the concentration of either enantiomer during the synthesis or purification of these derivatives, and the rotations presented in Tables I–III have been adjusted to those for enantiomerically pure derivatives using the known purity of the starting carbinols.

(12) The rotation of the acid phthalate of phenylmethylcarbinol does not fit well into this series as has been observed earlier. At one time this anomaly rendered the assignment of relative configurations of the phenylalkylcarbinols uncertain. However, (+)-phenylmethylcarbinol and (+)-phenylethylcarbinol have been interrelated by direct chemical means[13] and it is now certain that they have the same relative configuration.

(13) R. MacLeod, F. J. Welch, E. M. La Combe, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960).

TABLE I
MAXIMUM MOLECULAR ROTATIONS
OF HO–C(R)(Ph)–H AND DERIVATIVES[a]

	[M]D,[a] deg				
		Carbinol		Acid	
R	Benzoate (neat)	(neat)	(in benzene)	phthalate (in $CHCl_3$)	Acetate (neat)
Methyl		+53		−45	+194
Ethyl	−41[b,c]	+39		+100	+186
n-Propyl		+44	+65	+130	+200
Isopropyl	−98[b,c]	+37		+133	
Cyclohexyl	−95[d]		+54	+178	+165
n-Butyl		+28	+52	+200	+163
Isobutyl		+40	+54	+110	
t-Butyl	−240[b,e]		+45	+86	
Trifluoromethyl	−235	+56	+26	+69	+209

[a] Except for the trifluoromethyl compounds, all rotations were taken from R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960), unless otherwise noted. See ref 11 in text. [b] Compound prepared for the present study.[5] [c] Value given is for MD, not [M]D. Specific rotation could not be calculated because density was not available. [d] From M. P. Balfe, G. H. Beaven, and J. Kenyon, *J. Chem. Soc.*, 1857 (1950). [e] Rotation taken in benzene.

TABLE II
MAXIMUM MOLECULAR ROTATIONS
OF H–C(CH3)(R)–OH AND DERIVATIVES[a]

	[M]D,[a] deg			
R	Carbinol (neat)	Acetate (neat)	Benzoate (neat)	Acid phthalate (in $CHCl_3$)
Trifluoromethyl	−6.3	+29	+0.3[b]	+52
Ethyl	+10.3[c]	+30[d]	+70[e]	+88[c,f]
Isopropyl	+4.3	+25	+80	+89
n-Propyl	+12.1	+22		+95
n-Butyl	+12.0	+17		+117
t-Butyl	+7.8	+26	+93	+160

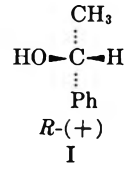
[a] Except for the trifluoromethyl compounds, all rotations are from P. G. Stevens, *J. Amer. Chem. Soc.*, **55**, 4237 (1933), unless otherwise noted. See ref 11 in text. [b] Value given is MD, not [M]D. Specific rotation could not be calculated because density was not available. [c] C. E. Wood, J. E. Such, and F. Scarf, *J. Chem. Soc.*, 1935 (1926). [d] R. H. Pickard and J. Kenyon, *ibid.*, **105**, 830 (1914). [e] J. Kenyon and R. H. Pickard, *ibid.*, **107**, 115 (1915). [f] Rotation taken in ethanol.

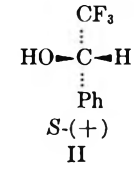
TABLE III
MAXIMUM MOLECULAR ROTATIONS
OF H–C(t-C4H9)(R)–OH AND DERIVATIVES[a]

	[M]D,[a] deg			
R	Carbinol (neat)	Acetate (neat)	Benzoate (neat)	Acid phthalate (in $CHCl_3$)
Trifluoromethyl	+8.7	−50[b]	+64[b]	+148
Methyl	+7.8	+26	+93	+160
Isopropyl	−14	+3.7	−0.5	0.0
Ethyl	−39	−44	−18	+3.3
n-Propyl	−55	−59	−20	+8.4
n-Butyl	−60	−51	−40	−13
Isobutyl	−78	−66	−43	−24

[a] Except for the trifluoromethyl compounds, all rotations were taken from W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *J. Amer. Chem. Soc.*, **81**, 2779 (1959). See ref 11 in text. [b] Value given is for MD, not [M]D. Specific rotation could not be calculated because density was not available.

in Table I. Since the absolute configuration of (+)-phenylmethylcarbinol (I) has been established unequivocally as *R*, (+)-phenyltrifluoromethylcarbinol (II) must have the absolute *S* configuration.

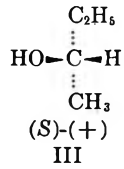

R-(+)
I

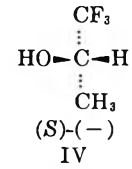

S-(+)
II

That (*S*)-phenyltrifluoromethylcarbinol (II) is configurationally related to (*R*)-phenylmethylcarbinol (I) results from the inversion in order of precedence assigned to the trifluoromethyl group and phenyl group compared with the other alkyl groups and phenyl according to the configurational nomenclature scheme of Cahn, Ingold, and Prelog.[14]

All the derivatives of both (−)-methyltrifluoromethylcarbinol and (+)-alkylmethylcarbinols have a positive rotational shift in progressing from the carbinols to the acetates, benzoates, and acid phthalates as represented in Table II. Except for the benzoate, the magnitudes of the shifts for the trifluoromethyl compounds are comparable with those of the nonfluorinated derivatives. Although the benzoate rotation was close to zero, there is no reason to believe that preparation of the benzoate was accompanied by any racemization since the preparations of the other benzoates, including those of the other trifluoromethyl compounds, was not accompanied by racemization. Despite this one nonideal fit to the Freudenberg series, it is not logically possible to fit the (+) enantiomer of methyltrifluoromethylcarbinol and its derivatives to this series, and thus the evidence strongly supports the conclusion that (−)-methyltrifluoromethylcarbinol is configurationally related to the other (+)-methylalkylcarbinols of Table II.

Since the absolute configuration of (+)-methylethylcarbinol (III), (+)-2-butanol, has been established as *S* with certainty,[15] (−)-methyltrifluoromethylcarbinol (IV) must have the absolute *S* configuration also.


(*S*)-(+)
III


(*S*)-(−)
IV

The optical rotations of the esters of (+)-*t*-butyltrifluoromethylcarbinol are compared with those of other *t*-butylalkylcarbinols in Table III. There is excellent correlation of increasing rotational shifts for these derivatives in going from the acetates to the benzoates to the acid phthalates with the exception of the isopropyl example which has already been discussed.[16] The correlations in going from the rotations of the neat carbinols to those of the acetate, however, are erratic. The rotational shift is slightly negative for the ethyl, *n*-propyl, and isobutyl compounds; slightly positive for the methyl, isopropyl, and *n*-butyl compounds; but strongly negative for the trifluoromethyl case. Never-

(14) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966).
(15) K. Wiberg, *J. Amer. Chem. Soc.*, **74**, 3891 (1952).
(16) W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *ibid.*, **81**, 2779 (1959).

theless it is not possible to fit the enantiomeric (−)-*t*-butyltrifluoromethylcarbinol and its derivatives logically into this series, and we are compelled to conclude that (+)-*t*-butyltrifluoromethylcarbinol is configurationally related to (+)-*t*-butylmethylcarbinol and the other (−)-*t*-butylalkylcarbinols of Table III. It is reasonably certain that the absolute configuration of (+)-*t*-butylmethylcarbinol is *S*[16,17] as represented by V and therefore the absolute configurations of the trifluoromethyl derivatives is *R* as represented in VI.

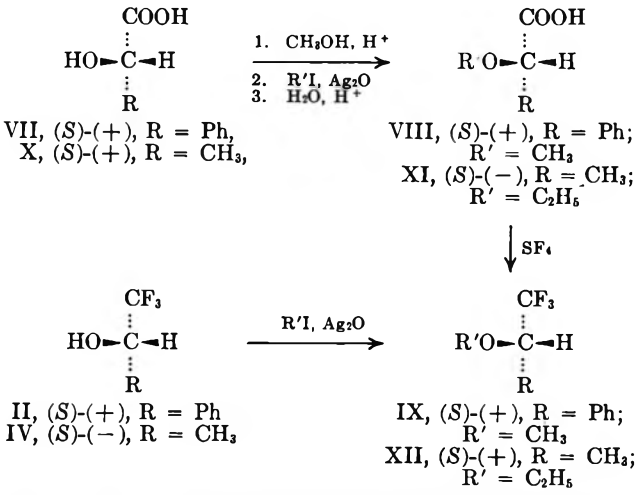
(*S*)-(+) V (*R*)-(+) VI

The configurational designations for V and VI are *S* and *R*, respectively, in spite of the fact that they are configurationally related. This is a result of the fact that in the Cahn–Ingold–Prelog rotational scheme *t*-butyl take precedence over methyl, but trifluoromethyl takes precedence over *t*-butyl.

Although the results from the studies of rotational shifts appeared to establish the absolute configuration of these three trifluoromethyl-substituted carbinols with reasonable certainty, several small points such as the anomalously low rotation of methyltrifluoromethyl benzoate and *t*-butyltrifluoromethyl acetate were not completely satisfactory. Of primary concern was the fundamental assumption that a trifluoromethyl group would act normally as another alkyl group comparable with methyl or ethyl in a Freudenberg series. Since this was the first such study involving the application of Freudenberg's generalization to a series including the trifluoromethyl group, we felt that it should be subjected to further verification. Furthermore some of our asymmetric reduction results[7] were difficult to rationalize with the absolute configuration found. We therefore undertook a direct chemical correlation which would be unequivocal.

The method chosen is outlined in Scheme I. The key reaction is the conversion of a carboxyl group into a trifluoromethyl group by the use of sulfur tetrafluoride.[18,19] This method under mild conditions does not cause racemization. Martin and Kagan[20] prepared a trifluoromethyl steroid without epimerization from the corresponding acid using sulfur tetrafluoride and hydrogen fluoride at room temperature. Raasch[21] treated both L-leucine and L-glutamic acid with sulfur tetrafluoride and recovered optically active trifluoromethyl-substituted amines, although in very low yields. Cram and Wingrove[22] treated (−)-methyl-3-phenylpropanoic acid and (+)-2-phenylbutanoic acid with sulfur tetrafluoride at 35–40° and recovered the corresponding optically active trifluoromethyl products in

SCHEME I[a]



[a] In actual practice the (*R*)-(+) enantiomer of IV was employed, and it gave the (*R*)-(−) enantiomer of XII. However, it is represented here as shown for the sake of clarity. The Experimental Section describes the actual isomer employed.

moderate yields. Furthermore it was determined that deuterium was not lost during the reaction from the α-deuterio derivative of 2-phenylbutanoic acid, confirming that racemization did not occur by this pathway. Finally it has been found by Della[23] that sulfur tetrafluoride at 70° converted *cis*- and *trans*-4-methyl- or 4-*t*-butyl-cyclohexanecarboxylic acids into the corresponding 1-trifluoromethyl-4-alkylcyclohexane without isomerization, although at 130° isomerization did occur.

Thus there is ample precedence for the use of this reaction for correlations of configurations as shown in Scheme I starting with mandelic acid (VII) or lactic acid (X). Because the alcoholic hydroxyl group is converted into the fluoro group by this reagent, it was necessary to protect it by conversion into the methyl or ethyl ether.

The preparation of (*S*)-(+)-O-methylmandelic acid (VIII) has been reported.[24] Upon treatment with sulfur tetrafluoride at 30° for 2 days a 10% yield of the desired trifluoromethyl derivative IX, $[\alpha]^{26}D$ +91.5° (neat), was obtained.[25] (+)-Phenyltrifluoromethylcarbinol (II), available from an asymmetric Grignard reduction,[4,5] was converted into the same dextrorotatory methyl ether (IX), without change in sign of rotation, upon treatment with methyl iodide in the presence of silver oxide. Thus, (+)-phenyltrifluoromethylcarbinol must have the same relative configuration as (+)-mandelic acid with a CF_3 group replacing the COOH group. Since the absolute configuration of (+)-mandelic acid is known with certainty to be *S*,[26] that for (+)-phenyltrifluoromethylcarbinol (II) must also be *S*.

When corrections are made for the known purity of the two starting materials VII and II, the rotation of the resultant ether, IX, obtained by the two different

(17) In spite of the doubt raised by H. C. Brown and D. B. Bigley, *J. Amer. Chem. Soc.*, **83**, 3166 (1961), concerning the absolute configurational assignment for *t*-butylmethylcarbinol this correlation appears well founded[16] although not absolute.

(18) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *ibid.*, **82**, 543 (1960).

(19) We wish to thank Dr. W. C. Smith, Marshall Laboratory, E. I. du Pont de Nemours and Co., and Dr. E. R. Larsen, Halogens Research Laboratory, The Dow Chemical Co., for helpful discussions concerning this reaction.

(20) D. J. Martin and F. Kagan, *J. Org. Chem.*, **27**, 1406 (1962).

(21) M. Raasch, *ibid.*, **27**, 1406 (1962).

(22) D. J. Cram and A. S. Wingrove, *J. Amer. Chem. Soc.*, **86**, 5490 (1964).

(23) E. W. Della, *Tetrahedron Lett.*, 3347 (1966).

(24) W. A. Bonner, *J. Amer. Chem. Soc.*, **73**, 3126 (1951).

(25) There was also collected a 10% yield of α,α-difluorotoluene and a 50% yield of benzaldehyde. These by-products can be readily rationalized by assuming that the initially formed acid fluoride undergoes internal decomposition to give carbon monoxide, methyl fluoride, and benzaldehyde. Benzaldehyde is known to be converted into α,α′-difluorotoluene upon treatment with sulfur tetrafluoride.[18]

(26) K. Mislow, *ibid.*, **73**, 3954 (1951).

methods, was approximately the same, namely $[\alpha]^{26}D$ +91.5° (neat) from (*S*)-O-methylmandelic acid and $[\alpha]^{26}D$ +95.4° (neat) from phenyltrifluoromethylcarbinol. Since no racemization would be expected in proceeding from II to IX it is reasonable to conclude that the sulfur tetrafluoride reaction proceeded with a maximum of 4% racemization. (*S*)-(−)-O-Ethyllactic acid[27] (XI) was converted into the corresponding dextrorotatory ether XII in 6% yield upon treatment with sulfur tetrafluoride for 4 days at 30°.[28] Levorotatory methyltrifluoromethylcarbinol IV[19] was converted with change in sign of rotation into the dextrorotatory ether XII by treatment with sodium and ethyl bromide.[29] It is, therefore, demonstrated that (−)-methyltrifluoromethylcarbinol (IV) has the same relative configuration as (+)-lactic acid (X) with a CF_3 group replacing the COOH group. Since the absolute configuration of (+)-lactic acid is known to be *S*, that of (−)-methyltrifluoromethylcarbinol must also be *S*.

When corrections are made for the enantiomeric purity of the starting materials, the specific rotations of the ethyl methyltrifluoromethylcarbinyl ether (XII) produced from lactic acid was $[\alpha]^{25}D$ +0.90° (neat), while that obtained from the methyltrifluoromethylcarbinol by the method of Henne and coworkers[29] was $[\alpha]^{25}D$ +0.68° (neat).[19] The preparation of ether XII from carbinol IV did not go to completion and unreacted carbinol which showed 19% racemization was recovered. If one assumes that all of the carbinol which was converted into the ether was racemized to this same extent, then the fully corrected rotation for XII made by this route would be $[\alpha]^{25}D$ +0.83 ± 0.05° (neat) which is just within experimental error of the $[\alpha]^{25}D$ +0.90 ± 0.02° (neat) value found for the derivative made from mandelic acid.

These direct chemical interconversions have established unequivocally the absolute configuration of methyltrifluoromethylcarbinol and phenyltrifluoromethylcarbinol. The configurational assignments in these two cases were the same as those arrived at by application of Freudenberg's rule of rotational shifts. The success of the Freudenberg rule in these two cases increases the confidence with which it can be applied to other cases involving the trifluoromethyl group. Specifically we can conclude that the configurational assignment for *t*-butyltrifluoromethylcarbinol (VI) based upon the Freudenberg correlation is secure.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. The analyses were performed by Messrs. E. Meir and J. Consul of the Stanford University Microanalytical Laboratory. The ir spectra were taken on a Perkin-Elmer 237B grating spectrophotometer. The nmr spectra were obtained on a Varian Associates A-60 spectrometer in deuteriochloroform solvent under the direction of Dr. L. J. Durham. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane as zero. The optical rotations were determined on a Carl-Zeiss half-shadow polarimeter. Solution rotations were always taken in a center-filled polarimeter tube with zero correction for the empty tube with end plates in place. Neat rotations with limited samples were taken of necessity in non-center-filled, micropolarimeter tubes.

Acetate, Benzoate, and Acid Phthalate Derivatives for Evaluation of Rotational Shifts.—These derivatives were prepared and purified by the usual procedures. A single example is described in detail for the synthesis of phenyltrifluoromethylcarbinyl acetate. Essentially this same procedure was employed for all the other derivatives by the substitution of benzoyl chloride or phthalic anhydride for the acetyl chloride and the appropriate carbinol for the phenyltrifluoromethylcarbinol. These esters were usually prepared from enantiomerically impure carbinols obtained from asymmetric Grignard reductions[4,5] or incompletely resolved fractions from the resolution studies.[9] Care was taken to ensure that one enantiomer of the derivative was not concentrated by selective crystallization during the preparation and purification procedures. Each derivative was therefore presumed to have the same enantiomeric purity as the alcohol from which it was prepared. The rotation of the enantiomerically pure carbinol was calculated by dividing the observed rotation of the derivative by the per cent enantiomeric purity of the starting carbinol and multiplying by 100.

Phenyltrifluoromethylcarbinyl Acetate.—A mixture of phenyl trifluoromethylcarbinol [3.0 g (17 mmol); $\alpha^{24}D$ +8.96° (neat, l = 1); $[\alpha]^{24}D$ +6.95° (neat); enantiomeric purity[9] 21.8%], acetyl chloride (1.5 g, 19 mmol, distilled prior to use), anhydrous pyridine (2 ml), and dry ether (15 ml) was heated under gentle reflux for 2 hr. Water (20 ml) was added to the reaction mixture, and the ether layer was separated and washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water, and finally dried ($MgSO_4$). After the ether was removed on a rotary evaporator, the residue (3.4 g, 92% crude yield) was distilled, and a portion of the fraction, bp 40–44° (0.7 mm), was preparatively chromatographed (6 ft × 1/2 in. WS-30 column at 200° and 60-ml/min He flow), and the purity of this final sample was confirmed by analytical vapor phase chromotography (vpc): $\alpha^{26}D$ +25.83° (neat, l = 1); corrected for enantiomeric purity of starting material, $[\alpha]^{26}D$ +96.0°; $[M]^{26}D$ +209° (neat); $n^{23}D$ 1.4424; d_4^{23} 1.230.

Anal. Calcd for $C_{10}H_9F_3O_2$: C, 55.05; H, 4.13. Found: C, 55.26; H, 4.22.

Phenyltrifluoromethylcarbinyl Benzoate.—By the above procedure the same sample of carbinol gave the benzoate in 94% crude yield: bp 110–114° (0.7 mm); $\alpha^{24}D$ −23.01° (neat); corrected for enantiomeric purity of starting material, $[\alpha]^{24}D$ −84°; $[M]^{24}D$ −235° (neat); $n^{25}D$ 1.5120; d^{24} 1.261.

Anal. Calcd for $C_{15}H_{11}F_3O_2$: C, 64.29; H, 3.93. Found: C, 64.50; H, 4.01.

Phenyltrifluoromethylcarbinyl Hydrogen Phthalate.—The classical procedure was employed[30] but without crystallization of the product. Using the same sample of carbinol as above, a 75% yield of white solid was obtained upon evaporation of the chloroform solution to dryness: mp 130–134°; $[\alpha]^{27}D$ +4.6° (*c* 8.1, $CHCl_3$); corrected to 100% enantiomeric purity, $[\alpha]^{27}D$ +21°; $[M]^{27}D$ +69° (*c* 8.1, $CHCl_3$). The ir spectrum of this material matched that of an analytical sample of inactive phenyltrifluoromethylcarbinyl hydrogen phthalate, mp 134–135°, prepared by Stevenot.[4]

***t*-Butyltrifluoromethylcarbinyl Acetate.**—*t*-Butyltrifluoromethylcarbinol [2.0 g, $\alpha^{28}D$ −3.74° (neat, l = 1), enantiomeric purity 60.3%] was converted into the acetate in the usual way but in low yield: $\alpha^{28}D$ +7.53° (neat, l = 0.5); corrected to 100% enantiomeric purity, $\alpha^{28}D$ +25°; $M^{28}D$ +50° (neat, not enough sample was available for density measurement); $n^{28}D$ 1.3608.

Anal. Calcd for $C_8H_{13}F_3O_2$: C, 48.48; H, 6.56. Found: C, 48.20; H, 6.49.

***t*-Butyltrifluoromethylcarbinyl Benzoate.**—Starting with the same sample of carbinol the benzoate was prepared: bp 94–96° (4 mm); $n^{28}D$ 1.5430; $\alpha^{27}D$ −7.47° (neat, l = 0.5); corrected to 100% enantiomeric purity, $\alpha^{27}D$ −24.8°; $M^{27}D$ −64° (neat, the density was not available).

***t*-Butyltrifluoromethylcarbinyl Hydrogen Phthalate.**—Using the same carbinol sample, a 67% yield of unrecrystallized hydrogen phthalate was obtained: mp 95–105°; $\alpha^{26}D$ −2.66° (*c* 4.555, $CHCl_3$, l = 2); corrected to 100% optical purity, $[\alpha]^{26}D$ −48.4°; $[M]^{26}D$ −148° (*c* 4.5, $CHCl_3$).

Anal. Calcd for $C_{14}H_{15}F_3O_4$: C, 55.26; H, 4.93. Found: C, 55.12; H, 5.22.

(27) T. Purdie and J. Irvine, *J. Chem. Soc.*, **75**, 483 (1899).

(28) Presumably the low yield was caused by the formation of side products corresponding to those observed in the mandelic acid case.[25] In this case, however, these would be gases and no attempt was made to recover them.

(29) A. L. Henne, M. A. Smook, and R. L. Pelley, *J. Amer. Chem. Soc.*, **72**, 4756 (1950).

(30) A. W. Ingersoll, *Org. Reactions*, **2**, 376 (1944).

Methyltrifluoromethylcarbinyl Acetate.—Methyltrifluoromethylcarbinol [2.4 g, $\alpha^{24}D$ −4.06° (neat, l = 1), enantiomeric purity 57%] was converted into the acetate in 76% distilled yield, bp 83–85°. Preparative gas chromatography (6 ft × 1/2 in. Carbowax 20M, 140°, 110-ml/min He flow rate) gave a sample: $n^{23}D$ 1.3295; $\alpha^{23}D$ +6.32° (neat, l = 0.5); corrected to 100% enantiomeric purity, $[\alpha]^{23}D$ +18.7°; $[M]^{23}D$ +29°.

Anal. Calcd for $C_5H_7F_3O_2$: C, 38.46; H, 4.49. Found: C, 38.46; H, 4.38.

The properties reported[31] for the racemic compound are bp 85.6°, $n^{15}D$ 1.3314, d^{15}_4 1.1823.

Methyltrifluoromethylcarbinyl Benzoate.—The benzoate was prepared from the same sample of carbinol in 68% distilled yield, bp 94–96° (14 mm). Preparative gas chromatography (6 ft × 1/2 in. Carbowax 20M, 200°, 86-ml/min He flow rate) gave a sample: $n^{21}D$ 1.4468; $\alpha^{21}D$ + 0.04 +0.01 (neat, l = 0.5); corrected to 100% enantiomeric purity, $\alpha^{21}D$ +0.14 ± 0.04° (neat, l = 1); $M^{21}D$ +0.3 ± 0.1° (neat).

Anal. Calcd for $C_{10}H_9F_3O_2$: C, 55.05; H, 4.13. Found: C, 55.00; He, 4.36.

Methyltrifluoromethylcarbinyl Hydrogen Phthalate.—The unrecrystallized hydrogen phthalate was prepared in 66% yield from the same sample of carbinol as used for the acetate and benzoate: mp 95–99°; $\alpha^{22}D$ +1.15° (*c* 5.081, $CHCl_3$, l = 2); corrected to 100% enantiomeric purity, $[\alpha]^{22}D$ +19.8°; $[M]^{22}D$ +52° (*c* 5, $CHCl_3$).

Anal. Calcd for $C_{11}H_9F_3O_4$: C, 50.38; H, 3.44. Found: C, 50.16; H, 3.64.

Ethylphenylcarbinyl Benzoate.—A sample of ethylphenylcarbinol,[8] $[\alpha]^{26}D$ −10.74° (neat, enantiomeric purity 36.9%), was converted into the benzoate, distilled, and purified by vpc (6 ft × 1/2 in. SE-30 silicon oil column, 250°, He flow rate 60 ml/min): $\alpha^{25}D$ +3.18° (neat, l = 0.5); corrected to 100% enantiomeric purity, $\alpha^{25}D$ +17.3°; $M^{25}D$ +41° (neat, density not available). This compound was not obtained analytically pure.

Isopropylphenylcarbinyl Benzoate.—A sample of isopropylphenylcarbinol,[8] $[\alpha]^{26}D$ −27.7° (*c* 4.3, ether, enantiomeric purity 58.1%), was converted into the benzoate in 98% crude yield, distilled, bp 132–134° (0.7 mm), and purified by vpc (6 ft × 1/2 in. SE-30 silicone oil column, 250°, He flow rate 84 ml/min): $\alpha^{26}D$ +11.20° (neat, l = 0.5); corrected to 100% enantiomeric purity, $\alpha^{26}D$ +38.6°; $M^{26}D$ +98° (neat, density not available).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.31; H, 7.09. Found: C, 80.02; H, 7.21.

***t*-Butylphenylcarbinyl Benzoate.**—A sample of *t*-butylphenylcarbinol,[8] $[\alpha]^{26}D$ +4.15 (*c* 4.8, ether, enantiomeric purity 11.5%), was converted into the distilled benzoate in 85% yield: mp 65–69°; $\alpha^{25}D$ −2.80° (*c* 13.6, benzene, l = 2); corrected to 100% enantiomeric purity $[\alpha]^{25}D$ −89.6°; $[M]^{25}D$ −240° (*c* 13.6, benzene).

(*S*)-(+)-Methyl Mandelate.—Mandelic acid {27 g, 180 mmol, $[\alpha]^{26}D$ +150.5° (*c* 1, water)}, which was 95% optically pure based on the maximum literature value[32] of $[\alpha]^{14}D$ −158° (*c* 1.6, water), was esterified using methanol and dry hydrogen chloride according to the method of Fischer and Speier[33] to give 21.9 g (74% yield) of (+)-methyl mandelate: bp 100–105° (1–5.1 mm); $[\alpha]^{25}D$ +172.9° (*c* 1, $CHCl_3$). On the basis of the maximum rotation in the literature[22] of $[\alpha]^{25}D$ +173.5° (*c* 1, $CHCl_3$) this ester was 99.6% optically pure.

(*S*)-(+)-O-Methylmandelic Acid[24] (VIII).—Methyl mandelate {21.0 g, 127 mmol, $[\alpha]^{25}D$ +172.9° (*c* 1, $CHCl_3$)} was refluxed for 24 hr with methyl iodide (460 g), silver oxide (30 g), and anhydrous calcium sulfate (40 g) to give 20 g (88% yield), $[\alpha]^{85}D$ +87.0° (*c* 1.182, acetone), of methyl O-methylmandelate. On the basis of the maximum reported rotation[22] of $[\alpha]^{24}D$ −89.1° (*c* 1.111, acetone) the product was 97.5% enantiomerically pure. This product, 20 g (110 mmol), $[\alpha]^{25}D$ +87.0° (*c* 1.182, acetone), was hydrolyzed with hot, dilute sulfuric acid. The product was recovered in two fractions from petroleum ether (bp 55–85°) as long white needles {fraction 1, 10 g, mp 64–66°, $[\alpha]^{25}D$ +150.1° (*c* 1.057, ethanol); and fraction 2, 4 g, mp 64–66 $[\alpha]^{23}D$ +135° (*c* 1.71, ethanol)}. On the basis of the maximum reported rotation[34] of $[\alpha]^{17}D$ −150° (ethanol), the acid in fraction 1 was 100% enantiomerically pure.

(*S*)-(+)-Methyl Phenyltrifluoromethylcarbinyl Ether (IX).—The above sample of (+)-O-Methylmandelic acid {5 g, 30 mmol, $[\alpha]^{25}D$ +150.1° (*c* 1.171, ethanol)} was treated with sulfur tetrafluoride (34 g, 310 mmol) at 30° for 2 days in a 300-ml stainless steel rocking autoclave.

The low-boiling gases were vented through dilute sodium hydroxide, and the reaction mixture was poured into pentane containing sodium fluoride. The pentane was filtered, dried (Na_2SO_4), and fractionally distilled. The first fraction [bp 30–60° (5–6 mm), 2.86 g] was subjected to preparative vpc separation (Carbowax 20M, 10 ft × 1/4 in., 130°, He flow rate 55 ml/min) to give four components with retention times of 11, 19, 43, and 55 min, respectively.

The most volatile component under these conditions (10% yield, retention time 11 min) was identified as α,α-difluorotoluene by the following properties: $n^{20}D$ 1.4570 (lit.[35] $n^{20}D$ 1.4577); nmr signal for aromatic proton at δ 7.44 (5 H, singlet) and benzylic proton 6.57 ppm (1 H, triplet, J = 56 cps); ir ν_{max}^{film} 3030, 2940, 1620, 1460, 1380, 1220, 1120–1000 (multiplet) 925, 850, 770, 700, and 660 cm^{-1}.

Anal. Calcd for $C_7H_6F_2$: C, 65.62; H, 4.73. Found: C, 65.88; H, 4.54.

The properties of the second fraction, 10% yield, with retention time of 19 min, corresponded to the desired methyl phenyltrifluoromethylcarbinyl ether (IX): $n^{25}D$ 1.4382; $\alpha^{26}D$ +56.95° (neat, l = 0.5); $[\alpha]^{26}D$ +91.5° (neat); nmr aromatic signal at δ 7.35 (5 H, singlet), methyl signal at 3.40 (3 H, singlet), methine signal centered at 4.40 ppm (1 H, quartet, J = 7 cps).

Anal. Calcd for $C_9H_9OF_3$: C, 56.84; H, 4.77. Found: C, 56.93; H, 4.82.

The rich ir spectrum of this sample [ν_{max}^{film} 2940, 1460, 1370, 1200–1100 (multiplet), 985, 760, and 710 cm^{-1}] was identical with that of the same ether made as described below from phenyltrifluoromethylcarbinol.

The third component, retention time 43 min, 50% yield, was identified as benzaldehyde, and the fourth component with the following properties has not been identified and may not be homogeneous: $n^{22}D$ 1.4490; nmr δ 3.55 (3 H, singlet), 7.43 (5 H, singlet), centered at 4.70 (1/2 H, triplet, J = 3 cps), and centered at 5.78 ppm (1/2 H, triplet, J = 3 cps) [the triplets were coupled (J = 64 cps) as determined at 100 Mc]; ir ν_{max}^{film} 2950, 1450, 1380, 1300, 1275, 1225, 1060, 980, 825, 760, 730, and 680 cm^{-1}.

Anal. Found: C, 57.72; H, 4.48.

(*S*)-(+)-Methyl Phenyltrifluoromethylcarbinyl Ether (IX).—(+)-Phenyltrifluoromethylcarbinol [1.2 g, 6.6 mmol, $\alpha^{25}D$ +7.70° (neat, l = 1)], which was 18.7% enantiomerically pure based on the maximum rotation[5,9] of $\alpha^{25}D$ +41.18° (neat, l = 1), was refluxed for 36 hr with methyl iodide (23 g), silver oxide (3 g), and anhydrous calcium sulfate, (3 g). The product was diluted with ether (25 ml), and the solid cake extracted with five 20-ml portions of ether. The combined ether extracts were dried (Na_2SO_4); the solvent was evaporated; and the residue was distilled to give 1.0 g (83% yield), bp 68–72° (15 mm). This product was purified by preparative vpc and showed a single peak upon reinjection (Carbowax 20M 10 ft × 1/4 in., 125°, He flow rate 55 ml/min, retention time 21 min): $n^{25}D$ 1.4381, d^{20}_4 1.243. The ir and nmr spectra of this sample were identical with those of the ether obtained by the sulfur tetrafluoride treatment of VIII. The observed rotation of this sample was $\alpha^{26}D$ +11.08° (neat, l = 0.5); the rotation corrected to 100% enantiomorphic purity was $[\alpha]^{26}D$ +95.3° (neat).

Anal. Calcd for $C_9H_9OF_3$: C, 56.84; H, 4.77. Found: C, 56.90; H, 4.73.

(*S*)-(−)-O-Ethyllactic Acid (XI).—(*S*)-(−)-Sodium lactate (40% solution Nutritional Biochemicals, Inc.) was converted according to the procedure of Purdie and Irvine[27] into (*S*)-(−)-ethyl O-ethyllactate, bp 150–155°, $n^{20}D$ 1.4005, $\alpha^{23}D$ −32.38° (neat, l = 0.5), $[\alpha]^{23}D$ −69.3° (neat), which was 87% enantiomerically pure based upon the maximum literature value $[\alpha]^{20}D$ −79.69° (neat).[27] This product (8.0 g, 55 mmol) was hydrolyzed with hot sulfuric acid according to the procedure of Purdie and Irvine[27] to give (*S*)-(−)-O-ethyllactic acid (XI): 5.92 g (92% yield); bp 114–116° (20 mm); $n^{20}D$ 1.4143; $\alpha^{23}D$ −57.58° (neat); $[\alpha]^{23}D$ −55.3° (neat). A portion of this material was purified by preparative vpc (Apiezon L, 5 ft × 1/4 in., 130°, He flow rate 25 ml/min, retention time 13 min): $n^{20}D$ 1.4163; $\alpha^{23}D$ −30.21° (neat, l = 0.5); $[\alpha]^{23}D$ −58.3° (neat). Based on the maximum literature value,[27] $[\alpha]^{20}D$ −66.36°, this material is 88% enantiomerically pure.

(31) F. Swartz, *Bull. Soc. Chim. Belges*, **38**, 99 (1929).
(32) G. W. Clough, *J. Chem. Soc.*, **127**, 2808 (1935).
(33) E. Fischer and A. Speier, *Ber.*, **28**, 3252 (1895).
(34) A. McKenzie and H. Wren, *J. Chem. Soc.*, **115**, 611 (1919).
(35) F. Swartz, *J. Chem. Phys.*, **20**, 65 (1922).

(*S*)-(+)-**Ethyl Methyltrifluoromethylcarbinyl Ether (XII).**—The above sample of (−)-O-ethyllactic acid (5.1 g, 43 mmol was treated with sulfur tetrafluoride (20 g, 186 mmol) for 4 days at 30° in a 300-ml stainless steel rocking autoclave. The product was processed as before and the fraction bp 30–90°, 700 mg) was purified by preparative vpc (Apiezon L, 5 ft × 1/4 in. column, 60°, He flow rate 25 ml/min, retention time 3 min) to give 340 mg (6% yield) of the desired ether (XII) as shown by the following properties: $n^{25}D$ 1.3195, d^{20}_4 1.042 (lit.[29] $n^{25}D$ 1.3219; d^{20}_4 1.062);[36] ν^{film}_{max} 3000, 2900, 1275, 1200–1100 (multiplet), and 1010 cm^{-1}; nmr spectrum centered at about δ 1.20 (6 H, unsymmetrical triplet, J = 7 cps) and centered at about 3.62 (3 H, poorly resolved multiplet, J = 7 cps); $\alpha^{25}D$ +0.41° (neat, l = 0.5), corrected to 100% enantiomeric purity, $[\alpha]^{25}D$ +0.90° (neat).

Anal. Calcd for $C_5H_9OF_3$: C, 42.25; H, 6.39. Found: C, 42.21; H, 6.45.

(*R*)-(−)-**Ethyl Methyltrifluoromethylcarbinyl Ether.**—According to the procedure described for the racemic compound[29] a sample of (+)-methyltrifluoromethylcarbinol [2.0 g, 17 mmol, $\alpha^{25}D$ 1.61° (neat, l = 0.5, 45% enantiomeric purity)], prepared by an asymmetric reduction[3,5,37] procedure, was treated first with sodium (0.4 g, 17 g-atoms) in dibutyl ether solvent (10 g) under nitrogen and then with ethyl bromide (10 g, 93 mmol) in a 300-ml stainless steel rocking autoclave at 30° for 12 hr, then at 100° for 6 hr. The autoclave was cooled, and the reaction mixture was poured from the autoclave which was rinsed out with butyl ether (two 5-ml portions) and ethyl bromide (two 5-ml portions). The reaction mixture was centrifuged to remove sodium bromide and the supernatant fractionated to give 600 mg (33% yield as calculated from the vpc analysis of this material). A portion of this product was purified by preparative vpc (Carbowax 20M, 10 ft × 1/4 in. column, 90°, He flow rate 40 ml/min) to give material, having ir and nmr spectra identical with those of the sample prepared from (−)-O-ethyllactic acid by the action of sulfur tetrafluoride. The rotation, however, was $\alpha^{25}D$ −0.16 ± 0.01° (neat, l = 0.5) which corresponds to $[\alpha]^{25}D$ −0.68 ± 0.05° (neat) when corrected for the 45% enantiomeric purity of the starting methyltrifluoromethylcarbinol.

Anal. Calcd for $C_5H_9OF_3$: C, 42.25; H, 6.39. Found: C, 41.95; H, 6.01.

Unreacted methyltrifluoromethylcarbinol, 0.27 g (13.5% recovery) was also isolated in the preparative vpc process. The ir spectrum of this carbinol was identical with that of the starting material, but the rotation was now $\alpha^{25}D$ −1.30° (neat, l = 0.5, 37% enantiomerically pure) indicating about 19% racemization. Racemization of a secondary alcohol would not be unexpected in the presence of any ketone or a trace of oxygen.[38] If one assumes that all of the carbinol which was converted into the ether was racemized to this same extent, then the corrected rotation for the (*R*)-(−)-ethyl methyltrifluoromethylcarbinyl ether prepared by this route would be $[\alpha]^{25}D$ −0.83 ± 0.05° (neat) which is not far from the rotation $[\alpha]^{25}D$ +0.90° (neat) observed for the enantiomer made *via* the sulfur tetrafluoride reaction on XII.

Registry No.—Phenyltrifluoromethylcarbinyl acetate, 17659-26-6; phenyltrifluoromethylcarbinyl benzoate, 17659-27-7; *t*-butyltrifluoromethylcarbinyl acetate, 17659-28-8; *t*-butyltrifluoromethylcarbinyl benzoate, 17659-29-9; *t*-butyltrifluoromethylcarbinyl hydrogen phthalate, 17659-30-2; methyltrifluoromethylcarbinyl acetate, 17659-31-3; methyltrifluoromethylcarbinyl benzoate, 17659-32-4; methyltrifluoromethylcarbinyl hydrogen phthalate, 17659-33-5; isopropylphenylcarbinyl benzoate, 17659-34-6; *t*-butylphenylcarbinyl benzoate, 17659-35-7; α,α-difluorotoluene, 2155-31-2; IX, 17659-36-8; XI, 17659-37-9; (*S*)-(+) XII, 17659-38-0; (*R*)-(−) XII, 17659-39-1.

(36) Our observed refractive index and density are significantly lower than the literature values. Since our product showed no impurities by vpc analysis, we assume that the material described in the literature was contaminated with some higher density, higher refractive index material, probably ethyl bromide.

(37) D. M. Feigl and H. S. Mosher, *Chem. Commun.*, 615 (1965).

(38) W. von E. Doering and T. C. Aschner, *J. Amer. Chem. Soc.*, **71**, 838 (1949).

Notes

Amino Acids and Peptides. XVIII.[1] Synthesis of a Tetrapeptide Sequence (A_1–A_4) of Glucagon

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The N-terminal A_1–A_4 sequence of the hyperglycemic hormone glucagon[2] has been prepared in the form of blocked derivatives by several groups in the last few years. The original scheme utilized the dipeptides N^{α}-benzyloxycarbonyl-L-histidyl-L-serine hydrazide, N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine hydrazide, and N^{α}-benzyloxycarbonyl-L-glutaminyl glycine for the construction of larger units.[3] Later, the dipeptide N^{α}-*t*-butyloxycarbonyl-L-histidyl-O-*t*-butyl-L-serine hydrazide was employed for a related synthesis.[4] The tetrapeptide N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine has been made by two procedures and used in a succeeding condensation reaction.[5] Finally, another variant of the tetrapeptide exists in the form of N^{α}-*t*-butyloxycarbonyl-L-histidyl-L-seryl-L-glutaminylglycine.[6]

In concluding our work on small glucagon fragments,[7-12] there are described here several new approaches to the A_1–A_4 sequence involving various protecting groups. For example, N^{α}-benzyloxycarbonyl-L-glutamine (I)[6,13-17] and glycine methyl ester hydrochloride (II)[12,18] were coupled by 2-ethyl-5-phenyloxazolium-3′-sulfonate[19,20] to yield N^{α}-benzyloxycarbonyl-L-glutaminylglycine methyl ester (III). Dipeptide III was formed in similar amount by the combination of N^{α}-benzyloxycarbonyl-L-glutamine 2,4,5-trichlorophenyl ester (IV)[21] or N^{α}-benzyloxycarbonyl-L-glutamine *p*-nitrophenyl ester (V)[22] with the glycine ester II. Removal of the N^{α}-benzyloxycarbonyl group of dipeptide III by hydrogenolysis in the presence of dilute acid gave L-glutaminylglycine methyl ester hydrochloride (VI). Treatment of L-serine (VII) with acetyl chloride[23] afforded O-acetyl-L-serine hydrochloride (VIII),[24,25] which was converted into N^{α}-benzyloxycarbonyl-O-acetyl-L-serine (IX).[26] Reaction with *p*-nitrophenol and N,N′-dicyclohexylcarbodiimide[27] produced the corresponding *p*-nitrophenyl ester (X).[28-30] Similarly, acid IX was joined with 2,4,5-trichlorophenol to yield N^{α}-benzyloxycarbonyl-O-acetyl-L-serine 2,4,5-trichlorophenyl ester (XI).

A reaction between amine VI and the activated ester X furnished N^{α}-benzyloxycarbonyl-O-acetyl-L-seryl-L-glutaminylglycine methyl ester (XII). The benzyloxycarbonyl moiety in tripeptide XII was cleaved with hydrogen bromide–acetic acid to yield O-acetyl-L-seryl-L-glutaminylglycine methyl ester hydrobromide (XIII). Alternatively, hydrogenolysis of XII formed O-acetyl-L-seryl-L-glutaminylglycine methyl ester (XIV). At this point, N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidine (XV)[31] was combined with 2,4,5-trichlorophenol to form N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-trichlorophenyl ester (XVI),[32] and neutralization of the salt XIII followed by addition of the activated ester XVI gave the desired N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-O-acetyl-L-serine-L-glutaminylglycine methyl ester (XVII).

A second synthesis of the tetrapeptide sequence was achieved in the following manner. The trichlorophenyl ester XVI and L-serine methyl ester afforded N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine methyl ester (XVIII),[5] which was hydrolyzed to the corresponding acid (XIX).[5] Addition of hydrazine to the ester XVIII produced N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine hydrazide (XX). An azide coupling between XX and the amine VI furnished an amorphous N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine methyl ester

(1) For the previous paper in this series, see B. Weinstein, *Experientia*, **24**, 406 (1968).
(2) P. P. Foà and G. Galansino, "Glucagon: Chemistry and Function in Health and Disease," Charles C. Thomas, Springfield, Ill., 1962.
(3) E. Schröder and H. Gibian, *Ann.*, **656**, 190 (1962).
(4) E. Schröder, *ibid.*, **670**, 127 (1963).
(5) H. C. Beyerman and J. S. Bontekoe, *Rec. Trav. Chim. Pays-Bas*, **83**, 255 (1964).
(6) E. Wünsch and A. Zwick, *Ber.*, **97**, 2497 (1964).
(7) A. A. Costopanagiotis, J. Preston, and B. Weinstein, *J. Org. Chem.*, **31**, 3398 (1966).
(8) T. A. Hylton, J. Preston, and B. Weinstein, *ibid.*, **31**, 3400 (1966).
(9) A. A. Costopanagiotis, J. Preston, and B. Weinstein, *Can. J. Chem.*, **45**, 759 (1967).
(10) B. O. Handford, T. A. Hylton, J. Preston, and B. Weinstein, *J. Org. Chem.*, **32**, 1243 (1967).
(11) B. O. Handford, T. A. Hylton, and B. Weinstein, *Ohio J. Sci.*, **68**, 104 (1968).
(12) A. A. Costopanagiotis, B. O. Handford, and B. Weinstein, *J. Org. Chem.*, **33**, 1261 (1968).
(13) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).
(14) H. K. Miller and A. Waelsch, *Arch. Biochem. Biophys.*, **35**, 176 (1952).
(15) R. A. Boissonnas, S. Guttmann, P.-A. Jaquenoud, and J.-P. Waller, *Helv. Chim. Acta*, **38**, 1401 (1955).
(16) S. Goldschmidt and C. Jutz, *Ber.*, **89**, 518 (1956).
(17) P. G. Katsoyannis, D. T. Gish, G. P. Hess, and V. du Vigneaud, *J. Amer. Chem. Soc.*, **80**, 2558 (1958).
(18) A commercial material purchased from Fluka A. G., Buchs SG, Switzerland.
(19) R. B. Woodward, R. A. Olofson, and H. Mayer, *Tetrahedron, Suppl.*, **8**, 321 (1966).
(20) A commercial material purchased from Pilot Chemicals, Watertown, Mass.
(21) J. Pless and R. A. Boissonnas, *Helv. Chem. Acta*, **46**, 1609 (1963).
(22) M. Bodanszky and V. du Vigneaud, *J. Amer. Chem. Soc.*, **81**, 5688 (1959).
(23) Y. Liwschitz, A. Zilkha, H. Borensztain, and M. Frankel, *J. Org. Chem.*, **21**, 1530 (1956).
(24) J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Amer. Chem. Soc.*, **78**, 1367 (1956).
(25) A commercial sample has been found to have physical constants in agreement with those of the material prepared by our procedure (Dr. M. Wilchek, Yeda Development Company, Israel, July 1963).
(26) M. Frankel and H. Halmann, *J. Chem. Soc.*, 2735 (1952).
(27) D. F. Elliott and D. W. Russel, *Biochem. J.*, **66**, 49P (1957).
(28) M. A. Ondetti, *J. Med. Chem.*, **6**, 10 (1963).
(29) E. D. Nicolaides and H. A. DeWald, U. S. Patent, 3,164,614; *Chem. Abstr.*, **63**, 674*f* (1966).
(30) M. Bodanszky and S. Lande, U. S. Patent 3,234,200; *Chem. Abstr.*, **64**, 12791*h* (1966).
(31) D. Theodoropoulos and G. Falsch, *Acta Chem. Scand.*, **12**, 1955 (1958).
(32) J. Pless and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1609 (1963).

(XXI). Alternatively, VI and N^{α}-benzyloxycarbonyl-L-serine (XXII) were joined by N,N′-dicyclohexylcarbodiimide[33] to yield N^{α}-benzyloxycarbonyl-L-seryl-L-glutaminylglycine methyl ester (XXIII). Hydrogenolysis formed L-seryl-L-glutaminylglycine methyl ester (XXIV), which on reaction with the trichlorophenyl ester XVI gave crystalline tetrapeptide XXI.

In a third approach, L-histidine hydrochloride monohydrate (XXV) was treated with methanol–sulfuric acid–hydrogen chloride to afford L-histidine methyl ester dihydrochloride (XXVI).[34] The older methanol–hydrogen chloride route is more troublesome.[35]

Neutralization of salt XXVI, followed by addition of *t*-butyloxycarbonyl azidoformate,[36] furnished N^{α}-*t*-butyloxycarbonyl-L-histidine methyl ester (XXVII). N^{α},N^{im}-di-*t*-butyloxycarbonyl-L-histidine methyl ester (XXVIII) was also isolated from this reaction; though it slowly decomposes to the mono-*t*-butyloxycarbonyl-substituted product XXVII, it too may be used in peptide synthesis. Routine hydrolysis of the ester XXVII yielded N^{α}-*t*-butyloxycarbonyl-L-histidine (XXIX).

The last scheme for the preparation of the tetrapeptide utilized N^{im}-benzyl-L-histidine (XXX),[37] which on blocking with *t*-butyloxycarbonyl azidoformate, gave N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidine (XXXI). It is noted here that this particular compound has been sought without success by others. The intermediate XXXI promises to be a valuable addition to the small list of histidine derivatives now employed in the general technique of stepwise synthesis.[38,39] Combination with 2,4,5-trichlorophenol then afforded N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-trichlorophenyl ester (XXXII). Addition of XXXII to the amine XXIV produced crystalline N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine methyl ester (XXXIII), whereas an attempt to prepare XXXIII by coupling the acid XXXI and the amine XXIV with N,N′-dicyclohexylcarbodiimide furnished only an oil.

The synthesis, isolation, and characterization of the various tetrapeptides completed the efforts directed toward the preparation of seven distinct glucagon fragments. Future reports in this series will deal with the combination of these blocked units to form larger and possibly physiologically active peptides.

Experimental Section[40]

N^{α}-Benzyloxycarbonyl-L-glutaminylglycine Methyl Ester (III).—N^{α}-Benzyloxycarbonyl-L-glutamine (13.31 g, 0.05 mol) {mp 134–136.5°; $[\alpha]^{26.8}D$ −6.9° (c 2.00, ethanol); $[\alpha]^{27.0}D$ −3.7° (c 2.00, glacial acetic acid)} {lit.[6,13–17] mp 138–139.5°, 135°, 133–137°; $[\alpha]D$ −7.1°, +5.8° (ethanol), and −1.7°, +7.6° (glacial acetic acid)} was dissolved in acetonitrile (250 ml) containing triethylamine (6.95 ml, 0.05 mol), and the solution was cooled to 5°. 2-Ethyl-5-phenyloxazolium-3′-sulfonate (12.63 g, 0.05 mol) was added with stirring, and the reaction mixture was allowed to warm to room temperature with complete solution occurring within 40 min. Finely powdered glycine methyl ester hydrochloride (6.27 g, 0.05 mol) was dissolved in hot N,N-dimethylformamide (250 ml), and triethylamine (6.95 ml, 0.05 mol) was added with rapid cooling (Dry Ice–isopropanol bath) to 0°. The resulting suspension was then added to the acetonitrile solution containing the "Woodward" intermediate. After 48 hr, the solution was evaporated almost to dryness and the residue dissolved in chloroform (1 l.) and washed rapidly with water (two 250-ml portions). Any delay after the first water wash may cause the chloroform phase to set to a gelatinous mass. Ethanol (200 ml) was added to the chloroform solution, and the mixture was evaporated to dryness. A solution of the residue in methanol (50 ml) deposited a hard, white, microcrystalline mass [mp 166–172°; 9.77 g (56%)]. Recrystallization form methanol–water (4:1) gave fine, white needles of N^{α}-benzyloxycarbonyl-L-glutaminylglycine methyl ester: mp 174–175°; $[\alpha]^{28.3}D$ −6.6° (c 1.00, N,N-dimethylformamide); R_f 0.64 (methanol); ν_{max} 3400 (NH), 2950 (CH), 1740 and 1700 (C=O), 1685 (urethan), 1655 (amide I), 1530 (amide II), 1240 and 1210 (CO), and 697 (Ph) cm^{-1}; λ_{max} 242, 247, 252, 257, 262, 264, and 268 mμ (ε 109, 132, 170, 210, 158, 172, and 113).

Anal. Calcd for $C_{16}H_{21}N_3O_6$ (351.4): C, 54.69; H, 6.02; N, 11.96. Found: C, 54.84; H, 6.02; N, 11.98.

The dipeptide was alternatively prepared in a like manner, but using acetonitrile (250 ml) in place of N,N-dimethylformamide as the solvent for glycine methyl ester hydrochloride. In this event, crude dipeptide (46%) separated in solid form from the reaction solution. Other coupling reactions included N^{α}-benzyloxycarbonyl-L-glutamine 2,4,5-trichlorophenyl ester with glycine methyl ester hydrochloride (51%) and N^{α}-benzyloxycarbonyl-L-glutamine *p*-nitrophenyl ester with glycine methyl ester hydrochloride (57%).

L-Glutaminylglycine Methyl Ester Hydrochloride (VI).—N^{α}-Benzyloxycarbonyl-L-glutaminylglycine methyl ester (3.514 g, 0.01 mol) was dissolved in warm methanol (50 ml) and hydrogenolyzed in the presence of 10% palladium-on-carbon catalyst (0.100 g) and hydrochloric acid (1 *N*, 10 ml) during 2 hr. Usually, it was necessary at the beginning of the hydrogenation to keep the solution warm with an infrared lamp to prevent separation of the starting material. Removal of the catalyst and evaporation of the methanol and water furnished oily L-glutaminylglycine methyl ester hydrochloride [2.173 g, 100%; R_f 0.10 (ninhydrin positive)].

O-Acetyl-L-serine Hydrochloride (VIII).—A mixture of L-serine (1.000 g, 0.01 mol) and glacial acetic acid–acetyl chloride (1:1, 30 ml) was allowed to stand at room temperature for 20 min, then ether was added to precipitate O-acetyl-L-serine hydrochloride (1.30 g, 76%): mp 160–161° dec; $[\alpha]^{26.0}D$ +18.3° (*c* 2.0, ethanol) {lit.[24,25] mp 160° dec; $[\alpha]^{27}D$ −7.4° (*c* 2.2, ethanol)}.

N^{α}-Benzyloxycarbonyl-O-acetyl-L-serine (IX).—Carbobenzyloxy chloride was added to a solution of O-acetyl-L-serine hydrochloride (4.800 g, 0.026 mol) in saturated sodium bicarbonate (150 ml) at room temperature. After 3.5 hr, the solution was washed with ether, acidified, and extracted with ethyl acetate. Washing, drying, and evaporation of the organic solution gave an oil (2.400 g, 33%) [lit.[26] oil].

N^{α}-Benzyloxycarbonyl-O-acetyl-L-serine *p*-Nitrophenyl Ester (X).—Oily N^{α}-benzyloxycarbonyl-O-acetyl-L-serine (7.110 g, 0.025 mol) was condensed with *p*-nitrophenol (4.173 g, 0.030 mol) using N,N′-dicyclohexylcarbodiimide (5.178 g, 0.025 mol) in ethyl acetate (50 ml) at 0°. After 3 hr, the N,N′-dicyclohexylurea was removed, and the ethyl acetate solution was washed with sodium bicarbonate (5%) and brine and dried. Evaporation gave a solid that was crystallized from ethanol (2.251 g, 23%): mp 98–99° (lit.[28–30] 94–96, 90–91, 74–76°).

(33) J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **72**, 1067 (1955).
(34) N. C. Davis, *J. Biol. Chem.*, **223**, 935 (1956).
(35) E. Fischer and L. H. Cone, *Ann.*, **363**, 107 (1908).
(36) L. A. Carpino, B. A. Carpino, P. J. Crowley, C. A. Giza, and P. H. Terry, *Org. Syn.*, **44**, 15 (1964).
(37) V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).
(38) J. E. Shields and H. Renner, *J. Amer. Chem. Soc.*, **88**, 2304 (1966).
(39) F. Weygand, W. Steglich, and P. Pietla, *Ber.*, **100**, 3841 (1967).
(40) Melting points are uncorrected. Microanalyses were provided by Messrs. Erich H. Meier and J. Consul, Microanalytical Laboratory, Stanford University. The optical rotation, infrared (potassium bromide) and ultraviolet (95% ethanol) measurements were obtained by Mmes. Dalia Aguilar and Linda D. Carroll. Thin layer chromatography employed silica gel G (freshly activated) as the support, methanol–chloroform (1:9) as the developer, and iodine for detection, unless otherwise stated. Evaporations were performed under reduced pressure (water pump) in a rotatory evaporator at minimum temperature, while high-boiling solvents were removed at vacuum pressure (0.2–0.5 mm). Magnesium sulfate was used for drying purposes. Acetonitrile and N,N-dimethylformamide were spectroscopic quality; other solvents were reagent grade and petroleum ether had bp 30–60°.

N^{α}-Benzyloxycarbonyl-O-acetyl-L-serine 2,4,5-Trichlorophenyl Ester (XI).—Oily N^{α}-benzyloxycarbonyl-O-acetyl-L-serine (3.821 g, 0.014 mol) was condensed with 2,4,5-trichlorophenol (3.160 g, 0.016 mol) using N,N′-dicyclohexylcarbodiimide (3.294 g, 0.014 mol) in ethyl acetate (50 ml) at −5°. The product was isolated as described in the previous procedure. Crystallization from benzene gave N^{α}-benzyloxycarbonyl-O-acetyl-L-serine 2,4,5-trichlorophenyl ester (2.900 g, 46%): mp 88–89°; ν_{max} 3330 (NH), 2930 (CH), 1765 (C=O), 1720 broad (C=O and urethan), 1225 (CO), and 698 (Ph) cm^{-1}; λ_{max} 267 mμ (ε 8100).

Anal. Calcd for $C_{19}H_{16}Cl_3NO_6$ (460.7); C, 50.51; H, 3.45; Cl, 23.08, N, 3.03. Found: C, 50.80; H, 3.54; Cl, 21.85; N, 3.30.

N^{α}-Benzyloxycarbonyl-O-acetyl-L-seryl-L-glutaminylglycine Methyl Ester (XII).—L-Glutaminylglycine methyl ester [freshly prepared from N^{α}-benzyloxycarbonyl-L-glutaminylglycine methyl ester (1.054 g, 0.0030 mol) and 10% palladium-on-carbon catalyst (0.100 g) in methanol (50 ml)] and N^{α}-benzyloxycarbonyl-O-acetyl-L-serine *p*-nitrophenyl ester (1.330 g, 0.0033 mol) in N,N-dimethylformamide (25 ml) was stirred for 2 days. After dilution with ether (100 ml), the gelatinous precipitate was filtered, washed with sodium bicarbonate (5%) and water, and dried. Crystallization from water gave N^{α}-benzyloxycarbonyl-O-acetyl-L-seryl-L-glutaminylglycine methyl ester (0.805 g, 52%): mp 210–212°; $[\alpha]^{25.0}D$ −6.8° (c 1.76, N,N-dimethylformamide); R_f 0.35; ν_{max} 3290 (OH), 2950 (CH), 1735 (C=O), 1655 broad (C=O and urethan), 1220 (CO), and 697 (Ph) cm^{-1}; λ_{max} 247, 252, 262, 264, 267, and 312 mμ (ε 282, 286, 313, 274, 285, 234, and 196).

Anal. Calcd for $C_{21}H_{28}N_4O_9$ (480.5); C, 52.49; H, 5.87; N, 11.66. Found: C, 52.68; H, 5.94; N, 11.40.

O-Acetyl-L-seryl-L-glutaminylglycine Methyl Ester Hydrobromide (XIII).—N^{α}-Benzyloxycarbonyl-O-acetyl-L-seryl-L-glutaminylglycine methyl ester (0.200 g, 0.00042 mol) was added to a mixture of hydrogen bromide–acetic acid (30%, 1 ml) and glacial acetic acid (1 ml). After stirring for 1 hr, the solution was diluted with ether (10 ml), and the precipitated solid was collected, washed with ether, and stored *in vacuo*. Owing to its hygroscopic nature, no physical data were obtained for this product.

O-Acetyl-L-seryl-L-glutaminylglycine Methyl Ester (XIV).—A suspension of N^{α}-benzyloxycarbonyl-O-acetyl-L-seryl-L-glutaminylglycine methyl ester (0.120 g, 0.00025 mol) in methanol (20 ml) containing 10% palladium-on-carbon catalyst (0.030 g) was hydrogenated for 2 hr. The catalyst was removed by filtration and evaporation of the solvent gave O-acetyl-L-seryl-L-glutaminylglycine methyl ester as a white solid (0.087 g, 100%): R_f 0.10 (ninhydrin positive).

N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidine (XV).—This compound was obtained from N^{im}-benzyl-L-histidine (6.100 g, 0.025 mol) and carbobenzoxy chloride (5 ml) in lithium hydroxide (1 *N*, 25 ml) and dioxane (15 ml) in the usual manner (7.450 g, 79%): mp 214–215° dec; $[\alpha]^{26.0}D$ +6.4° (c 5, glacial acetic acid) {lit.[31] mp 210–213°; $[\alpha]^{21}D$ +5.2° (c 5, glacial acetic acid)}.

N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-Trichlorophenyl Ester (XVI).—This compound was obtained from N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidine (3.794 g, 0.01 mol), 2,4,5-trichlorophenol (2.369 g, 0.012 mol), and N,N′-dicyclohexylcarbodiimide (2.063 g, 0.01 mol) in N,N-dimethylformamide (25 ml) in the usual manner (4.099 g, 73%): mp 108–109° (lit.[32] mp 107–108°).

N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-O-acetyl-L-seryl-L-glutaminylglycine Methyl Ester (XVII).—The aforementioned O-acetyl-L-seryl-L-glutaminylglycine methyl ester hydrobromide in N,N-dimethylformamide (3 ml) was treated in turn with tri-*n*-butylamine (0.077 g, 0.00042 mol) and N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-trichlorophenyl ester (0.235 g, 0.0024 mol) and stirred overnight at room temperature. Addition of ether gave a solid, which was collected, washed with ammonium hydroxide (1 *N*), hydrochloric acid (1 *N*), and water, and dried. Crystallization from N,N-dimethylformamide and then ethanol gave N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-O-acetyl-L-seryl-L-glutaminylglycine methyl ester (0.087 g, 21%): mp 197–199°.

Anal. Calcd for $C_{34}H_{41}N_7O_{10}$ (707.7): C, 57.70; H, 5.84; N, 13.86. Found: C, 57.37; H, 6.10; N, 13.90.

N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine Methyl Ester (XVIII).—N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-trichlorophenyl ester (1.118 g, 0.002 mol) was added to a mixture of L-serine methyl ester hydrochloride (0.312 g, 0.002 mol) and triethylamine (0.30 ml, 0.002 mol) in methylene dichloride (20 ml). After 8 hr, the organic phase was washed with sodium bicarbonate (2%) and water, dried, and evaporated to dryness. Crystallization from methanol–ethyl acetate (1:3) gave white needles of N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine methyl ester (0.801 g, 83%): mp 173.5–175° (lit.[5] mp 173–174°).

N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine (XIX).—This compound was obtained by treating N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine methyl ester (0.240 g, 0.0005 mol) with sodium hydroxide (1 *N*) in dioxane (0.4 ml) in the usual manner (0.138 g, 59%): mp 181–182° (lit.[5] mp 182°).

N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine Hydrazide (XX).—Hydrazine (0.6 ml, 95%) was added to a solution of N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine methyl ester (1.100 g, 0.023 mol) in ethanol (20 ml) at −10°. After 10 hr, the mixture was allowed to stand at room temperature for 48 hr. The precipitate was filtered, washed with cold ethanol, and dried. Crystallization from N,N-dimethylformamide–water (1:1) gave N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine hydrazide (0.939 g, 85%): mp 147.5–149.0°.

Anal. Calcd for $C_{24}H_{28}N_6O_5$ (480.5): C, 59.99; H, 5.87; N, 17.49. Found: C, 59.89; H, 5.94; N, 17.41.

N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine Methyl Ester (XXI). A. By Use of N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-serine Hydrazide.—A solution of N^{α}-benzyloxycarbonyl-L-histidyl-L-serine hydrazide (0.192 g, 0.0004 mol) in hydrochloric acid (1 *N*, 2 ml) was cooled to 0° and treated with sodium nitrite (0.028 g, 0.0004 mol). After standing for 10 min, the solution was neutralized with potassium carbonate (5%), and the precipitated azide was collected and washed with cold water, then dissolved in N,N-dimethylformamide (1 ml), and added to a solution of L-glutaminylglycine methyl ester in N,N-dimethylformamide (3 ml), previously prepared by neutralization of the corresponding hydrochloride salt (0.087 g, 0.0004 mol). The reaction stood for 24 hr at 0°, then at room temperature for 48 hr. Afterward, the solution was evaporated, and the residue was extracted with ethyl acetate (30 ml). The organic phase was washed with water, sodium bicarbonate (5%), hydrochloric acid (5%), and brine, and dried. The addition of ether to the ethyl acetate solution formed a gum. Reprecipitation in turn from methanol–ethyl acetate and N,N-dimethylformamide–ether gave amorphous N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine methyl ester (0.040 g, 15%): mp 247–250° dec.

B. By Use of N^{α}-Benzyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-Trichlorophenyl Ester.—A solution of L-seryl-L-glutaminylglycine methyl ester (0.576 g, 0.00020 mol) and N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-trichlorophenyl ester (0.124 g, 0.00022 mol) in N,N-dimethylformamide (3 ml) was stirred for 2 days. Sodium bicarbonate (5%, 15 ml) was added to the reaction mixture, stirring was continued for 30 min, then the solid was filtered and washed with water. Crystallization from N,N-dimethylformamide–water gave tiny, white needles of N^{α}-benzyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine methyl ester (0.036 g, 30%): mp 246–248° dec; R_f 0.50; ν_{max} 3290 (OH), 2945 (CH), 1725 (C=O), 1660 very broad (C=O and urethan), 1160 (CO), and 692 (Ph) cm^{-1}.

Anal. Calcd for $C_{32}H_{39}H_7O_9$ (665.7): C, 57.73; H, 5.91; N, 14.73. Found: C, 57.85; H, 6.02; N, 14.70.

N^{α}-Benzyloxycarbonyl-L-Seryl-L-glutaminylglycine Methyl Ester (XXIII).—The aforementioned L-glutaminylglycine methyl ester hydrochloride (0.01 mol) and N^{α}-benzyloxycarbonyl-L-serine (2.392 g, 0.01 mol) were dissolved in N,N-dimethylformamide (50 ml). The reactants were first cooled to −40°; then triethylamine (1.39 ml, 0.01 mol) and N,N′-dicyclohexylcarbodiimide (2.166 g, 0.0105 mol) were added to the chilled solution. After 1 hr at −40°, 3 hr at −20°, and 48 hr in the cold room, the mixture was taken almost to dryness, and the residue was shaken with water. The N,N′-dicyclohexylurea was removed, the filtrate was evaporated to dryness, and the solid was crystallized from a minimum volume of hot methanol. Recrystallization from hot methanol–water (1:1) deposited colorless needles of N^{α}-benzyloxycarbonyl-L-seryl-L-glutaminylglycine methyl ester (2.622 g, 60%): mp 200.5–202.0°; $[\alpha]^{26.7}D$ −2.0° (c 1.0, N,N-dimethylformamide); R_f 0.60 (butanol–acetic acid–water), 0.63 (methanol); ν_{max} 3300 broad (OH), 2950 (CH), 1720 broad

(C=O), 1665 broad (C=O and urethan), 1220 (C—O) and 698 (Ph) cm^{-1}; λ_{max} 252, 257, 264, and 268 mμ (ε 223, 263, 220, and 170).

Anal. Calcd for $C_{19}H_{26}N_4O_8$ (438.4): C, 52.05; H, 5.98; N, 12.78. Found: C, 52.06; H, 5.79; N, 13.00.

If the coupling reaction was initiated at 0° and then allowed to attain room temperature, there resulted lower yields (29 and 25%) of the tripeptide. The tripeptide was alternatively prepared by use of 2-ethyl-5-phenyloxazolium-3′-sulfonate, but only an oily product was obtained in spite of many crystallization attempts.

L-Seryl-L-glutaminylglycine Methyl Ester (XXIV).—A solution of N^{α}-benzyloxycarbonyl-L-seryl-L-glutaminylglycine methyl ester (0.078 g, 0.00018 mol) in methanol (30 ml) was hydrogenolyzed in the presence of 10% palladium-on-carbon catalyst (0.021g) for 1 hr. Filtration of the catalyst and evaporation of the solvent gave oily L-seryl-L-glutaminylglycine methyl ester (0.053 g, 100%): R_f 0.25 (ninhydrin positive).

L-Histidine Methyl Ester Dihydrochloride (XXVI).—This compound was obtained by refluxing for 1 hr a solution of L-histidine hydrochloride (37.5 g, 0.196 mol) in methanol (350 ml) containing sulfuric acid (10 ml), then saturating with hydrogen chloride gas for 2 hr. After standing in the cold room overnight, the product was filtered and dried *in vacuo* (41.0 g, 87%): mp 205–206° dec (lit.[34] mp 200–201°); $[\alpha]^{24.2}D$ +11.0° (*c* 1.17, water).

N^{α}-*t*-Butyloxycarbonyl-L-histidine Methyl Ester (XXVII).—A suspension of L-histidine methyl ester dihydrochloride g, 0.100 mol) in chloroform (100 ml) at 0° was treated with ammonia gas for 10 min. After filtration of the precipitated ammonium chloride, the chloroform was evaporated, and the oily residue was dissolved in pyridine (25 ml) and treated with *t*-butyloxycarbonyl azidoformate (15.730 g, 0.11 mol). After standing for 72 hr at room temperature, the solvent was removed, and the oily residue was dissolved in ethyl acetate, washed with water to remove traces of histidine, and exhaustively extracted with citric acid (0.5 *M*). The combined acid phases were covered with an equal volume of fresh ethyl acetate, and solid sodium hydrogen carbonate was added portionwise with vigorous stirring until the aqueous solution was basic (pH 8.5). The organic layer was washed with brine, dried, and on concentration furnished colorless needles of N^{α}-*t*-butyloxycarbonyl-L-histidine methyl ester: mp 125.5–126.0°; $[\alpha]^{27.6}D$ −11.7° (*c* 1.0, methanol); $[\alpha]^{27.3}D$ −13.0° (*c* 2.0, pyridine) {lit.[6] mp 124–125°; $[\alpha]^{20}D$ −13.6° (*c* 2.0, pyridine)}; R_f 0.27; ν_{max} 3462 (NH), 2972 (CH), 1750, and 1705 (C=O), 1685 (urethan), 1390 and 1365 (*t*-butyl), and 1160 broad (CO) cm^{-1}; λ_{max} 270 very broad mμ (ε 107).

Anal. Calcd for $C_{12}H_{19}N_3O_4$ (269.3): C, 53.52; H, 7.11; N, 15.60. Found: C, 53.39; H, 6.95; N, 15.63.

N^{α},N^{im}-Di-*t*-butyloxycarbonyl-L-histidine Methyl Ester (XXVIII).—The original ethyl acetate solution from the aforementioned preparation was washed twice more with citric acid, saturated hydrogen carbonate solution, and brine, dried, and taken to dryness. The residual oil was dissolved as rapidly as possible in the minimum quantity of warm diisopropyl ether. The tepid solution was seeded with a sample of N-*t*-butyloxycarbonyl-L-histidine methyl ester and allowed to stand for several hours at room temperature, whereupon the deposited crystals were discarded. The decanted liquor was kept at 0° and slowly deposited clusters of colorless needles, recrystallization of which under the same conditions gave N^{α},N^{im}-di-*t*-butyloxycarbonyl-L-histidine methyl ester: mp *ca.* 90°; R_f 0.73; ν_{max} 3380 (NH), 2975 (CH), 1750 and 1710 (C=O), 1685 (urethan), 1387 and 1330 (*t*-butyl), and 1160 broad (CO) cm^{-1}; λ_{max} 236 mμ (ε 2910).

Anal. Calcd for $C_{17}H_{27}N_3O_6$ (369.4): C, 55.27; H, 7.37; N, 11.37. Found: C, 55.41; H, 7.38; N, 11.27.

This compound decomposes slowly at room temperature and more rapidly in solution.

N^{α}-*t*-Butyloxycarbonyl-L-histidine (XXIX).—Sodium hydroxide (1 *N*, 10 ml) was added with stirring to a solution of N^{α}-*t*-butyloxycarbonyl-L-histidine methyl ester (2.693 g, 0.01 mol) in dioxane (10 ml). After 30 min the solution was evaporated to a small volume, diluted with water, washed with ethyl acetate, and stirred with a strong cation-exchange resin (Bio Rad AG50W-X2, 200–400 mesh, exchange capacity 0.7 mequiv/ml of resin bed, analytical grade, 14.3 ml, 0.01 equiv) for 5 min. The resin was removed, and the water solution was evaporated to yield an oil, which was dissolved in the minimum volume of cold methanol, and acetonitrile added to opalescence at room temperature. A few drops of methanol restored a clear solution, which deposited glistening parallelepipeds of N^{α}-*t*-butyloxycarbonyl-L-histidine (1.818 g, 71%): mp 191.0–191.5°; $[\alpha]^{27.6}D$ −10.6° (c 1.0, N,N-dimethylformamide); ν_{max} 3400 (OH), 2975 (CH), 1705 (C=O), 1390 and 1367 (*t*-butyl), and 1168 (C—O); λ_{max} 214 mμ (ε 5850).

Anal. Calcd for $C_{11}H_{17}N_3O_4$ (255.3): C, 51.76; H, 6.71; N, 16.46. Found: C, 51.75; H, 6.92; N, 16.38.

This compound becomes pale yellow and finally pale pink at room temperature.

N^{im}-Benzyl-L-histidine (XXX).—Benzyl chloride was added to a sodium–liquid ammonia solution of L-histidine hydrochloride monohydrate (41.92 g, 0.20 mol) according to the original literature procedure (22.055 g, 45%): mp 200–201° dec; $[\alpha]^{26.7}D$ +19.1° (*c* 1.0, 2 *N* hydrochloric acid) {lit.[36] mp 248–249°; $[\alpha]^{34}D$ +20.5° (*c* 2, water containing 1 equiv of hydrochloric acid)}; R_f 0.16 (butanol–acetic acid–water), 0.17 (methanol). Other preparations had mp 243–246 dec.

N^{α}-*t*-Butyloxycarbonyl-N^{im}-benzyl-L-histidine (XXXI).—*t*-Butyloxycarbonyl azidoformate (5.36 ml, 0.0375 mol) in methanol (25 ml) was added to a solution of N^{im}-benzyl-L-histidine (6.133 g, 0.025 mol) in lithium hydroxide (1 *N*, 25 ml). The reaction mixture was stirred at *ca.* 40° for 72 hr, then taken to dryness, and the residue was triturated with cold water (50 ml) and chloroform (20 ml). The suspension was filtered; the aqueous filtrate was washed again with chloroform, neutralized at 0° with dilute sulfuric acid (1 *N*, 25.0 ml), and evaporated to dryness. The solid was thoroughly extracted with cold acetone, and the combined organic phases were filtered and concentrated to a small volume. On standing at room temperature there were deposited colorless needles of N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidine (3.510 g, 41%): mp 189–190°; $[\alpha]^{28.3}D$ +23.2° (*c* 1.0, methanol); R_f 0.38 (butanol–acetic acid–water); neut equiv 352; ν_{max} 3400 (NH), 3030 (OH), 2970 (CH), 1695 very broad (C=O and urethan), 1387 and 1362 (*t*-butyl), 1245 (CO), 1170 (OH), and 710 (Ph) cm^{-1}; λ_{max} 246, 252, 257, 261, 264, and 267 mμ (ε 150, 164, 202, 171, 162, and 123).

Anal. Calcd for $C_{18}H_{23}N_3O_4$ (345.4): C, 62.59; H, 6.71; N, 12.17. Found: C, 62.46; H, 6.78; N, 12.09.

N^{α}-*t*-Butyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-Trichlorophenyl Ester (XXXII).—To a solution of N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidine (0.691 g, 0.002 mol) in methylene chloride (20 ml) at −20° was added 2,4,5-trichlorophenol (0.395 g, 0.002 mole) and N,N′-dicyclohexylcarbodiimide (0.412 g, 0.002 mol). After stirring for 4 hr at −20° and 48 hr at 0°, the reaction mixture was taken almost to dryness, and the residue was suspended in chilled ethyl acetate. The N,N′-dicyclohexylurea was removed, and the organic solution was washed with cold, saturated sodium bicarbonate solution and brine and dried. Rapid concentration of the ethyl acetate solution at 10°, then addition of chilled diisopropyl ether to the opalescence point, followed by sufficient ethyl acetate to give a clear solution at 10°, and prolonged storage in a cold room furnished the product as white needles. Recrystallization using the above conditions led to N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-trichlorophenyl ester (0.615 g, 59%): mp 123.5–124.5°; $[\alpha]^{25.7}D$ −9.9° (c 1.0, chloroform); R_f 0.76; ν_{max} 3420 (NH), 2975 (CH), 1777 (C=O), 1710 (urethan), 1395 and 1368 (*t*-butyl), 1120 (CO), and 697 (Ph); λ_{max} 289 and 300 (sh) mμ (ε 208 and 179).

Anal. Calcd for $C_{24}H_{24}Cl_3N_3O_4$ (524.8); C, 54.92; H, 4.61; Cl, 20.27; N, 8.01. Found: C, 43.72; H, 4.70; Cl, 20.09, N, 7.94.

N^{α}-*t*-Butyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine Methyl Ester (XXXIII).—N^{α}-Benzyloxycarbonyl-L-seryl-L-glutaminylglycine methyl ester (0.438 g, 0.001 mol) in N,N-dimethylformamide (10 ml) was hydrogenated in the presence of 10% palladium-on-charcoal catalyst (0.025 g) and acetic acid (0.06 ml, 0.001 mol). On removal of the catalyst, the solution was cooled to −20° and N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidine 2,4,5-trichlorophenyl ester (0.525 g, 0.001 mol) was added with stirring. After 1 hr, the reaction was maintained at 0° for 5 days. The solvent was evaporated to leave an oil which was dissolved in a small quantity of methanol. The addition of ethyl acetate precipitated a white solid, which was collected and washed immediately with ether. Reprecipitation in the same fashion gave N^{α}-*t*-butyloxycarbonyl-N^{im}-benzyl-L-histidyl-L-seryl-L-glutaminylglycine methyl ester as a white powder (0.321 g, 51%): mp 188–190° dec; $[\alpha]^{26.3}D$

$-14.1°$ (c 1.0, methanol); R_f 0.60 (methanol); ν_{max} 3300 broad (OH), 2900 (CH), 1740 (C=O), 1670 very broad (C=O and urethan), 1393 and 1669 (*t*-butyl), 1165 (CO), and 695 (Ph) cm^{-1}; λ_{max} 247, 252, 258, 261, 264, and 267 mμ (ϵ 162, 160, 180, 143, 145, and 100).

Anal. Calcd for $C_{29}H_{41}N_7O_9 \cdot H_2O$ (649.7): C, 53.61; H, 6.66; N, 15.09. Found: C, 53.88; H, 6.46; N, 15.62.

The tetrapeptide was alternatively prepared by use of N,N'-dicyclohexylcarbodiimide, but only an oily product was obtained in spite of many crystallization attempts.

Registry No.—III, 17115-09-2; XI, 17791-44-5; XII, 17791-45-6; XVII, 17791-46-7; XX, 17791-47-8; XXI, 17791-48-9; XXIII, 17791-49-0; XXVII, 2488-14-4; XXVIII, 17791-51-4; XXIX, 17791-52-5; XXXI, 13734-45-7; XXXII, 17791-54-7; XXXIII, 17818-04-1.

Acknowledgment.—The authors are indebted to the National Science Foundation for Grant GB-587, which supported this investigation.

Angular Methylation of 4-Methyl-$\Delta^{4(10)}$-1-octalone[1]

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This Note reports the direct angular methylationof 4-methyl-$\Delta^{4(10)}$-1-octalone (**1** → **2**), a synthetic step previously suggested[2] for $\Delta^{4(10)}$-1-octalones in general but unrealized[3] in one attempt to methylate $\Delta^{4(10)}$-1-octalone itself. In conjunction with a synthesis of $\Delta^{4(10)}$-1-octalones *via* 1,4 cycloaddition to 1-vinylcyclohexenes[4] the present work forms the basis of a useful synthetic approach to germacrane and elemane sesquiterpenes.[5]

4-Methyl-$\Delta^{4(10)}$-1-octalone (**1**) is rapidly and completely isomerized by ethanolic sodium hydroxide to its corresponding conjugated double-bond isomer (**7**).[6] The dire consequences of this isomerization were anticipated, but their establishment proved to be useful.[7] Addition of methyl iodide to the enolate mixture formed by stirring equimolar amounts of **7** and sodium hydride in dimethoxyethane for 36 hr to ensure partial, if not complete, equilibration of enolate ions gave a multicomponent distillate in 85% yield from which the predominant component (47% by glpc) was isolated and shown to be 4,9-dimethyl-$\Delta^{5(10)}$-1-octalone, a product of angular methylation but with undesirable double-bond isomerization. Thus, of the five interconvertible enolates in this system, the most stable is the $\Delta^{1(9),5(10)}$-hexalin, in accord with the relative stabilities of the unsubstituted hexalins and other related systems.[8]

Methylation of **7** under conditions favoring kinetic control of enolate formation[9] yielded no trace of **2**. Treatment of **7** in dimethoxyethane at room temperature with an excess of both sodium hydride and methyl iodide gave in high yield 2,2,4-trimethyl-Δ^9-1-octalone (**9**) *via* the glpc detectable intermediates, *cis*- and *trans*-2,4-dimethyl-Δ^9-1-octalones (**8**, see the lower half of Scheme I). This result is consistent with exemplary data indicating that α' protons of α,β-unsaturated ketones can be more acidic than γ protons in the kinetic, if not thermodynamic, sense.[10]

In relation to the angular methylation of **1**, the foregoing results emphasized the need for a procedure involving kinetic control of enolate formation from the β,γ-unsaturated ketone. Treatment of **1** in dimethoxyethane at room temperature with 1 equiv of sodium hydride and excess methyl iodide afforded a multicomponent distillate in 83% yield, from which was obtained, by repetitive preparative glpc, a sample of the desired ketone **2**. Determination of the efficacy of this chosen[11] procedure was effected by analyzing the reaction of **1** with an excess of both sodium hydride and methyl iodide. Analysis and separation were simplified by treating each aliquot removed from the reaction vessel with base to ensure complete isomerization of β,γ-unsaturated ketones **5** and **6** to α,β-unsaturated ketones **8** and **9**. Results of the glpc analysis are shown in Table I and Figure 1. A seven-component mixture developed and converged to a single final product which was isolated and character-

TABLE I

"KINETIC" METHYLATION OF 1[a]

Time min	%						
	4	*trans*[b] **3**	**2**	*cis*[b] **3**	*trans*[b] **8**	**7**	*cis*[b] **8**
0						100	
18			3.3			96.7	
33			18.4			81.0	0.6
42		0.8	41.1	1.7	1.2	48.2	6.8
49		2.1	57.0	5.7	2.1	24.5	8.4
60	1.1	7.5	66.6	12.7	0.4	0.7	10.6
82	10.0	27.7	18.4	41.4	0.6	0.3	1.4
159	55.5	18.5		26.0			
258	76.3	10.7		13.0			
645	88.9	9.9		1.2			
1530	99.4	0.3		0.3			
2055	99.6	0.1		0.3			

[a] Compounds are listed in order of increasing glpc retention time. Other detectable peaks never amounted to more than 0.8%. [b] Arbitrary isomer assignments based on a rationalization of steric interference with adsorption.

(1) This investigation was supported by Public Health Service Research Grant GM 09759 and GM 14133 from the Division of General Medical Sciences, U. S. Public Health Service. Acknowledgment is also made of National Science Foundation Grant G 19108 which contributed to the purchase of the nmr spectrometer used in this research.

(2) A. J. Birch, J. A. K. Quartey, and H. Smith, *J. Chem. Soc.*, 1768 (1952).

(3) J. A. K. Quartey, *J. Ind. Chem. Soc.*, **37**, 731 (1960).

(4) P. S. Wharton and B. T. Aw, *J. Org. Chem.*, **31**, 3787 (1966); B. T. Aw and C. E. Sundin, Ph.D. Theses, University of Wisconsin, 1966–1967.

(5) The continuation is most simply envisaged *via* the fragmentation sequence developed by J. A. Marshall and G. L. Bundy [*Chem. Commun.*, 854 (1967)].

(6) The 4-methyl group does not stabilize the β,γ-unsaturated isomer sufficiently to produce a detectable amount at equilibrium. *Cf.* K. G. Lewis and G. J. William, *Tetrahedron Lett.*, 4573 (1965).

(7) For a general discussion of the alkylation of α,β-unsaturated ketones, see J. M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963).

(8) R. B. Bates, R. H. Carnighan, and C. E. Staples, *J. Amer. Chem. Soc.*, **85**, 3030 (1963), and references therein; M. S. Newman, V. DeVries, and R. Darlak, *J. Org. Chem.*, **31**, 2171 (1966).

(9) For a general discussion of enolate anions, their formation, and alkylation, see H. O. House, *Rec. Chem. Progr.*, **28**, 98 (1967).

(10) A. J. Birch, *J. Chem. Soc.*, 2325 (1950); H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962).

(11) (a) Trityl and amide ions have been used extensively as bases to obtain enolates from ketones. We did not investigate these and other procedures. (b) See ref 9 and H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 7.

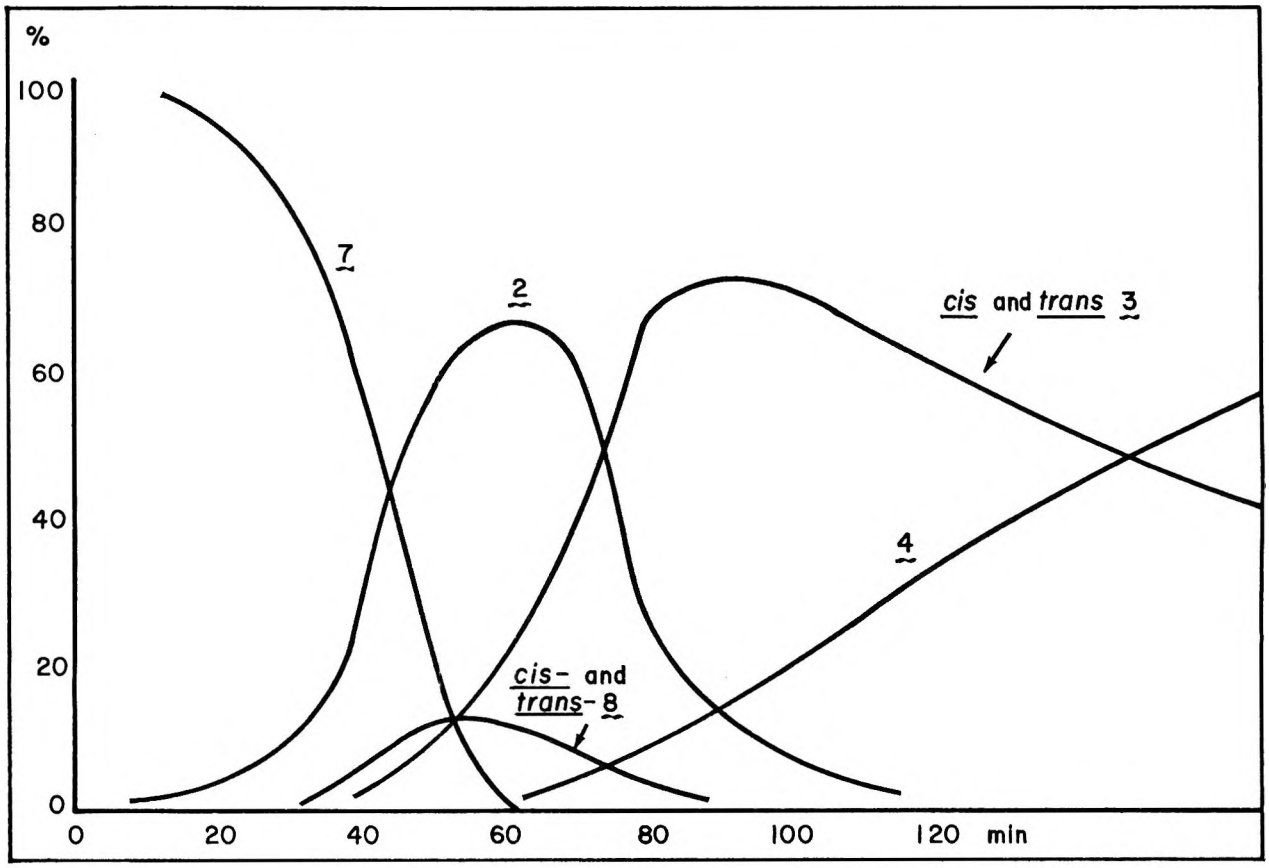
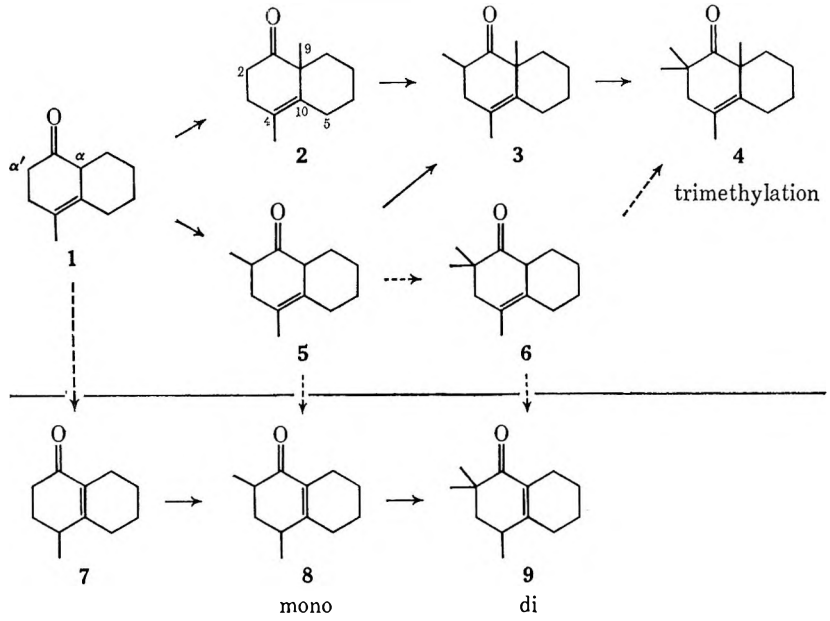


Figure 1.—Kinetic methylation of 4-methyl-$\Delta^{4(10)}$-1-octalone (1).

SCHEME I



ized as **4**.[12] This ketone was one of a group of four β,γ-unsaturated ketones well separated from a group of three α,β-unsaturated ketones by glpc retention times. Comparison with the retention times of components formed in the "kinetic" methylation of **7** revealed the presence of *cis* and *trans* **8**, *but complete absence of* **9**, establishing the formation of *cis* and *trans* **8** exclusively by isomerization of *cis* and *trans* **5** in the work-up and not by formation during the reaction (either by isomerization of **5**, or by isomerization of **1** followed by methylation). The over-all pattern of methylation of **1** is therefore completely defined by the upper half of Scheme I.

Figure 1 reveals that, under the chosen conditions, the maximum realizable yield of **2** is at least 55% (66% based on recovered distillate), a demonstration that direct angular methylation of $\Delta^{4(10)}$-1-octalones represents a viable synthetic procedure. This contrasts with the indirect approaches which have been employed

(12) (a) Although not expected, competitive γ and O alkylation would have complicated the observed methylation pattern; see ref 7. (b) Conditions were not controlled and no over-all kinetic analysis of the results was attempted. For convenience in sampling at short reaction times the reaction was started at 0° and then allowed to warm to room temperature.

to introduce an angular methyl group into 1-decalones.[11b] The effect of the 4(10) double bond is apparent in a comparison of the (apparent)[13] kinetic acidities of the α and α' protons of **1** and *trans*-1-decalone: the α proton is seven times *less* acidic than the α' protons in *trans*-1-decalone[14] and four times *more* acidic in **1**.[12b,15]

Experimental Section

Physical Data.—Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were recorded on Perkin-Elmer 137 Infracord and Beckman IR-8 spectrometers. Nmr spectra were recorded on Varian A-60 and A-60A spectrometers using tetramethylsilane as an internal standard. Mass spectra were obtained on a Consolidated CEC 103 spectrometer with samples introduced *via* a heated glass inlet system maintained at 200°. Glpc data were obtained using (1) capillary columns in conjunction with a Perkin-Elmer F-11 unit (flame ionization) and (2) packed columns in conjunction with an Aerograph A-90-P2 unit (thermal conductivity). Component composition is given in terms of peak areas determined by using a Disc chart integrator. Glpc columns used were (1) Ucon Polar 50-HB-2000, 150 ft capillary; (2) 5% Carbowax on Teflon 6, 5 ft × 1/4 in.; (3) 20% didecylphthalate on 60/80 Chromosorb P, 5 ft × 1/4 in.; (4) 20% SF-96 on 60/80 firebrick, 5 ft × 1/4 in.

Materials and Procedure.—Dimethoxyethane was distilled from lithium aluminum hydride and stored over molecular sieves (activated Linde Type 13X). Methyl iodide was distilled and stored over molecular sieves. Where not described, the work-up was typically carried out by pouring the reaction mixture into saturated sodium chloride solution containing a small amount of sodium thiosulfate. The aqueous phase was extracted with several portions of ether; the ether extracts were combined and washed several times with saturated sodium chloride solution. The ether solution was dried over sodium or magnesium sulfate, filtered, and evaporated under reduced pressure.

4-Methyl-Δ^9-1-octalone[4] (**7**) was recovered in 98% yield from base-catalyzed isomerization of 4-methyl-$\Delta^{4(10)}$-1-octalone: glpc (column 1, 85°) 38 min (98%); ir max 6.02 μ; uv max (95% EtOH) 247 mμ (ϵ 12,500); mass spectrum (70 eV) *m/e* (rel intensity) 164 (13), 149 (5), 136 (19), 122 (16), 107 (16), 93 (4), 51 (100).

2,2,4-Trimethyl- and 2,4-Dimethyl-Δ^9-1-octalones (**9** and **8**).—To a solution of 976 mg (5.95 mmol) of **7** in 18 ml of dimethoxyethane and 2 ml of methyl iodide was added, with stirring under nitrogen, 262 mg (5.92 mmol) of sodium hydride as a 54% mull. After stirring at room temperature for 18 hr a test for sodium hydride was negative. Work-up afforded 982 mg of a colorless distillate (bath temp 70–90° at 0.1 mm): glpc (column 1, 75°) 43 (0.3), 48 (7.6), 52 (91.4), and 56 min (0.7%); the 52 min component corresponded to the starting material. To a solution of 941 mg of distillate in 17 ml of dimethoxyethane and 2 ml of methyl iodide was added 769 mg (17.9 mmol) of sodium hydride as a 60% mull. After 62 hr at room temperature work-up yielded 1.01 g of distillate: glpc (column 1, 75°) 27 (1.2), 43 (41.5), 48 (51.8), and 56 min (5.5%). Preparative glpc (column 2, 130°) afforded an analytical sample of the 43 min component (**9**): ir max (film) 5.99 μ; nmr (CCl_4) δ 1.02 (s, 6), 1.09 (d, 3, J = 8 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 192 (42), 177 (4), 163 (2), 149 (15), 137 (34), 136 (100), 135 (31), 121 (10), 107 (23), 95 (95).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.45; H, 10.35.

Preparative glpc also afforded an analytical sample of the 48 min component (**8**): ir max (film) 5.99 μ; nmr (CCl_4) δ 1.08 (d, 3, J = 9.5 Hz) and 1.18 (d, 3, J = 9.0 Hz).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.66; H, 10.16.

4,9-Dimethyl-$\Delta^{5(10)}$-1-octalone.—To a solution of 1.27 g (7.76 mmol) of **7** in 18 ml of dimethoxyethane was added 322 mg (7.79 mmol) of sodium hydride as a 58% mull. After stirring under nitrogen at room temperature for 36 hr the dark brown solution was cooled in an ice–water bath. Methyl iodide (0.7 ml) was added, and the mixture was stirred for 5 min. Work-up gave 1.18 g of distillate (bath temp 50–80° at 0.2 mm): glpc (column 1, 75°) 11 (1.9), 26 (10.3), 27 (1.1), 29 (46.8), 32 (5.7), 51 (27.7), 58 (2.2) and 63 min (4.3%). Preparative glpc (column 2, 142° and column 3, 140°) afforded an analytical sample of the 29 min component, 4,9-dimethyl-$\Delta^{5(10)}$-1-octalone: ir max (film) 5.82 μ; nmr (CCl_4) δ 1.07 (d, 3, J = 6.7 Hz), 1.25 (s, 3) and 5.42 (m, 1); mass spectrum (70 eV) *m/e* (rel intensity) 178 (88), 163 (36), 149 (11), 136 (61), 135 (73), 123 (83), 122 (15), 121 (28), 107 (62), 93 (100).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.65; H, 10.16.

4,9-Dimethyl-$\Delta^{4(10)}$-1-octalone (**2**).—To a solution of 733 mg (4.46 mmol) of **1** in 17 ml of dimethoxyethane and 2 ml of methyl iodide was added 205 mg (4.62 mmol) of sodium hydride as a 54% mull. The mixture was stirred under nitrogen at room temperature for 1.5 hr. Work-up afforded 661 mg of distillate (bath temp 50–70° at 0.2 mm): glpc (column 1, 100°) 18 (3.8), 19 (0.8), 21 (6.9), 23 (64.2), and 25 min (24.2%).[16] Preparative glpc (column 4, 144°) yielded an analytical sample of the 23 min component (**2**): ir max (film) 5.83 μ; nmr (CCl_4) δ 1.19 (s, 3) and 1.69 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 178 (6), 163 (2), 149 (1), 121 (15), 107 (10), 93 (25), 39 (100).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C 80.73; H, 10.22.

2,2,4,9-Tetramethyl-$\Delta^{4(10)}$-1-octalone (**4**).—To a solution of 374 mg (2.28 mmol) of **1** in 13 ml of dimethoxyethane and 0.5 ml of methyl iodide was added 600 mg (13.4 mmol) of sodium hydride as a 54% mull. The mixture was stirred under nitrogen at room temperature for 10 hr. Work-up afforded 430 mg of distillate (bath temp 75° at 0.3 mm): glpc (column 4, 130°) 21 (0.4), 32 (6.6), and 51 min (92.4%), from which was obtained an analytical sample of the 51 min component (**4**): ir max (film) 5.86 μ; nmr (CCl_4) δ 1.08 (s, 6), 1.12 (s, 3), and 1.71 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 206 (32), 191 (7), 163 (29), 150 (19), 136 (100), 122 (17), 121 (85), 107 (55), 93 (74).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.29; H, 10.73.

Glpc Analysis of "Kinetic" Methylation of 4-Methyl-$\Delta^{4(10)}$-1-octalone (**1**).—To a mixture of 2.06 g (49.6 mmol) of sodium hydride as a 58% mull, 50 ml of dimethoxyethane and 4 ml of methyl iodide, contained in a flask cooled in ice–water, was added a solution of 944 mg (5.74 mmol) of **1** in 10 ml of dimethoxyethane. The mixture was allowed to warm to room temperature and was stirred at this temperature under nitrogen. (After 14 hr a further 16 mmol of sodium hydride was added.) Aliquots were removed at intervals and added to 5-ml portions of cold 95% ethanol. Each solution was then boiled for 10 min, cooled, worked up, and analyzed by glpc (column 1, 75°); 22, 27, 29, 32, 40, 45, 50, and 56 min components were observed. The results are recorded in Table I in the text.

TABLE II

"KINETIC" METHYLATION OF **7**[a]

Time, min	%			
	9	*trans*[b] **8**	**7**	*cis*[b] **8**
11			100	
29		3.6	96.2	0.2
55		26.8	68.2	5.0
98	0.3	38.1	54.8	6.8
161	2.3	56.3	31.0	10.3
230	8.4	71.0	9.7	10.9
520	32.6	61.3	0.2	5.9
2260[c]	73.1	25.5		1.4
7450[d]	90.1	9.9		

[a] Compounds are listed in order of increasing glpc retention times. [b] Arbitrary isomer assignments based on a rationalization of steric interference with adsorption. [c] 1.0% at 22 min. [d] 3.4% at 22 min.

(13) The possibility of *partial* equilibration of enolates cannot be discounted.

(14) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(15) The relative kinetic acidity of the α' proton of **5** is even less, the 2-methyl group suppressing the formation of **6**. See H. O. House and V. Kramar, *ibid.*, **28**, 3362 (1963).

(16) This experiment was carried out before adopting a standard base treatment in the work-up which ensured complete isomerization. The glpc results cannot therefore be directly correlated with those of other runs because of uncertainty with respect to the extent of isomerization.

Glpc Analysis of "Kinetic" Methylation of 4-Methyl-Δ^9-1-octalone (7).—To a solution of 1.19 g (7.25 mmol) of **7** in 30 ml of dimethoxyethane and 4 ml of methyl iodide was added 115.8 mmol of sodium hydride obtained by removing the hydrocarbon from 5.63 g of mull by washing with dimethoxyethane. The mixture was stirred under nitrogen at room temperature.[17] Aliquots were removed at intervals, worked up, and analysed by glpc (column 1, 75°); 42, 47, 51, and 55 min components were observed. The results are recorded in Table II which appears on p 4257.

Registry No.—**1**, 13207-25-5; **2**, 17408-20-7; **4**, 17408-21-8; **7**, 13207-04-0; **8**, 17408-23-0; **9**, 17393-19-0; 4,9-demethyl-$\Delta^{5(10)}$-1-octalone, 17408-24-1.

(17) The hydrogen evolved was measured but its rate of evolution was not found to be useful for determining the extent of reaction.

Cope Rearrangement of *trans,trans*-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene[1]

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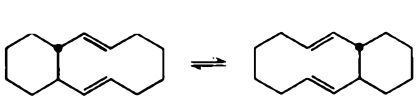
trans,trans-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene[2] has been partially resolved into one of its enantiomers, $[\alpha]D$ −58°, by selective reaction of optically active diisopinocampheylborane with the racemate.[3] Optically active diene racemizes in 2,2,4-trimethylpentane solution with first-order kinetics which yield an energy of activation of 25 kcal mol^{-1} with a frequency factor of 3×10^{11} sec^{-1} (half-life at 50° *ca.* 24 hr). These data are consistent with the occurrence of the Cope rearrangement A ⇌ B, which is facilitated relative to the



A B

rearrangement of *dl*-3,4-dimethylhexa-1,5-diene (which proceeds at 180°)[4] by the combination of strain and conformation of the double bonds in the medium ring.[5] The system A ⇌ B is unusual in its possession of the basic symmetry of the Cope rearrangement[6] combined with its susceptibility to extremely accurate kinetic measurement.

Experimental Section

Optically Active *trans,trans*-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene.—In a 25-ml flask equipped with a pressure-equalizing dropping funnel was placed 0.076 g (2.02 mmol) of sodium borohydride, 2.0 ml of diglyme, and 0.716 g (5.25 mmol) of (+)-α-pinene, bp 153.0–154.5°, $[\alpha]^{21}D$ +53.2° (*c* 3.69, 95% ethanol). The flask was cooled to ice-bath temperature, and the contents were stirred under nitrogen throughout the course of the reaction. Boron trifluoride etherate (0.372 g, 2.62 mmol), diluted with 6.0 ml of diglyme, was first added. After 4 hr, 1.001 g (5.26 mmol) of diene, mp 48.0–49.0°, was added. After a further 4 hr, the reaction mixture was diluted with 50 ml of distilled water and extracted three times with 50-ml portions of pentane. The combined pentane extracts were washed three times with 50-ml portions of distilled water and then dried. Removal of solvent under reduced pressure and below 25° afforded 1.773 g of a clear colorless oil. The oil was dissolved in 75 ml of pentane and extracted with three 75-ml portions of 20% silver nitrate solution. The combined silver nitrate extracts were washed three times with 50-ml portions of pentane and then added to 150 ml of concentrated ammonium hydroxide at ice-bath temperature. The mixture was extracted four times with 25-ml portions of pentane. The combined pentane extracts were washed twice with 25-ml portions of distilled water and then dried. Removal of solvent under reduced pressure and below 25° afforded 0.375 g of solid, mp 41.0–46.0°, $[\alpha]^{23}D$ −58.2° (c 3.65, chloroform), whose ir spectrum (CCl_4) was identical with that of pure diene. Capillary glpc indicated that the solid consisted of a single major component (99%).

Racemization of Optically Active *trans,trans*-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene.—For each kinetic run, a solution of optically active diene in 2,2,4-trimethylpentane was prepared in a 25-ml volumetric flask, and the flask was suspended in a constant-temperature bath with ±0.03° temperature control. After allowing at least 30 min for the solution to reach thermal equilibrium, 2.0-ml aliquots were periodically removed and, except for measurements at 30°, quenched at ice-bath temperature. The optical rotation of these aliquots was measured at the sodium 589-mμ line at *ca.* 23° with an estimated accuracy of ±0.004°. Infinity points were measured after at least ten half-lives. The results of these measurements are compiled in Table I.

TABLE I

RACEMIZATION DATA[a]

Temp, °C	α_0	α_∞	k_α,[b] sec^{-1}
29.85	−0.452	+0.008[c]	$7.36 \pm 0.54^d \times 10^{-7}$
48.86	−0.570	+0.024	$7.74 \pm 0.50^d \times 10^{-6}$
59.58	−0.435	+0.10	$3.17 \pm 0.17^d \times 10^{-5}$

[a] *Ca.* 0.02 *M* diene in 2,2,4-trimethylpentane. [b] $2k_{Cope} = k_a = 2.303/t \times \log(\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)$. [c] Measured after finally heating for 71 hr at 60°. [d] Standard deviation.

After the kinetic run at 48.86°, evaporation of solvent yielded a solid, mp 43.0–47.0°, whose ir spectrum (CCl_4) was identical with that of pure diene.

Registry No.—(−)-*trans,trans*-2,8-*trans*-Bicyclo[8.4.0]tetradecadiene, 17510-76-8; (±)-*trans,trans*-2,8-*trans*-bicyclo[8.4.0]tetradecadiene, 17510-77-9.

(1) This investigation was supported by Public Health Service Research Grant GM 09759 from the Division of General Medical Sciences, U. S. Public Health Service, and by a National Institutes of Health Predoctoral Fellowship to R. A. K. Acknowledgment is also made of National Science Foundation Grant G19108 which contributed to the purchase of the nmr spectrometer used in this research.

(2) P. S. Wharton, Y. Sumi, and R. A. Kretchmer, *J. Org. Chem.*, **30**, 234 (1965).

(3) This resolution is a direct application of an established method of synthesis of optically active alcohols from olefins. The reaction of *trans* double bonds is normally very slow, not so those of our strained diene. See H. C. Brown and N. R. Ayyangar, *J. Amer. Chem. Soc.*, **86**, 397, 1071 (1964).

(4) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(5) The parent system, *trans,trans*-1,5-cyclodecadiene, is reported to undergo the Cope rearrangement at slightly higher temperatures, rearranging irreversibly over a period of 3 days at 70° to *trans*-1,2-divinylcyclohexane: C. A. Grob, H. Link, and P. W. Schiess, *Helv. Chim. Acta*, **46**, 483 (1963).

(6) The observed rearrangement is degenerate in a previously unobserved sense; reactant and product are structurally identical but enantiomeric. For the first of several reported degenerate Cope rearrangements, previously observed solely by nmr spectroscopy, see W. von E. Doering and W. R. Roth, *Angew. Chem. Intern. Ed. Engl.*, **2**, 115 (1963). For an example of asymmetric induction in the Cope rearrangement, see R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).

Isotopic Rearrangement of 2-Phenyl-2-^{14}C-butane. Relationship to Other Lewis Acid Catalyzed Reactions of *sec*-Alkylbenzenes[1]

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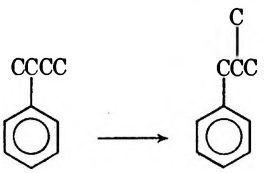
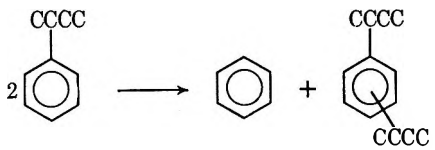
The surprising rearrangement of *sec*-butylbenzene to isobutylbenzene, induced by heating with aluminum chloride at 80 to 100°, was reported in 1959.[2] Dis-



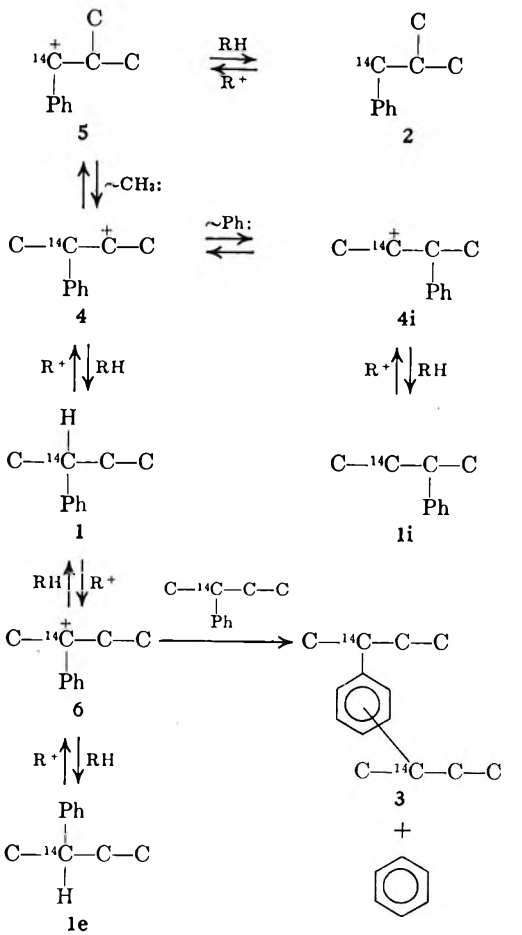
proportionation (transalkylation) of *sec*-butylbenzene takes place at lower temperatures (*e.g.*, 25°, $AlCl_3$[2a] or HF + BF_3 catalyst[3]) without side-chain rearrangement.



Another kind of rearrangement of *sec*-butylbenzene might be expected on the basis of the behavior of higher *sec*-alkylbenzenes. 2- and 3-phenylpentanes are interconverted by aluminum chloride at 25°,[4,5] and 2-phenyldodecane is isomerized to an equilibrium mixture of 2-, 3-, 4-, 5-, and 6-phenyldodecanes at 50°.[6] An investigation of the analogous rearrangement of *sec*-butylbenzene, which can only be observed in the case of an isotopically labeled molecule such as 2-phenyl-2-^{14}C-butane (**1**, Scheme I), is the subject of this paper.

This system has several interesting features. (1) It is the simplest one in which a shift of a phenyl group between secondary carbon atoms can occur. (2) The end result of rearrangement is a 1:1 distribution of the isotopic isomers, **1** and **1i** (neglecting a small isotope effect). (3) The expected phenyl shift can be detected with precision by radiochemical analysis in molecules which can be shown by spectroscopic and chromatographic analysis to have undergone no other kind of rearrangement.

SCHEME I



The results of six experiments in which 2-phenyl-2-^{14}C-butane (**1**) was treated with aluminum halide catalysts are presented in Table I. With water-acti-

TABLE I

REARRANGEMENT OF 2-PHENYL-2-^{14}C-BUTANE TO 2-PHENYL-3-^{14}C-BUTANE

Temp, °C	Time, min	Catalyst[a]	2-Phenyl-2-^{14}C-butane remaining, %
25	60	$AlCl_3 + H_2O$[b]	50[c]
0	60	$AlCl_3 + H_2O$[b]	79[d]
−14	15	$AlCl_3 + H_2O$[b]	100[d]
−14	15	$AlBr_3$	100[e]
−17	15	$AlBr_3$	100[f]

[a] 2-Phenyl-2-^{14}C-butane: AlX_3 mole ratio = 3:1. [b] $AlCl_3$: H_2O mole ratio = 1:1. [c] Two experiments. Starting materials: 10 g of 2-phenyl-2-^{14}C-butane in each, (1) 0.607 μCi/mmol and (2) 0.293 μCi/mmol. [d] Starting material: 10 g of 2-phenyl-2-^{14}C-butane, 0.607 μCi/mmol. [e] Starting material: 8.0 g of 2-phenyl-2-^{14}C-butane. [f] Starting material: 7.9 g of 2-phenyl-2-^{14}C-butane, 0.293 μCi/mmol.

vated aluminum chloride at 25°, rearrangement to 2-phenyl-3-^{14}C-butane (**1i**) occurred, producing the equilibrium mixture (1:1) of the isotopic isomers in 1 hr, but, at −14 to −17° with the same catalyst or with anhydrous aluminum bromide, no rearrangement occurred in 15 min. After 1 hr at 0° with $AlCl_3$ + H_2O, 21% rearrangement had occurred. Disproportionation to benzene and di-*sec*-butylbenzene [mainly *meta* and *para* isomers (**3**)] occurred in all experiments,

(1) (a) Part XVIII of the series "New Friedel–Crafts Chemistry." Part XVII, A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 926 (1966). (b) Supported by the Robert A. Welch Foundation.

(2) (a) R. M. Roberts, Y. W. Han, C. H. Schmid, D. A. Davis, *J. Amer. Chem. Soc.*, **81**, 640 (1959); (b) C. D. Nenitzescu, I. Necsoiu, A. Glatz, and M. Zalman, *Chem. Ber.*, **92**, 10 (1959).

(3) D. A. McCaulay and A. P. Lien, *J. Amer. Chem. Soc.*, **75**, 2411 (1953). The catalyst was HF·BF_3.

(4) R. L. Burwell, Jr., and A. D. Shields, *ibid.*, **77**, 2766 (1955).

(5) R. M. Roberts, J. R. Baker, and S. E. McGuire, unpublished results.

(6) A. C. Olson, *Ind. Eng. Chem.*, **52**, 833 (1960).

but no rearrangement to isobutylbenzene (2) (or other isomers[7,8]).

It is interesting to consider the reaction pathways by which 2-phenyl-2-^{14}C-butane (1) may be converted into four different kinds of products (1i, 1e, 2, and 3, Scheme I). Isomerization to 2-phenyl-3-^{14}C-butane (1i) and to isobutylbenzene (2) may both involve the intermediate secondary carbonium ion 4. On the basis of stability of the carbonium ions produced, competition between the phenyl and methyl shifts would be expected to be in favor of the latter, since the charge on 5 may be delocalized by the benzene ring. The experimental observation that the isotopic isomerization (1 $\rightleftarrows$ 1i) reaches equilibrium under conditions that produce no *sec*-butylbenzene–isobutylbenzene isomerization (1 $\rightleftarrows$ 2) seems to indicate that participation of the phenyl group in the 1,2 shift is a more important factor than the stabilization of the ion 5.

The fact that the production of 3 and benzene by disproportion is an even more facile reaction than the isotopic isomerization may be rationalized, however, on the basis that the tertiary benzylic carbonium ion 6 is formed much more readily than the aliphatic secondary ion 4,[9] and the disproportionation proceeds by the Pines–Streitwieser alkylation–dealkylation mechanism.[10] This explanation is consistent also with the observation[4] that racemization of optically active 2-phenylpentane by aluminum chloride is much more rapid than isomerization to 3-phenylpentane. Although our 2-phenyl-2-^{14}C-butane was not optically active, racemization of asymmetric molecules would undoubtedly follow the pathway 1 $\rightleftarrows$ 6 $\rightleftarrows$ 1e, which involves the same intermediate (6) required for the disproportionation.[11]

Experimental Section

Synthesis of 2-Phenyl-2-^{14}C-butane (1).—The radioactive title compound was synthesized by methods described previously. $C_6H_5{}^{14}COCH_3$ was prepared from $CH_3{}^{14}CO_2Na$, benzene, and $AlCl_3$;[8a] treatment of $C_6H_5{}^{14}COCH_3$ with ethylmagnesium bromide was followed by catalytic reduction of the crude product to give 1.[8b,c] This product (and the 2-phenylbutane recovered after reaction with $AlCl_3$) was converted into *p*-nitrobenzoic acid by reaction with concentrated nitric acid (reflux, 24 hr). The crude *p*-nitrobenzoic acid was purified by dissolving it in aqueous NaOH solution, extracting nonacidic organic impurities into ether, and reprecipitating the *p*-nitrobenzoic acid by the addtion of concentrated HCl. It was recrystallized from aqueous ethanol and sublimed under reduced pressure; radioassay was carried out by wet combustion to CO_2, which was counted on a vibrating-reed electrometer.[8a]

Reaction of 2-Phenyl-2-^{14}C-butane with Aluminum Halides.—Details of six experiments are given in Table I. The reaction mixtures were stirred with Teflon-covered magnetic stirring bars, decomposed with crushed ice and HCl, and worked up by addition of ether and extraction in the usual way.[8] *sec*-Butylbenzene (2-phenylbutane) was recovered by fractional distillation; vpc showed it to be free of *n*-butyl- and *t*-butylbenzene isomers; and it indicated the absence of isobutylbenzene.[12] Disproportionation to benzene and di-*sec*-butylbenzene in even the lowest temperature reactions was demonstrated, both by vpc and by the fractional distillations of the reaction mixtures. The amount of *sec*-butylbenzene recovered ranged from 30% at 25° to 60% at −14°.

Registry No.—1, 17398-79-7.

(7) Skeletal rearrangements to isobutyl-, *t*-butyl-, or *n*-butylbenzene would have been detected by vpc or ir analysis.[8] Rearrangement to 2-phenyl-1- or -4-^{14}C-butane is unlikely on the basis of requiring primary carbonium ion intermediates and also because a loss of more than 50% of the ^{14}C from the 2 position would probably have been observed in the 25° experiments.

(8) (a) R. M. Roberts and J. E. Douglass, *J. Org. Chem.*, **28**, 1225 (1963); (b) R. M. Roberts, G. A. Ropp, and O. K. Neville, *J. Amer. Chem. Soc.*, **77**, 1764 (1955); (c) R. M. Roberts and S. G. Brandenberger, *ibid.*, **79**, 5484 (1957).

(9) The intermediate ion 4 may not only be produced directly from 1 by intermolecular hydride abstraction as shown in Scheme I, but also from 6 by intramolecular hydride shift. It is probably impossible to distinguish experimentally between these alternatives, and actually it is likely that 4 is produced in both ways. The rationalization of the relative ease of formation of products 1i, 1e, 2, and 3 on the basis of the stability of the intermediates 4 and 6 has the same relevance whether 4 is formed directly from 1 or indirectly *via* 6.

(10) (a) H. Pines and J. T. Arrigo, *J. Amer. Chem. Soc.*, **80**, 4369 (1958); (b) A. Streitwieser, Jr., and L. Reif, *ibid.*, **86**, 1988 (1964).

(11) By analogy with the behavior of 2-phenylpentane,[4] racemization of optically active 2-phenylbutane would be expected to be still faster than disproportionation.

(12) Analysis of the butylbenzenes by vpc and ir is described by R. M. Roberts and D. Shiengthong, *J. Amer. Chem. Soc.*, **82**, 732 (1960).

The Solvent Isotope Effect in the Acid-Catalyzed Isomerization of *cis*-Stilbenes[1,2]

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It has been pointed out several times in recent years that deuterium isotope effects should vary with structure in a rational manner, reaching a maximum in situations where the hydrogen isotope is symmetrically disposed in the transition state. Westheimer has presented these concepts in more quantitative terms.[5] He assumes that A–H and B react to form A and B–H by way of a linear transition state A–H–B, and finds that the isotope effect is at a maximum when k_1 is equal to k_2, where k_1 and k_2 represent the stretching force constants of the A–H and H–B bonds in the transition state.

Bell and Goodall,[6] in a particularly careful study have observed that the deuterium isotope effect is at a maximum for the ionization of deuterated nitroparaffins when the proton transfer is between two acid–base systems of approximately equal pK. The recent study by Goodall and Long[7] has likewise shown that a very similar result obtains in the reverse reaction involving deuterated acids in deuterated medium.

In recent studies from these laboratories we have examined in some detail the mechanism of the acid-catalyzed isomerization of a group of substituted *cis*-stilbenes.[8] As the rate-limiting step was shown to be the initial proton transfer from the acidic medium to the organic substrate, this series of compounds represents a useful group in which to examine the variation of the solvent isotope effect as a function of structure.

(1) Supported in part by grants from the National Science Foundation (NSF G-13125 and NSF GP-1572) and by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of these funds.

(2) A portion of this work has been reported in a preliminary communication: D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Amer. Chem. Soc.*, **86**, 3584 (1964).

(3) Shell Fellow in Chemistry, 1963–1964.

(4) National Science Foundation Cooperative Fellow, 1962–1964.

(5) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

(6) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc., Ser. A*, **294**, 273 (1966).

(7) D. M. Goodall and F. A. Long, *J. Amer. Chem. Soc.*, **90**, 239 (1968).

(8) D. S. Noyce, D. R. Hartter, and F. B. Miles, *ibid.*, **90**, 4633 (1968).

We have measured the solvent isotope effect on the rate of isomerization of ten substituted *cis*-stilbenes. The results are tabulated in Tables I and II. Table I gives the results of the rate measurements in the deuterated medium, and Table II gives the values of the solvent isotope effect, extrapolated to a common acidity. It is immediately apparent from these results that there is a distinct trend in the magnitude of the solvent isotope effect, tending to higher values as the stability of the resulting carbonium ion is increased by the appropriate interaction with the substituent in the aromatic moiety. In the extreme, *cis*-4,4′-dimethoxystilbene gives a solvent isotope effect of 6.0, whereas *cis*-4-nitrostilbene gives a solvent isotope effect of only 2.9.

TABLE I

RATE OF ISOMERIZATION OF *cis*-STILBENES IN D_2SO_4 AT 25.00°

No.	Compound[a] X	Compound[a] Y	Wt % D_2SO_4[b]	$k \times 10^5$, sec^{-1}	$-D_0$[c]
1	4-Methoxy	4′-Methoxy	39.04	18.5	2.48
			42.44	42.7	2.83
			45.89	105.	3.21
			49.12	274.	3.55
2	4-Methoxy	4′-Methyl	41.83	19.6	2.77
			48.11	100.	3.44
			50.58	202.	3.71
3	4-Methoxy	H	45.16	45.2	3.14
			49.18	110.	3.56
			51.07	167.	3.75
4	4-Methoxy	3′-Nitro	42.43	4.12	2.83
			51.53	46.7	3.83
5	4-Methoxy	4′-Nitro	47.90	13.1	3.42
			51.32	41.2	3.79
			54.27	74.0	4.12
			57.41	262.	4.46
			58.18	251.	4.51
6	4-Methyl	H	55.32	36.5	4.25
			57.64	71.1	4.53
7	4-Methyl	4′-Nitro	54.61	3.16	4.15
			66.39	172.	5.76
8	H	3′-Methoxy	60.27	15.2	4.83
			62.67	49.1	5.18
			64.98	116.	5.54
9	H	4′-Nitro	64.91	7.0	5.53
			67.04	17.8	5.88
			69.90	54.7	6.36

[a] Substituted *cis*-stilbenes $XC_6H_4CH{=}CHC_6H_4Y$. [b] Weight % D_2SO_4 in the final solution, containing 5% ethanol. [c] For definition, see Experimental Section.

TABLE II

VALUES OF THE KINETIC SOLVENT ISOTOPE EFFECT FOR THE ISOMERIZATION OF *cis*-STILBENES $XC_6H_4CH{=}CHC_6H_4Y$

X	Y	$(k_{H_2O}/k_{H_2O})-4$[a]
4-CH_3O	4′-CH_3O	6.0
4-CH_3O	4-CH_3	3.5
4-CH_3O	H	4.2
4-CH_3O	3′-NO_2	3.5
4-CH_3O	4′-NO_2	3.7
4-CH_3	H	2.8
4-CH_3	4′-NO_2	3.5
H	H	2.4[b]
H	3′-CH_3O	2.5
H	4′-NO_2	2.9

[a] Rates compared by extrapolation or interpolation to $H_0 = -4.00$. $H_0 = D_0 = -4.00$ corresponds to 55.25% H_2SO_4 and to 53.21% D_2SO_4, and to mole fraction sulfate = 0.191. [b] Data given in previous paper.[8]

The Hammond postulate[9] states that, if two species differ greatly in stability, the transition state for their interconversion resembles structurally the less stable of the two species. Thus, one would expect the transition state for protonation of stilbene to resemble the product of the protonation reaction, a carbonium ion of the form ArC^+HCH_2Ar'. One can then extend this postulate by saying that as the stability of ArC^+HCH_2–Ar′ is increased, one would expect the transition state for protonation of stilbene to resemble this carbonium ion to a lesser and lesser extent. That is, the more stable the carbonium ion is, the stronger one would expect the O–H bond to be and the weaker one would expect the C–H bond to be in the transition state.

A trend in the solvent isotope effects was observed by Noyce, Avarbock, and Reed[10] in the acid-catalyzed *cis–trans* isomerization of cinnamic acids. The kinetic solvent isotope effect for isomerization of *cis*-*p*-methoxycinnamic acid is 4.5 while for *cis*-cinnamic acid it is 3.8. This, then, is a case in which proton transfer is more than "half complete" at the transition state.[11]

An example of the opposite trend is shown in the data of Kuivila and Nahabedian[12] in the study of the acid-catalyzed protodeboronation of areneboronic acids.

The trends observed in the present study, though clear, also show that there are additional factors involved, which prelude a complete analysis of the present situation.

In recent study by Schubert, Lamm, and Keeffe,[13] similar perturbations were observed in the hydration of substituted styrenes.

Experimental Section

The preparation of all compounds used in the present study has been reported previously.[8] For studies of the rate of isomerization in deuterated media a 5-ml aliquot of the desired *cis*-stilbene in ordinary ethanol was diluted with deuteriosulfuric acid in D_2O (99.8% *d*) to 100 ml. The titer of the final solution is that given in Tables I and II. The proton pool is thus about 99% *d*. Kinetics were followed by observing the appearance of the absorption band for the *trans* isomer.

Högfeldt and Bigeleisen[14] have concluded that $H_0 = D_0$ at the same molarity of acid. As the molar volumes of H_2O and H_2SO_4 are nearly equal to the molar volumes of D_2O and D_2SO_4, respectively,[15] we have made comparisons at the same mole fraction sulfate, and assumed that $D_0 \equiv H_0$ under these conditions.

Registry No.—Table I: 1, 2510-75-0; 2, 17555-94-1; 3, 1657-53-0; 4, 17555-96-3; 5, 4648-14-0; 6, 1657-45-0; 7, 17556-09-1; 8, 14168-83-3; 9, 6624-53-9.

(9) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(10) D. S. Noyce, H. S. Avarbock, and W. L. Reed, *ibid.*, **84**, 1647 (1962).

(11) Westheimer[5] points out the difficulty with the idea of "partial bond breaking" in the transition state, and that of more direct concern is the relationship of k_1 to k_2, the force constants for the A–H and H–B bonds in the transition state. Nevertheless the descriptive phrase is useful.

(12) H. G. Kuivila and K. V. Nahabedian, *ibid.*, **83**, 2159, 2164 (1961); K. V. Nahabedian and N. G. Kuivila, *ibid.*, **83**, 2167 (1961).

(13) W. M. Schubert, B. Lamm, and J. R. Keeffe, *ibid.*, **86**, 4727 (1964).

(14) E. Högfeldt and J. Bigeleisen, *ibid.*, **82**, 15 (1960).

(15) R. H. Flowers, R. J. Gillespie, J. V. Oubridge, and C. Solomons, *J. Chem. Soc.*, 667 (1958).

Reactions of Picryl Ethers with Hindered Amines[1]

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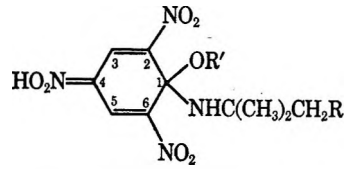
By treating a hindered picryl ether with a hindered amine we have succeeded in forming *neutral* Meisenheimer prototype complexes[2,3] (I) in solution at low temperature and salts of the complexes with 2 mol of the amine. Meisenheimer complexes have recently[4-6] been established as quinoid ionic structures in which the bonding at C-1 is covalent.[7] They are not charge-transfer complexes.

We have found, however, that steric interference of large groups on C-1 with nitro groups at C-2 and C-6 is insufficient to lock the nonbenzenoid ring into a nonplanar structure of sufficient stability to be isolated at room temperature. Even when the ether is picryl mesityl ether and the amine has the tertiary butyl shape the Meisenheimer complex (Ic) forms at −57°, but the deep red color gives way to the bright yellow of a substituted picramide as the solution in tetrahydrofuran warms to ambient temperatures. At the temperature of a Dry Ice bath the red solution of Ic is stable for days, but the neutral complex defies isolation.

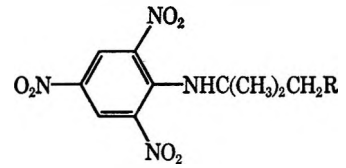
We have verified the findings of Servis[4] with respect to nmr spectra of the Meisenheimer complex Ia. In tetrahydrofuran, a single peak for the two equivalent aromatic protons at C-3 and C-5 (δ 8.40) was observed. In addition, however, the two protons on N at C-4 and O at C-1 in Ia are also clearly distinguishable (NO_2H, δ 11.9, br, and NH, 6.06, br). The peak at δ 11.9 disappears as the color of the solution changes from red to yellow, signalling the change to IIa.

In deuterated dimethyl sulfoxide as solvent, picryl phenyl ether was allowed to react with *t*-butylamine to give equivalent changes in the nmr spectrum at room temperature. When 2 mol of amine was used the low-field peak due to NO_2H was not observed. Instead a broad signal at δ 4.06 (3 H) appeared, which we interpret to be the salt of Ia. In the same solvent the still more hindered picryl mesityl ether gave the same deep red color of the Meisenheimer complex (Ic) and a similar nmr spectrum, and formed the salt of Ic with excess amine.

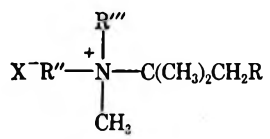
Trinitroanisole, a less hindered ether, gave red solutions of Ib and Id in methanol at low temperatures with the appropriate hindered amine, but picramides formed rapidly even at low temperature. In toluene as solvent, however, the trinitroanisole acted as a methylating agent for the hindered amines, and not even a fleeting red color could be detected. The alkylation does not occur at room temperature, but the insoluble picrate salts III precipitate rapidly from boiling toluene. Alkylation of a tertiary amine, N,N-dimethyl-β-naphthylamine (and others), by trinitroanisole to give the yellow quaternary picrate salt has been observed[8] when the deep red molecular compound of the two components is heated above the melting point of the molecular compound.

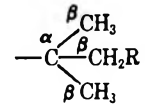


Ia, R = H; R′ = C_6H_5
b, R = H; R′ = CH_3
c, R = H; R′ = $C_6H_2(CH_3)_3$
d, R = OH; R′ = CH_3



IIa, R = H
b, R = OH





the α,β system

IIIa, R = OH; R″ = CH_3; R‴ = CH_3; X = $^-OC_6H_2(NO_2)_3$
b, R = OH; R″ = CH_3; R‴ = CH_3; X = Cl^-
c, R = OH; R″ = H; R‴ = H; X = $^-OC_6H_2(NO_2)_3$
d, R = H; R″ = H; R‴ = CH_3; X = $^-OC_6H_2(NO_2)_3$

The behavior of *t*-butylamine and 2-amino-2-methyl-1-propanol toward alkylation by trinitroanisole was somewhat different, probably a result of solubilities in toluene. With 2 mol (or 5 mol) of trinitroanisole to 1 mol of *t*-butylamine refluxing in toluene dimethylation occurred to an extent of 50% (IIId), and the substituted picramide was formed in 21% yield (IIa). A lower ratio of trinitroanisole to amine gave the same products but no isolable monomethylated product.

On the other hand, with 1.5 mol of trinitroanisole to 1 mol of 2-amino-2-methyl-1-propanol, 19% quaternary trimethylated salt (IIIa) and 21% monomethylated salt (IIIc) were obtained. Excess trinitroanisole increased trimethylation to 36%, but dialkylation was not observed.

Dimethylation of *t*-butylamine by trinitroanisole (50% yield) is not conspicuously better than the Leuckart method (32%),[9] but the isolation of the product is simple. Unhindered amines such as benzylamine form the substituted picramides so rapidly that alkylation is not a competing reaction even in toluene.

Experimental Section

Melting points are uncorrected. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(1) The Varian A-60A nmr spectrometer used in this research was purchased under a National Science Foundation research instrument grant. The work was supported in part by National Institutes of Health Grant CA-07521 and in part by the National Science Foundation through its academic year institute program.

(2) C. L. Jackson and F. H. Gazzolo, *Am. Chem. J.*, **23**, 376 (1900); C. L. Jackson and R. B. Earle, *ibid.*, **29**, 89 (1903).

(3) J. Meisenheimer, *Ann.*, **323**, 205 (1902).

(4) K. L. Servis, *J. Amer. Chem. Soc.*, **87**, 5495 (1965); **89**, 1508 (1967).

(5) W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *J. Org. Chem.*, **32**, 2506 (1967).

(6) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); C. A. Fyfe, *Tetrahedron Lett.*, 659 (1968). Other pertinent papers will be found in ref 4 and 5.

(7) M. R. Crampton and V. Gold, *J. Chem. Soc.*, 4293 (1964).

(8) E. Hertel and J. VanCleef, *Ber.*, **61**, 1545 (1928). See also Clapp in "Chemistry of the Coordination Compounds," J. C. Bailar, Jr., Ed., Reinhold Publishing Corp., New York, N. Y., 1956, Chapter 17.

(9) A. Y. Khorlin, L. A. Vorotnikova, N. K. Kochetkov, *Zh. Obshch. Khim.*, **31**, 1827 (1961).

Infrared (ir) spectra were taken using a Perkin-Elmer Model 337 spectrophotometer in Nujol mulls, unless otherwise stated. The nmr spectra were recorded on a Varian A-60A spectrometer using tetramethylsilane as an internal reference. Thin layer chromatography (tlc) was carried out on microscopic slides employing Kieselgel G (Merck) as absorbent. The spots could be detected on the chromatogram from the color of the compounds.

Tetrahydrofuran was refluxed over lithium aluminum hydride and distilled before use. *t*-Butylamine was refluxed over potassium hydroxide and distilled. Dimethyl sulfoxide-d_6 (99.5% deuterated) was obtained from Stohler Isotope Chemicals and used directly.

Trinitroanisole was prepared by nitration of 2,4-dinitroanisole and recrystallized from methanol, mp 67–67.5° (lit.[10] mp 67–68°). Phenyl picryl ether was obtained in 85% yield from picryl chloride and alcoholic sodium phenoxide: mp 157–158° (lit.[11] mp 153°); nmr (DMSO-d_6, 10%) δ 9.26 (s, 2), 7.26 (m, 5).

Picryl Mesityl Ether.—Picryl mesityl ether was prepared by the method just mentioned in 80% yield: mp 154–155°; nmr (DMSO-d_6, 10%) δ 9.13 (s, 2), 6.93 (s, 2), 2.23 (s, 3), 2.06 (s, 6).

Anal. Calcd for $C_{12}H_{13}N_3O_7$: C, 51.87; H, 3.74; N, 12.10. Found: C, 52.12; H, 3.62; N, 12.01.

Neutral Meisenheimer Complex Ia.—Picryl phenyl ether (1 g, 0.0032 mol) in 2.75 ml of tetrahydrofuran (1 *M* sol) at −60° was treated with 0.233 g of *t*-butylamine in 3.18 ml of tetrahydrofuran (1 *M* sol) also at −60°. The nmr spectrum of the mixture was recorded at −57°: δ 11.9 (br, 1, NO_2H), 8.40 (s, 2 at C-3, C-5), 6.96 (m, 5), 6.06 (br, 1, NH), 1.16 (s, 9).

When a second portion of amine solution was added to the picryl phenyl ether solution, the signals δ 11.9 and 6.06 were replaced by 4.06 (br, 3), but the other peaks remained at the same places.

Other Meisenheimer complexes (Ib–d) were formed in like manner at Dry Ice temperatures.

N-β-Hydroxy-*t*-butyl-2,4,6-trinitroaniline (IIb).—A methanol (100 ml) solution of trinitroanisole (5.0 g, 0.021 mol) and 2-amino-2-methyl-1-propanol (1.83 g, 0.021 mol) was kept at room temperature for 30 min. Removal of the methanol gave 6.15 g (90%) of the substituted picramide IIb, mp 95–100°. Two recrystallizations from absolute ethanol gave a yellow compound, mp 106–108.5°, pure by tlc (R_f 0.38 on Kieselgel G; solvent, benzene with 5% methanol). The impure picramide has been made before from picryl chloride and the same amino alcohol[12] but has not been characterized.

Anal. Calcd for $C_{10}H_{12}N_4O_7$: C, 40.00; H, 4.03; N, 18.66. Found: C, 40.59, H, 4.38; N, 17.61, 17.58.

It is not unusual to find low nitrogen content by analysis in compounds that are explosive, and the purity of the picramide IIb was confirmed by the absence of stray peaks in the nmr spectrum: nmr ($CDCl_3$, 5.4%) δ 1.30 (s, 6), 2.11 (unresolved triplet, 1, OH), 3.48 (diffuse doublet, 2, CH_2), 8.41 (br, 1, NH), 8.97 (s, 2). The NH proton moved downfield 5 cps by the addition of a trace of pyridine, whereas the OH signal spread into a broad band between δ 2.83 and 1.97. The methylene doublet changed into a sharp singlet indicating that the coupling between OH and CH_2 protons ceased after pyridine addition.

The ir spectrum of IId showed a broad OH and NH band at 3600–3100 cm^{-1} and the primary alcohol band at 1042 cm^{-1}.

When excess amino alcohol was used in the reaction with trinitroanisole the reaction did not stop at the picramide stage but formed 5,7-dinitro-3,3-dimethylbenzomorpholine by cyclic elimination of the elements of nitrous acid. Stronger bases give higher yields of dinitrobenzomorpholines.[12] The structure of 5,7-dinitro-3,3-dimethylbenzomorpholine has been previously proved[12] but is here substantiated by an nmr spectrum (deuterioacetone, 3.5%): δ 1.52 (s, 6), 3.72 (s, 1, NH), 4.10 (s, 2), 7.77 (d, J = 3 Hz, C-8), 8.63 (d, J = 3 Hz, C-6). The NH proton was unaffected by the addition of pyridine.

The picramide IIa[13] was made in a similar manner: mp 94–95°; 95%; nmr ($CDCl_3$) δ 1.56 (s, 9), 3.33 (br, 1, NH), 8.53 (s, 2).

Trimethyl-β-hydroxy-*t*-butylammonium Picrate (IIIa) and Hydrochloride (IIIb).—Trinitroanisole (5 g, 0.021 mol) in 16 ml of dry toluene was brought to reflux, and 1.4 g (0.015 mol) of 2-amino-2-methyl-1-propanol in 10 ml of toluene was added dropwise in 20 min and then refluxed 0.5 hr more. Removal of the solvent gave a brown viscous oil. The oil was dissolved in a minimum of methanol and triturated with ether to give 1.1 g (19%) of crude trimethyl-β-hydroxy-*t*-butylammonium picrate, mp 225–228° dec. Recrystallization from methanol–ether and then methanol gave a pure sample, mp 245–246° dec. The picrate is slightly soluble in water. Tlc (R_f 0.43 on Kieselgel G; solvent, 1-propanol–chloroform–water 2:1:0.2) gave a single spot.

With an excess of trinitroanisole and slow addition of the amino alcohol, the yield of the picrate was raised to 36%: nmr (deuterioacetone, 5%) δ 1.53 (t, 6, $J_{^{14}NH\beta}$ = 2 Hz), 3.33 [s, 9, $N(CH_3)_3$], 3.93 (t, 2, $J_{^{14}NH\beta}$ = 2 Hz), 8.63 (s, 2 aromatic). At δ 2.95 a broad peak, possibly due to the OH signal, became sharp after addition of pyridine.

The picrate was converted into trimethyl-β-hydroxy-*t*-butylammonium chloride by treatment with hydrochloric acid. Two recrystallizations from methanol–ethyl acetate and one from ethanol gave a white product: mp 242–245° dec; nmr (methanol-d_4) δ 1.45 (t, 6, $J_{^{14}NH\beta}$ = 2 Hz), 3.20 (s, 9) 3.81 (t, 2, $J_{^{14}NH\beta}$ = 2 Hz).

Anal. Calcd for $C_7H_{18}NOCl$: C, 50.14; H, 10.82; N, 8.35. Found: C, 50.21; H, 10.78; N, 8.16.

Methyl-β-hydroxy-*t*-butylammonium Picrate (IIIc).—The mother liquor from the preparation of the trimethylated derivative of 2-methyl-2-amino-1-propanol (previous paragraph) was concentrated and triturated with chloroform. On standing (with refrigeration) 1.1 g (21%) of the monoalkylated derivative was obtained as the picrate. Repeated recrystallization gave the analytical sample: mp 174–176°; nmr (deuterioacetone, 10%) δ 1.47 (s, 6), 2.86 (s, 3, N–CH_3), 3.76 (s, 2, CH_2), 8.71 (s, 2, aromatic). The remaining three protons appeared in two broad diffuse curves at 7.26–8.6 (1 H) and 4.0–5.2 (1 < H < 2) but were brought together in a nicely rounded peak of the correct integrated area centered at δ 6.06 by the addition of pyridine. The R_f value of 0.46 was observed for the compound when the previously mentioned tlc system was used.

Anal. Calcd for $C_{11}H_{16}N_4O_8$: C, 39.74; H, 4.86; N, 16.87. Found: C, 39.56; H, 5.04; N, 17.02.

N,N-Dimethyl-*t*-butylammonium Picrate (IIId).—In the manner just described 4.08 g (0.02 mol) of trinitroanisole and 0.73 g (0.01 mol) of *t*-butylamine gave 2.27 g (50%) (after recrystallization from methanol) of N,N-dimethyl-*t*-butylammonium picrate, mp 278–280° dec. The analytical sample was sublimed at 150° (0.06 mm): nmr (DMSO-d_6, 10%) δ 1.33 (s, 9), 2.76 (s, 6, NCH_3), 3.03 (s, 1, NH), 8.60 (s, 2).

Anal. Calcd for $C_{12}H_{18}N_4O_7$: C, 43.63; H, 5.45; N, 16.96. Found: C, 44.11; H, 5.33; N, 17.17.

From the toluene solution, a 21% yield of N-*t*-butyl-2,4,6-trinitroanisole (IIa) was recovered. The yield of IIId was not changed when 0.05 mol of trinitroanisole was used in a similar experiment.

Registry No.—Picryl mesityl ether, 17691-66-6; 5,7-dinitro-3,3-dimethylbenzomorpholine, 17691-69-9; Ia, 17691-67-7; IIb, 17691-68-8; IIIa, 17691-70-2; IIIb, 17691-71-3; IIIc, 17691-72-4; IIId, 17691-73-5.

Acknowledgment.—We had the benefit of valuable conversations with Dr. Ronald G. Lawler concerning the spectra reported in this paper.

(10) E. Chapman, A. G. Perkins, and R. Robinson, *J. Chem. Soc.*, 3030 (1927).

(11) C. Willgerodt, *Ber.*, **12**, 1277 (1879); C. L. Jackson and R. B. Earle, *Am. Chem. J.*, **29**, 212 (1903).

(12) H. R. Jurgens, A. L. Burton, A. Eichenbaum, and L. B. Clapp, *J. Org. Chem.*, **25**, 1710 (1960).

(13) I. D. Rae, *Aust. J. Chem.*, **18**, 1807 (1965).

1-Methyl-4-phenyl-2(1H)-quinazolinone

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In the course of investigations in the quinazoline field we discovered an interesting series of reactions leading to 1-methyl-4-phenyl-2(1H)-quinazolinone (**4**),

a compound which to our knowledge has not been described previously in the literature.

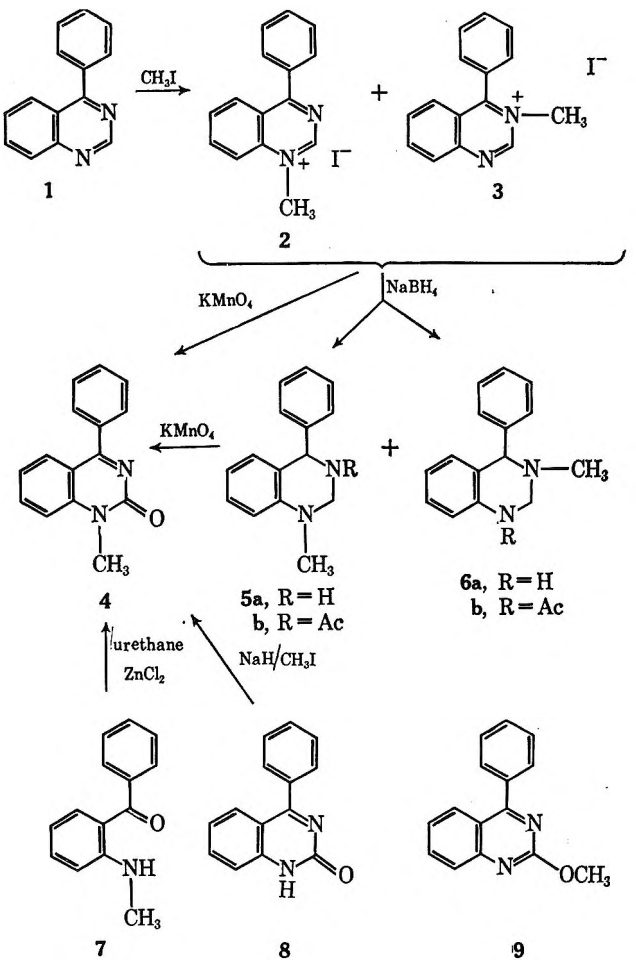
Refluxing 4-phenylquinazoline (**1**) with methyl iodide resulted in a highly crystalline product which, according to nmr evidence (two distinct methyl singlets in an integration ratio of approximately 7:1), consisted of a mixture of the two methiodides **2** and **3**. Our tentative assignment of structure **2** to the major component is (a) based on the limited number of quaternization experiments of 4-substituted quinazolines reported in the literature,[1,2] which invariably resulted in quaternization of N-1 and (b) substantiated by the lower magnetic field position of the stronger methyl signal.

This is the first time to our knowledge that a 4-substituted quinazoline is shown to give a mixture of the N-1 and the N-3 methiodide. It must be pointed out, however, that the experimental evidence in previous quaternizations of this type[1,2] does not prove exclusive reaction at N-1, since the salts obtained were characterized only by melting point and elemental analysis. In particular no nmr spectra are mentioned in those investigations. Based on our finding it seems quite probable that those quaternary salts also contained some of the N-3 isomer. Unfortunately we have not been able to separate our mixture of methiodides by fractional crystallization or by chromatography owing to their very similar physical properties.

Unambiguous proof of structure **2** for the major product of quaternization was obtained through further chemical transformations. Reduction to the 1,2,3,4-tetrahydroquinazoline stage was achieved with sodium borohydride under mild conditions and in essentially quantitative yield.[3] It was obvious from the nmr spectrum that the expected 7:1 mixture (oil) of 1-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (**5a**) and 3-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (**6a**) has resulted (Scheme I). Again the lower field position of the stronger methyl signal points to 1-methyl 4-phenyl-1,2,3,4-tetrahydroquinazoline (**5a**) as the major product. The individual components **5a** and **6a** were obtained as colorless oils by column chromatography of this mixture on silica gel and were characterized by conversion into the crystalline acetyl derivatives **5b** and **6b**, respectively. The nmr spectra of the free bases (**5a**, **6a**) and their N-acetyl derivatives (**5b**, **6b**) conclusively confirmed our originally tentative assignment of structures **2** and **5a** as the major products. It is interesting to note that the C-2 methylene group appears in the 1-methyl compounds (**5a**, **5b**) as a singlet while in the 3-methyl compounds (**6a**, **6b**) it occurs as an AB pattern (J_{AB} = 11 cps).

We now intended to reintroduce the 3,4 double bond in **5a** by oxidation with potassium permanganate. This oxidation led, however, in good yield to a compound $C_{15}H_{12}N_2O$, the infrared spectrum of which showed an amide carbonyl absorption at 1665 cm^{-1} and a C=N

SCHEME I



absorption at 1610 cm^{-1}. Microanalysis and ir and nmr spectra are consistent with the structure of 1-methyl-4-phenyl-2(1H)-quinazolinone (**4**). The closest analogy to this type of oxidation might be considered the conversion of 3-phenyl-1,2,3,4-tetrahydroquinazoline into 3-phenyl-4(3H)-quinazolinone[4] with potassium permanganate. The 2(1H)-quinazolinone **4** was also isolated on direct oxidation of the quaternary salt **2** with permanganate, although in lower yield. We assume that the latter oxidation is initiated by covalent hydration across the 1,2 double bond in analogy to the proposed mechanism[5] of mild oxidation of a number of quinazolines, not substituted in position 4, to 4(3H)-quinazolinones. Characteristically, the permanganate oxidation of either 4-phenyl-3,4-dihydroquinazoline or 4-phenyl-1,2,3,4-tetrahydroquinazoline, under both acidic or alkaline conditions, gave exclusively 4-phenylquinazoline (**1**); *i.e.*, the oxidation did not proceed beyond the quinazoline stage. This strongly indicates that covalent hydration at C-2 plays a significant role only when N-1 is quaternized.

Two other independent synthetic pathways, namely (a) condensation of 2-methylaminobenzophenone (**7**) with urethan and (b) N-methylation of 4-phenyl-2(1H)-quinazolinone (**8**) through its sodium salt, provided 1-methyl-4-phenyl-2(1H)-quinazolinone (**4**), which was in every respect identical with the product of potassium permanganate oxidation of **2** or **5a**. The

(1) W. L. F. Armarego, "Heterocyclic Compounds," Vol. XXIV, Interscience Publishers, New York, N. Y., 1967, p 56.

(2) G. F. Duffin, *Advan. Heterocycl. Chem.*, **3**, 29 (1964).

(3) In our hands, sodium borohydride has proved very satisfactory for the reduction of a number of other quinazolines, *e.g.*, 3,4-dihydroquinazoline, 4-phenylquinazoline (**1**), and 4-phenyl-3,4-dihydroquinazoline, to the corresponding 1,2,3,4-tetrahydroquinazolines. We are aware of only one publication on metal hydride reductions of quinazolines by R. F. Smith, P. C. Briggs, R. A. Kent, J. A. Albright, and E. J. Walsh, *ibid.*, **2**, 157 (1965), the results of which do not appear to be very conclusive.

(4) C. Paal and M. Busch, *Ber.*, **22**, 2683 (1889).

(5) See ref 1, p 54.

methylation of 4-phenyl-2(1H)-quinazolinone (**8**) also gave a less polar by-product (approximately 5% yield) which was isolated from the mother liquor by chromatography on aluminium oxide and identified by ir and nmr spectral analysis as 2-methoxy-4-phenylquinazoline (**9**). Both O- and N-alkylation of quinazolinones have been reported previously[6] and reflect the lactam–lactim tautomerism of these systems. Steric factors seem to influence the ratio of N- to O-alkylation drastically. When we treated, *e.g.*, the sodium salt of **8** with isopropyl iodide, 2-isopropoxy-4-phenylquinazoline became the major reaction product while 1-isopropyl-4-phenyl-2(1H)-quinazolinone was obtained in only 1–2% yield.

We have applied the methods mentioned above to the preparation of numerous variously substituted 2(1H)-quinazolinones with excellent results. These will be published elsewhere[7] in connection with a discussion of their biological activities.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are not corrected. Ultraviolet spectra were measured on a Model 14 Cary spectrophotometer in alcoholic solution; infrared spectra, on a Model 237 Perkin-Elmer spectrophotometer in methylene chloride; nmr spectra, in deuteriochloroform solution, (unless otherwise stated) with tetramethylsilane as an internal standard, on a Varian A-60 instrument. Microanalyses were carried out in our analytical unit.

4-Phenylquinazoline (**1**).—A solution of 2.3 g (14.6 mmol, 10% excess) of potassium permanganate in 44 ml of water was added within 5 min at room temperature to 4.16 g (20 mmol) of 4-phenyl-3,4-dihydroquinazoline,[8] dissolved in 200 ml of pure dioxane. After standing for 1 hr the slight excess of $KMnO_4$ was destroyed with a few drops of formic acid; the dioxane solution was filtered from the inorganic precipitate; and this filtrate was evaporated to dryness *in vacuo*. The obtained residue was dissolved in 50 ml of methylene chloride and extracted twice with sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated. From ether, 3.65 g (89%) of 4-phenylquinazoline resulted as coarse white crystals, mp 99–100°.[9] In the ir (CH_2Cl_2) typical quinazoline bands[10] at ν_{max} 1485, 1565, and 1615 cm^{-1} were observed.

Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.5; H, 4.9; N, 13.6. Found: C, 81.4; H, 5.2; N, 13.5.

1-Methyl-4-phenylquinazolinium Iodide (**2**).—A solution of 7.30 g (35 mmol) of 4-phenylquinazoline in 50 ml of methyl iodide was refluxed for 6 hr. The crystalline reaction product was filtered off and washed with diethyl ether (7.73 g), mp 183–184° dec. From the filtrate an additional amount (2.80 g) of the same product was obtained (85% total). On recrystallization from methylene chloride–ethyl acetate yellow prisms, mp 180° dec, resulted. In the nmr spectrum ($CDCl_3/CD_3SOCD_3$) the methyl group appeared as two singlets at δ 4.77 and 4.35 in a ratio of *ca.* 7:1. By the same token the proton on C-2 showed up as two singlets at δ 10.41 and 9.90 in the same ratio. The product obtained represented therefore a mixture of 1-methyl-4-phenylquinazolinium iodide (**2**) and 3-methyl-4-phenylquinazolinium iodide (**3**) in a ratio of 7:1.

Anal. Calcd for $C_{15}H_{13}IN_2$: C, 51.7; H, 3.8; N, 8.0. Found: C, 51.4; H, 3.7; N, 7.8.

1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (**5a**).—To a solution of 7.73 g (22 mmol) of 4-phenylquinazoline methiodide (mixture as described in previous experiment) in 100 ml of ethanol and 50 ml of methylene chloride were added 2.5 g of sodium borohydride in several portions at room temperature. After stirring for an additional 45 min at room temperature the excess sodium borohydride was carefully decomposed by addition of acetic acid. The solution was then concentrated to a small volume *in vacuo* and distributed between methylene chloride and 0.5 *N* sodium hydroxide. The organic phase was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo* to obtain 5.0 g (theoretical amount) of a mixture of 1-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline and 3-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline as a colorless oil which resisted all attempt of crystallization: ir (CH_2Cl_2) ν_{max} 3350, 1610, and 1500 cm^{-1}; nmr spectrum singlets at δ 2.78 and 2.35 (CH_3), 3.95 and 3.73 (2 H), 5.10 and 4.50 (1 H), of all these pairs of singlets appearing in a ratio of *ca.* 7:1. This mixture was used without further purification in the following permanganate oxidation.

In an other experiment the crude reduction mixture (3.0 g) was separated on a column of 150 g of silica gel, using chloroform as an eluent. The efficiency of the separation was followed by tlc.

From the first fractions 1.8 g of fairly pure 1-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (**5a**) were obtained as a colorless oil, which resisted all attempts of crystallization. In nmr ($CDCl_3$) singlets appeared at δ 2.80 (N_1–CH_3) and 4.0 (methine H). Acetylation with acetic anhydride–pyridine at room temperature gave 3-acetyl-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (**5b**): mp 89–91° (from ether); ir (CH_2Cl_2) ν_{max} 1605 cm^{-1} (amide); nmr ($CDCl_3$) singlets at δ 2.20 (acetyl) and 2.92 (N–CH_3).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.8; N, 10.5. Found: C, 76.3; H, 6.7; N, 10.4.

Later fractions yielded 0.42 g of practically pure 3-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (**6a**) as an oil: nmr ($CDCl_3$) singlets at δ 2.38 (N_3–CH_3) and 4.55 (C-4 methine) and AB pattern (J_{AB} = 11 cps) centered at δ 3.90 (C-2 methylene). On acetylation 1-acetyl-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinazolone (**6b**) was obtained in white prisms (ether): mp 117–118°; ir (CH_2Cl_2) ν_{max} 1655 cm^{-1} (amide); nmr ($CDCl_3$) singlets at δ 2.32, 2.35 ($COCH_3$ and N–CH_3), and 2.55 (C-4 methine), AB pattern (J_{AB} = 11 cps) centered at 4.50 (C-2 methylene).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.8; N, 10.5. Found: C, 76.5; H, 7.0; N, 10.3.

1-Methyl-4-phenyl-2(1H)-quinazolinone (**4**). **A. Oxidation of 1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline** (**5a**) **with $KMnO_4$.**—To a solution of 4.48 g (20 mmol) of crude 1-methyl-4-phenyl-1,2,3,4-tetrahydroquinazoline (described in the previous experiment) in 180 ml of pure dioxane was added dropwise under stirring at room temperature a solution of 5.0 g of potassium permanganate in 90 ml of water. The slight excess of $KMnO_4$ (purple color persisted for 10 min after the addition) was destroyed with a few drops of formic acid. After filtration of the precipitated manganese dioxide the filtrate was concentrated *in vacuo;* methylene chloride was added; and the obtained solution was extracted with dilute sodium bicarbonate. The organic phase was dried over sodium sulfate and evaporated to dryness. The crystalline residue (3.91 g) was recrystallized from ethyl acetate to obtain 2.50 g of pure 1-methyl-4-phenyl-2(1H)-quinazolinone as pale yellow prisms, mp 142–143°. From the mother liquor 0.46 g of the same product resulted (63%): uv (ethanol) λ_{max} 230 mμ (ϵ 38,800), 270 (10,500), and 357 (5380); ir (CH_2Cl_2) 1665, and 1600 cm^{-1} (shoulder); nmr singlet at δ 3.73 (CH_3).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.2; H, 5.1; N, 11.9; O, 6.8. Found: C, 76.5; H, 5.3; N, 11.7; O, 7.1.

B.—Condensation of 2-Methylaminobenzophenone (**7**) **with Ethyl Carbamate.**—A mixture of 2.11 g (10 mmol) of 2-methylaminobenzophenone, 4.0 g of ethyl carbamate, and 50 mg of zinc chloride was heated for 1.5 hr to 180–190° (oil-bath temperature). The reaction mixture was distributed between methylene chloride and water; the organic phase was dried over sodium sulfate and evaporated to a crystalline residue *in vacuo*. On recrystallization from ethyl acetate 1.96 g (82%) of 1-methyl-4-phenyl-2(1H)-quinazolinone resulted, mp 141–143°. This product was identical in melting point, mixture melting point, thin layer chromatography, and infrared spectrum with the compound obtained under A.

C. Methylation of 4-Phenyl-2(1H)-quinazolinone (**8**).—The sodium salt of 4-phenyl-2(1H)-quinazolinone was prepared by heating a mixture of 222 mg (1 mmol) of 4-phenyl-2(1H)-quinazolinone and 80 mg of sodium hydride (50% suspension in

(6) See ref 1, p 235.

(7) H. Ott and E. I. Takesve, paper in preparation.

(8) T. Higashino, Yakugaku Zasshi, **80**, 245 (1960); *Chem. Abstr.*, **54**, 13125*e* (1960).

(9) The melting point reported for 4-phenylquinazoline by K. Schofield, *J. Chem. Soc.*, 1927 (1952), is identical with ours, but the analytical values given are incorrect.

(10) H. Culbertson, J. C. Decius, and B. E. Christensen, *J. Amer. Chem. Soc.*, **74**, 4834 (1952).

mineral oil) in 3 ml of dimethylacetamide for 15 min to 40–50°. Then 0.4 ml of methyl iodide was added, and the above temperature was maintained until this reaction mixture showed a pH of 7 (after approximately 15 min). Water was added and the aqueous phase was extracted three times with methylene chloride. The combined organic phases were dried over sodium sulfate and evaporated to dryness, and the thoroughly dried residue (240 mg) crystallized from ethyl acetate to give 120 mg (68%) of 1-methyl-4-phenyl-2(1H)-quinazolinone, mp 143°. This product was again identical in melting point, mixture melting point, thin layer chromatography, and infrared spectrum with the compound obtained under A.

Since a small amount of a less polar by-product was observed in this reaction it was repeated on a larger scale (5.2 g of **8**); most of the starting material (**8**) and the N-methyl compound (**4**) were removed from the crude mixture by crystallization, and the mother liquor (1.25 g) was chromatographed on 80 g of aluminum oxide with methylene chloride as an eluent. From the first fractions (340 mg), 2-methoxy-4-phenylquinazoline (**9**) crystallized from petroleum ether: 115 mg; mp 87–89°; typical quinazoline bands[10] in ir (CH_2Cl_2) at ν_{max} 1470, 1570, and 1615 cm^{-1}; nmr ($CDCl_3$) singlet at δ 4.20 (O-methyl).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.1; N, 11.9. Found: C, 75.9; H, 5.2; N, 11.6.

Registry No.—**1**, 17629-01-5; **2**, 17629-02-6; **3**, 17629-03-7; **4**, 17629-04-8; **5a**, 17629-05-9; **5b**, 17629-06-0; **6a**, 17629-07-1; **6b**, 17629-08-2; **9**, 17629-09-3.

Chemiluminescence from the Reaction of Phthalimido Oxalate with Hydrogen Peroxide and Fluorescent Compounds

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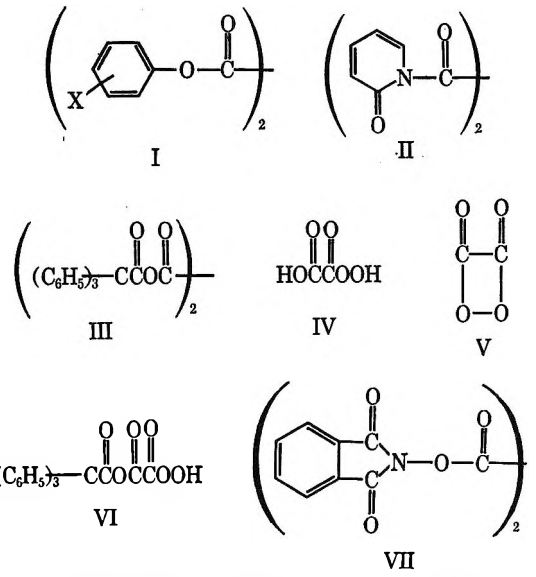
Chemiluminescence has been reported from a wide variety of organic reactions.[1] However, most reactions produce light with low efficiency. The quantum yields obtained from these classical reactions are below 0.01 einstein mol^{-1} the efficiency of the well known luminol reaction.[2] Unusually high emission efficiencies have been obtained from the reaction of several oxalic acid derivatives with hydrogen peroxide and fluorescent compounds. Electronegatively substituted aryl oxalates[3] (I), pyridonylglyoxals[4] (II), and certain oxalic anhydrides[5] (III) produced 0.24 0.16, and 0.14 einstein mol^{-1}, respectively, whereas oxalyl chloride[6] gave up to 0.05 einstein mol^{-1} and



X is an electron-withdrawing group such as $-NO_2$, $-Cl$

oxamides[7] 0.01 einstein mol^{-1}. Three peroxyoxalic acid derivatives IV, V, and VI have been suggested as intermediates depending on the oxalic acid derivative and reaction conditions.[3,5,6] The concerted multiple bond cleavage decomposition of these intermediates could release sufficient energy to excite a fluorescent compound.[8]

The primary requirement for peroxyoxalate chemiluminescence appears to be an oxalic acid derivative which reacts rapidly with hydrogen peroxide. However, not all reactive oxalates produce equal emission efficiency probably due to the different competing dark side reactions and possible quenching by-products. Therefore, to further examine these points and to broaden the scope of peroxalate chemiluminescence we prepared diphthalimido oxalate VII.

Esters of N-hydroxyphthalimide react rapidly with amino acid esters and are useful intermediates of peptide synthesis.[9] Thus, diphthalimido oxalate might be expected to react readily with hydrogen peroxide and could conceivably give chemiluminescence in the presence of a fluorescer.

Preliminary qualitative experiments indicated that VII indeed produced chemiluminescent light on reaction with hydrogen peroxide and 9,10-diphenylanthracene in dimethyl phthalate solution. The light intensity was increased by bases and quenched by strong acids. A similar base–acid effect was observed in connection with the oxalic ester reaction.[3] A good agreement of the chemiluminescence and fluorescence spectra indicates that the light-emitting species is the first singlet excited state of the fluorescer.

Absolute quantum yield measurements were carried out in dimethyl phthalate and the results are collected in Table I. A quantum yield of 0.087 einstein mol^{-1} was obtained at 1×10^{-3} *M* phthalimido oxalate in the presence of the usually inefficient fluorescer 9,10-diphenylanthracene[3-5] [bis(2,4-dinitrophenyl)oxalate

(1) Recent reviews: F. McCapra, *Quart. Rev.* (London), **20**, 485 (1966); K. D. Gundermann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 566 (1965); V. I. Papisova, V. Y. Shlyapintokh, and R. F. Vasilev, *Russ. Chem. Rev.*, **34**, 599 (1965); E. J. Bowen, *Pure Appl. Chem.*, **9**, 473 (1964). See also L. J. Bollyky, R. H. Whitman, R. A. Clarke, and M. M. Rauhut, *J. Org. Chem.*, **32**, 1663 (1967).

(2) J. Lee and H. H. Seliger, *Photochem. Photobiol.*, **4**, 1015 (1965); M. M. Rauhut, A. M. Semsel, and B. G. Roberts, *J. Org. Chem.*, **31**, 2431 (1966).

(3) L. J. Bollyky, M. Loy, B. G. Roberts, R. H. Whitman, A. V. Iannotta, A. M. Semsel, and M. M. Rauhut, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. O169; M. M. Rauhut, L. J. Bollyky, B. G. Roberts, M. Loy, R. H. Whitman, A. V. Iannotta, A. M. Semsel, and R. A. Clarke, *J. Amer. Chem. Soc.*, **89**, 6515 (1967).

(4) L. J. Bollyky, B. G. Roberts, R. H. Whitman, and J. E. Lancaster, *J. Org. Chem.*, in press.

(5) L. J. Bollyky, R. H. Whitman, B. G. Roberts, and M. M. Rauhut, *J. Amer. Chem. Soc.*, **89**, 6523 (1967).

(6) M. M. Rauhut, B. G. Roberts, and A. M. Semsel, *ibid.*, **88**, 3604 (1966).

(7) D. R. Maulding, R. A. Clarke, B. G. Roberts, and M. M. Rauhut, *J. Org. Chem.*, **33**, 250 (1968).

(8) M. M. Rauhut, D. Sheehan, R. A. Clarke, and A. M. Semsel, *Photochem. Photobiol.*, **4**, 1097 (1965).

(9) G. H. L. Nefkens and G. E. Tesser, *J. Amer. Chem. Soc.*, **83**, 1263 (1961); G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. Trav. Chim.*, **81**, 683 (1962).

TABLE I

QUANTUM YIELD OF THE PHTHALIMIDO OXALATE REACTION[a]

Phthalimido oxalate, $M \times 10^2$	H_2O_2, $M \times 10^2$	I_{max}, ft lambert cm^{-1}	$t^1/_4$,[b] min	Quantum yield,[c] einstein $mol^{-1} \times 10^2$
0.1	2.4	0.01	94.0	8.7
0.1[d]	3.4	0.04	6.7	2.6
1.0	2.4	0.01	307.0	2.3
1.0[d]	3.4	0.09	10.1	1.4
1.0	9.0	0.01	269.0	1.9
1.0[e]	9.0	0.03	169.0	2.7
1.0[f]	9.0	0.04	184.0	4.3

[a] In the presence of 6×10^{-4} M 9,10-diphenylanthracene in dimethyl phthalate solution at 25°. [b] The time of light decay from maximum to one-quarter intensity. [c] Based on phthalimido oxalate. [d] In 1,3-propylene carbonate. [e] 1×10^{-1} M H_2O added. [f] 8.3×10^{-6} M Et_3N added.

produced 0.165 einstein mol^{-1} under similar conditions, and 0.29 einstein mol^{-1} with rubrene].[3]

Increasing the concentration of VII decreased the quantum yield. The addition of triethylamine or water decreased the chemiluminescent lifetime and moderated the efficiency loss. The lifetime was shorter and the reaction was less efficient in propylene carbonate solution than in dimethyl phthalate.

The results are insufficient for a definite statement about the mechanism. However, it is likely that the phthalamido oxalate reaction proceeds through a 1,2-dioxetanedione V intermediate, first proposed in connection with the aryl oxalate reaction.[3] By analogy to the phthalamido oxalate reaction, reactive oxalates of other substituted hydroxylamines and oximes should also produce chemiluminescence. Carboxylic esters of N-hydroxypiperidine and other hydroxylamines have been prepared and used in peptide synthesis.[10] We found that the reaction of an admittedly atypical oxime ester bis(heptafluorobutyramideoxime) oxalate[11] $C_3F_7C(NH_2)=NC(O)C(O)N=(NH_2)CC_3F_7$ with hydrogen peroxide and fluorescer produced only weak light emission.

Experimental Section

Materials.—Dimethyl phthalate and propylene carbonate were fractionally distilled. Oxalyl chloride and N-hydroxyphthalimide (Aldrich) were used without purification. 9,10-Diphenylanthracene (Aldrich) was recrystallized from a mixture of absolute ethanol and chloroform to obtain material, mp 250–251° (lit.[12] mp 250–251°). Hydrogen peroxide solutions were prepared from the 98% reagent (Becco Chemical Division, FMC Co.) and were analyzed iodometrically.[13]

Diphthalimido Oxalate.—To a rapidly stirred solution of 1.63 g (0.01 mol) N-hydroxyphthalimide in 100 ml of freshly distilled (from $LiAlH_4$) 1,2-dimethoxyethane, 0.43 ml (0.005 mol) of oxalyl chloride and 1.4 ml of triethylamine were added at 25°. After 1-hr stirring the mixture was evaporated to dryness under vacuum and the solid residue was digested with three 30-ml portions of chloroform to obtain a white crystalline product, mp 233–234° dec, in 42% yield which showed infrared absorption at 1817, 1795, 1758, and 1735 cm^{-1} in methylene chloride solution.

Anal. Calcd for $C_{18}H_8O_8$: C, 56.85; H, 2.12; N, 7.37. Found: C, 56.79; H, 2.08; N, 7.49.

Bis(heptafluorobutyramidoxime)oxalate was prepared by the method of H. C. Brown and C. R. Wetzel,[11] mp 180–181° (acetone–ether 1:1) [lit.[11] mp 195–196° (xylene)].

Anal. Calcd for $C_{10}H_4F_{14}N_4O_4$: C, 23.54; N, 10.98; F, 52.14. Found: C, 23.54; N, 11.0; F, 52.04.

Qualitative Chemiluminescence Tests.—Approximately 3–5 mg of diphthalimido oxalate was added to a 5-ml solution of 1 mg of 9,10-diphenylanthracene and 0.2 ml of 1 M H_2O_2 (in DMe) in anhydrous 1,2-dimethoxyethane (DMe) at 25°. In other experiments the solution also contained 0.2 g of KOH, 0.2 g of KOH + 0.1 ml of water, and 0.2 ml of methanesulfonic acid and 0.2 ml of water. The chemiluminescent light was observed visually in a dark room, and the results are collected in Table II.

TABLE II

QUALITATIVE CHEMILUMINESCENCE TESTS[a]

H_2O_2	H_2O_2 + KOH	H_2O_2 + KOH + H_2O	CH_3SO_3H + H_2O
S (long)	S (short)	MS (long)	W (long)

[a] Qualitative intensities are based on the oxalyl dichloride–hydrogen peroxide reaction taken as strong (S). Other designations are M, medium; W, weak but clearly visible.

Chemiluminescence Emission Measurements.—Procedures and instrumentation for the determinations of absolute emission intensities, spectra, and quantum yields have been described previously.[6,14] Chemiluminescent reactions were initiated by injecting an aliquot of stock hydrogen peroxide solution from an all glass syringe into the combined aliquots of the other reactants in a stirred 3-ml cylindrical cuvette attached to a spectroradiometer. The raw intensity data from the radiometer was converted to einsteins sec^{-1} ml^{-1} by a Scientific Data 925 Computer programmed with the calibration data.

Registry No.—VII, 17447-57-3; hydrogen peroxide, 7722-84-1.

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(10) S. M. Beaumont, B. O. Handford, J. H. Jones, and G. T. Young, *Chem. Commun.*, 53 (1965).

(11) H. C. Brown and C. R. Wetzel, *J. Org. Chem.*, **30**, 3724, 3729, 3734 (1965).

(12) G. Wittig and R. W. Hoffmann, *Ber.*, **95**, 2718 (1962).

(13) I. W. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N. Y., 1948, p 630.

(14) B. G. Roberts and R. C. Hirt, *Appl. Spectrosc.*, **21**, 250 (1967).

Alcohol Formation in the Aprotic Bamford–Stevens Reaction. III.[1] On the Nature of the Precursors

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The unusual formation of alcohols from certain aldehyde tosylhydrazones **1** in the aprotic Bamford–Stevens reaction has been explained according to the mechanism outlined in Scheme I.[2] N-Methyl-2-pyrrolidone (N-MP) is particularly effective in the last step though any solvent with >CH–CO–N<: present can be used.[3] Whereas the proton donation by **1**, the intermediacy of

(1) References 2 and 3 should be considered papers I and II, respectively, of this series.

(2) J. W. Wilt, C. A. Schneider, H. F. Dabek, Jr., J. F. Kraemer, and W. J. Wagner, *J. Org. Chem.*, **31**, 1543 (1966).

(3) J. W. Wilt, R. G. Stein, and W. J. Wagner, *ibid.*, **32**, 2097 (1967).

SCHEME I

$$RCH{=}NNHSO_2\text{-}p\text{-Tol} \xrightarrow[-H^+]{\text{base}} {}^-O_2S\text{-}p\text{-Tol} + RCHN_2 \xrightarrow[\Delta]{} \underset{\mathbf{1}}{} RCH{:} + N_2$$

$$RCH{:}\text{ or } RCHN_2 + \mathbf{1} \xrightarrow[-\mathbf{1}^-]{} RCH_2^+ \text{ or } RCH_2N_2^+ \xrightarrow{{}^-O_2S\text{-}p\text{-Tol}} RCH_2OSO\text{-}p\text{-Tol}$$

$$RCH_2OSO\text{-}p\text{-Tol} \xrightarrow{\text{solvent}} RCH_2OH$$

sulfinic esters, and the mechanism of their cleavage to the alcohol product seem well established by earlier work,[2,3] the evidence for a diazoalkane precursor to the sulfinic ester has been indirect. Others had observed diazoalkane formation from tosylhydrazones under other conditions[4] and even had isolated them in some cases, but it was felt that a direct study of them under these alcohol-forming conditions was needed to complete the above studies.

Because the diazoalkanes from the earlier studied systems would be anticipated to be rather unstable, we chose diphenyldiazomethane (2) as the test substance. This choice seemed acceptable for two reasons. First, it is stable enough to be weighed into the reaction stoichiometrically. Second, 2 cannot give rise to products by hydride shifts or insertion. This is crucial because alcohol formation demands the absence of such intramolecular processes. The cases reported earlier met this requirement and 2 serves nicely as perhaps a simpler example.[5]

Results

Diphenyldiazomethane (2) was treated with *p*-toluenesulfinic acid in hot NMP, and the products were compared with those obtained by heating benzhydryl *p*-toluenesulfinate (6) alone in NMP. The results are gathered in Table I.

TABLE I

REACTIONS IN NMP AT 160–180°

	Products, %[b]		
Reaction[a]	Ph_2CHOH (3)	$(Ph_2CH)_2O$ (4)	$Ph_2CHSO_2\text{-}p\text{-Tol}$ (5)
Ph_2CN_2 (2) + *p*-$TolSO_2H$	75.5	10.4	14.1
$Ph_2CHOSO\text{-}p\text{-Tol}$ (6) + Δ	72.2	11.5	16.3

[a] The reaction of 2 was commenced at 115° and brought slowly to 160° as nitrogen evolved. [b] Composition values. The isolated yields were 60–70%.

Discussion

It seems inescapable that the sulfinic ester 6 is formed from 2 and gives rise to the products shown in Table I because the product spectrum is essentially the same regardless of starting material. Such identity in both the nature and percentage of the several products is a compelling argument for the intermediacy of both diazoalkanes and sulfinic esters in the formation of the alcohol product under these conditions.

As for the products themselves, the cleavage of 6 to 3 is another case of aprotic solvolysis by NMP, as reported.[3] The ether 4 and the sulfone 5 each represent the product of an alternative process from 6. Benzhydryl *p*-toluenesulfinate (6) is known to rearrange thermally to the sulfone 5 by a dissociation–recombination mechanism.[6] Because 6 concomitantly forms the alcohol 3 in NMP, some benzhydryl cation is trapped by 3 to form 4. The two processes removing the cation are roughly comparable in rate as evidenced by the yields of 4 and 5, but neither compares to the cleavage affording 3—a result in accord with the extreme rapidity of this cleavage.[3] The entire process can be seen in Scheme II. With these results we feel the reaction sequence given in Scheme I is finally secure.

SCHEME II

$$2 \xrightarrow[-N_2]{p\text{-Tol-}SO_2H} 6 \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} Ph_2CH^+ + {}^-O_2S\text{-}p\text{-Tol} \longrightarrow 5$$

$$6 \xrightarrow[\Delta]{\text{NMP}} 3 \qquad Ph_2CH^+ \xrightarrow{-H^+} 4$$

Experimental Section

Melting points were taken on a calibrated Fisher-Johns block and are uncorrected for stem exposure. Infrared spectra were determined on a Perkin-Elmer Model 21 instrument. Only characteristic functional absorption is given, in microns. Nuclear magnetic resonance spectra were taken on a Varian A-60A spectrometer using tetramethylsilane as an internal standard. The chemical shifts are given in parts per million (δ) units.

Preparations. **Diphenyldiazomethane** (2) was prepared as described[7] by oxidation of benzophenone hydrazone with mercuric oxide. **Benzhydrol** (3) was obtained as reported[8] by reduction of benzophenone with zinc dust [mp 66–67°; δ^{CCl_4} 7.17 s (C_6H_5–) 5.42 d (–CHOH–, J = 4 cps), 3.70 d (–OH); λ^{Nujol} 3.00 (–OH), 9.68, 9.8 (C–O) (lit.[8] mp 69°)]. **Benzhydryl ether** (4) was made from 3 and hydrochloric acid as described[9] [mp 106–107°; δ^{CDCl_3} 7.37 m (C_6H_5–), 5.45 s (–CHO–); λ^{Nujol} 8.49, 9.3, 9.55, 9.75, 9.94 (C–O) (lit.[9] mp 109–110°)]. **Benzhydryl *p*-tolyl sulfone** (5) resulted from the displacement reaction of sodium *p*-toluenesulfinate upon benzhydryl hydrogen phthalate as reported[10] [mp 188–189°; δ^{CDCl_3} 7.72–7.10 m (Ar–H), 5.33 s (–CH–SO_2–), 2.37 s (Ar–CH_3); λ^{Nujol} 7.63, 7.70, 7.79, 8.80 (–SO_2–) (lit.[6] mp 188–189°)]. **Benzhydryl *p*-toluenesulfinate** (6) was synthesized from 3 and *p*-toluenesulfinyl chloride by the literature method,[6] mp 83.5–84° (lit.[6] mp 84°). The compound is not too stable on standing (it forms 5); so it was used immediately upon its preparation. ***p*-Toluenesulfinic acid** was dried under vacuum and used quickly after its preparation by acidification of its sodium salt, prepared as reported.[11] N-Methyl-2-pyrrolidone (NMP) was purified as described.[3]

Reaction of 2 with *p*-Toluenesulfinic Acid.—The acid (7.8 g, 50 mmol) in NMP (100 ml) was held at 115° while 2 (9.7 g, 50 mmol) was added over a 30-min period, then raised to 160° until no further nitrogen evolved. The cooled solution was diluted with water (300 ml) and extracted with ether (three 100-ml portions). The combined ether extracts were washed with base, then water, dried, and freed of solvent. Column chromatography on alumina (100 g) followed. Ether 4 (0.5 g, 6.4%) was eluted with benzene–hexane; sulfone 5 (1.4 g, 8.7%), with benzene–ether; and the alcohol 3 (4.3 g, 46.5%), with ether–acetone. Identification was made by mixture melting point and comparison of spectra with those of authentic materials, giving

(4) *Cf.* W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, p 48.

(5) We have earlier[2] suggested the term "constrained carbenes" for those divalent carbon species incapable of intramolecular stabilization.

(6) A. H. Wragg, J. S. McMadyen, and T. S. Stevens, *J. Chem. Soc.*, 3603 (1958).

(7) L. I. Smith and K. L. Howard, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 351.

(8) F. Y. Miselogle and H. Sonnenborn, III, ref 7, Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p 90.

(9) A. M. Ward, *J. Chem. Soc.*, 2285 (1927).

(10) M. P. Balfe, M. A. Doughty, J. Kenyon, and R. Poplett, *ibid.*, 605 (1942).

(11) F. C. Whitmore and F. H. Hamilton, ref 7, Coll.Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p 492.

the percentage composition listed in Table I. Small amounts of *p*-tolyl disulfide and benzophenone ketazine were also formed.

Reaction of 6.—A similar decomposition of **6** (50 mmol) in NMP (100 ml) at 160–180° for 1 hr gave a combined yield of 70% of product, isolated exactly as above and with the composition given in Table I.

Registry No.—**2**, 883-40-9; *p*-toluenesulfinic acid, 536-57-2; **6**, 17447-59-5; NMP, 872-50-4.

Transannular Nitrogen–Carbonyl Interaction. Generation of an α-Acetoxy Quaternary Ammonium Salt

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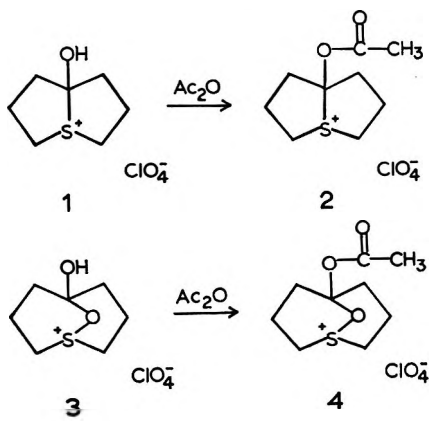
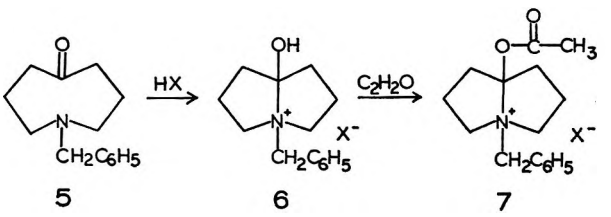
Earlier work on transannular interactions and reactions in this laboratory provided examples of α-acetoxysulfonium salts[1] and -oxosulfonium salts.[2,3]

For example, it was found that the perchlorate salt of 1-thiacyclooctan-5-one, which is in the transannular form 5-hydroxy-1-thioniabicyclo[3.3.0]octane perchlorate (**1**),[4] was converted with acetic anhydride into 5-acetoxy-1-thioniabicyclo[3.3.0]octane perchlorate (**2**).[1] The salt of 1-thiacyclooctan-5-one 1-oxide, also in the transannular form 5-hydroxy-9-oxa-1-thioniabicyclo[3.3.1]nonane perchlorate (**3**), gave 5-acetoxy-9-oxa-1-thioniabicyclo[3.3.1]nonane perchlorate (**4**) with acetic anhydride at room temperature.[2]



The salts of 1-alkyl-1-azacyclooctan-5-ones generally exist in the transannular form,[5,6] and we have now been able to acetylate the α-*t*-hydroxyl group of the transannular salt of an eight-membered-ring amino ketone by means of ketene.[7] Specifically the perchlorate and picrate salts of 1-benzyl-1-azacyclooctan-5-one (**5**)[8] are in the transannular form (**6a**, **b**), as evidenced by their infrared and nmr spectra. Neither salt exhibits ir absorption in the region 1620–1800 cm^{-1}, and both show hydroxyl absorption. The nmr spectrum of the perchlorate shows a singlet for the benzyl CH_2 protons in both acetonitrile-d_3 and trifluoroacetic acid. Splitting of



a, X = ClO_4 ; b, X = $C_6H_2N_3O_7$

these protons would be expected if the salt were in the alternative N-protonated form. The hydroxy proton of **6a** is observed in acetonitrile-d_3 as a broad singlet, δ 5.1–5.7, which disappears upon the addition of deuterium oxide.

The reaction of 1-benzyl-5-hydroxy-1-azoniabicyclo[3.3.0]octane perchlorate (**6a**) and of the picrate (**6b**) in acetonitrile with ketene led to 5-acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane perchlorate and picrate (**7a**, **b**). The structure proof was based on elemental analyses and on ir and nmr spectral evidence. Each compound exhibits only one ir absorption maximum in the carbonyl region (ν_{max}^{KBr} 1746 cm^{-1} for **7a**, 1750 cm^{-1} for **7b**) corresponding to an ester function. The nmr spectrum of the perchlorate **7a** is much like that of its precursor **6a** with the exception of a new sharp singlet at δ 2.20 (CD_3CN) and loss of the signal for the hydroxyl proton. For comparison, the corresponding 1-thionia analog **2** had ν_{max}^{Nujol} 1737 cm^{-1} (C=O)[1] and δ 2.33 in CF_3COOH (CH_3CO).[2]

The prediction that 5-acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane perchlorate (**7a**) would behave as a powerful acetylating agent was verified qualitatively in two rather extreme examples. Acetylation of piperidine with **7a** at −20° in methylene chloride solution was complete in less than 2 min. Acetylation of potassium acetate to give acetic anhydride was accomplished in a melt of the two solids within a total manipulation time of less than 5 min.

Experimental Section

1-Benzyl-5-hydroxy-1-azoniabicyclo[3.3.0]octane Perchlorate (6a).—This salt was obtained quantitatively from 1-benzyl-1-azacyclooctan-5-one[8] and was recrystallized as colorless needles from acetone–ether: mp 144–145.5°; $\nu_{max}^{Fluorolube}$ 3260 cm^{-1}; ν_{max}^{KBr} 3290 cm^{-1}; ν_{max}^{Nujol} 3280 (OH), no absorption 1620–2000 cm^{-1}; nmr (CD_3CN) δ from TMS 2.0–2.6 (8 H), 2.85–3.4 (2 H), 3.5–4.0 (2 H) (all series of multiplets, ring protons), 4.25 (2 H, s, benzyl CH_2), 5.1–5.7 (1 H, br s, OH, disappears with D_2O), 7.74 (5 H, s, C_6H_5). In trifluoroacetic acid the nmr spectrum was similar except that no signal for the OH proton was observable.

(1) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Amer. Chem. Soc.*, **82**, 4075 (1960).
(2) N. J. Leonard and C. R. Johnson, *ibid.*, **84**, 3701 (1962).
(3) N. J. Leonard and W. L. Rippie, *J. Org. Chem.*, **28**, 1957 (1963).
(4) For current nomenclature, see IUPAC 1957 Rules, *J. Amer. Chem. Soc.*, **82**, 5545 (1960), especially p 5572.
(5) (a) N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *ibid.*, **80**, 4858 (1958); (b) N. J. Leonard, D. F. Morrow, and M. T. Rogers, *ibid.*, **79**, 5476 (1957), and earlier papers in the series.
(6) (a) N. J. Leonard, *Rec. Chem. Progr.*, **17**, 243 (1956); (b) N. J. Leonard and M. Ōki, *J. Jap. Chem.*, **10**, 1003 (1956).
(7) NOTE ADDED IN PROOF.—R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken [*J. Org. Chem.*, **33**, 3187 (1968)] have converted **6** into **7** by warming with acetic anhydride on the steam bath.
(8) N. J. Leonard and T. Sato, *ibid.*, in press.

Anal. Calcd for $C_{14}H_{20}ClNO_5$: C, 52.91; H, 6.34; N, 4.41. Found: C, 52.87; H, 6.34; N, 4.20.

5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Perchlorate (7a).—To a solution of 0.50 g (0.16 mmol) of 1-benzyl-5-hydroxy-1-azoniabicyclo[3.3.0]octane perchlorate in 75 ml of anhydrous acetonitrile was added ketene at 0°, with stirring, by passing a dry nitrogen stream over liquid ketene at −20°. After addition of ketene for 15 min, during which the colorless solution turned yellow-orange. The solution was treated with charcoal, filtered, and concentrated to give a light yellow oil. Recrystallization from acetonitrile–ether gave colorless needles: mp 194–195° (reported[7] mp 190–195°, then mp 203–204°); yield 0.31 g (53%); ν_{max}^{KBr} 1746 cm^{-1}; ν_{max}^{Nujol} 1755, 1080, 710 cm^{-1}; nmr (CD_3CN) δ 2.20 (3 H, s, CH_3CO), 1.9–2.8 (8 H, series of multiplets, ring protons), 2.9–4.0 (4 H, series of multiplets, ring protons), 4.50 (2 H, s, benzyl CH_2), 7.53 (5 H, s, C_6H_5).

Anal. Calcd for $C_{16}H_{22}ClNO_6$: C, 53.41; H, 6.16; N, 3.89. Found: C, 53.49; H, 6.17; N, 3.98.

1-Benzyl-5-hydroxy-1-azoniabicyclo[3.3.0]octane Picrate (6b).—This salt was obtained from 1-benzyl-1-azacyclooctan-5-one:[8] mp 207–208°; ν_{max}^{Nujol} 3100, 1625, 1607, 1565, 1462, 710 cm^{-1}; ν_{max}^{KBr} 3180, 1620, 1580, 1430, 1320, 710 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.55. Found: C, 54.04; H, 4.88; N, 12.21.

5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Picrate (7b).—The picrate was prepared from 6b and ketene in the same manner as described for the perchlorate salt to yield yellow needles: mp 124–125°; yield 50%; ν_{max}^{KBr} 1750 cm^{-1}; nmr (CD_3CN) δ 2.21 (3 H, s, CH_3CO), 2.05–2.83 (8 H, series of multiplets, ring protons), 3.0–4.0 (4 H, series of multiplets, ring protons), 4.49 (2 H, s, benzyl CH_2), 7.53 (5 H, s, C_6H_5), 8.58 (2 H, s, picrate H's).

Anal. Calcd for $C_{22}H_{24}N_4O_9$: C, 54.10; H, 4.95; N, 11.47. Found: C, 54.37; H, 5.05; N, 11.77.

Acetylation of Piperidine with 5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Perchlorate (7a).—To 24 mg (0.28 mmol) of piperidine in 60 ml of methylene chloride was added 50 mg (0.14 mmol) of 5-acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane perchlorate at −20° with magnetic stirring. After 2 min, the solution was concentrated under vacuum pump pressure at 0° to a yellow oil. The time for concentration was less than 6 min. The presence of N-acetylpiperidine and 1-benzyl-1-azacyclooctane-5-one was evidenced by both thin-layer chromatography and by comparison of the nmr spectrum of the mixture with the spectra of the authentic samples. No starting material (7a) was found in the reaction mixture by either method of analysis.

Acetylation of Potassium Acetate with 5-Acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane Perchlorate (7a).—A sealed capillary tube containing 6 mg (16.7 μmol) of 5-acetoxy-1-benzyl-1-azoniabicyclo[3.3.0]octane perchlorate and 3 mg (30.6 μmol) of vacuum dried potassium acetate[9] was heated at 195° for 1 min, during which melting occurred. The end of the tube containing the melt was cooled to −78°, and the upper two-thirds of the tube was heated with an electric dryer to cause volatile materials to condense in the lower part of the tube.

Heating of the lower third of the capillary tube then served as a gas chromatograph inlet system. Analysis of the volatile components using an 8 ft, 20% diisodecyl phthalate column on Chromosorb W led to identification of acetic anhydride as the major volatile component of the reaction mixture. Comparison of the peak areas of the reaction mixture with peak areas of known amounts of acetic anhydride generated using a similar capillary inlet system indicated that greater than 90% of the acetic anhydride expected was produced in the acetylation reaction. The presence of 1-benzyl-1-azacyclooctane-5-one was shown by thin-layer chromatographic analysis of the less volatile residue in the capillary tube.

Registry No.—6a, 16853-07-9; 6b, 17555-90-7; 7a, 16853-91-1; 7b, 17555-92-9.

Acknowledgment.—The authors are grateful for the support of this research by the National Science Foundation (Grant GP-2012, currently GP-8407X).

(9) Attempts to powder the reagents finely prior to insertion into the capillary led to brownish mulls. This could indicate that reaction is occurring even under these conditions.

Improved Synthesis of *anti*-Benzaldoxime. Concomitant Cleavage and Formylation of Nitrones

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Received June 11, 1968

Recent interest in alkylation of *anti*-benzaldoxime[1] to form nitrones[2,3] and in the hydrolysis of nitrones to N-hydroxyamino compounds[3,4] has emphasized the fact that no satisfactory procedure is available in the literature for the preparation of this starting material. The published procedures[5-7] involving sodium carbonate neutralization of the oxime hydrochloride have not been successfully carried out on a large scale[2] and are suitable only for the preparation of a few grams of transiently stable[6] *anti*-oxime, rapid reversion to the low-melting *syn*-oxime occurring during work-up and handling.

In connection with our synthetic program on hadacidin, a growth inhibitor isolated from *Penicillium frequentans* Westling,[8] it was necessary to develop a procedure for the preparation and use of *anti*-benzaldoxime on a large scale.

The *syn*-oxime, obtained by conventional means from benzaldehyde and hydroxylamine, is converted into a hydrochloride on treatment with anhydrous hydrogen chloride in a variety of solvents. Brady and Dunn described[6] the preparation of two isomeric hydrochlorides, the β hydrochloride, prepared at higher temperatures, affording the very unstable *anti*-oxime on neutralization.

We have developed a procedure in which the hydrochloride is prepared in refluxing benzene to ensure complete conversion into the β form, which is isolated with exclusion of atmospheric moisture and is then neutralized in a rapid sequence of dissolution in excess caustic, reacidification with ammonium chloride, and extraction with ethyl ether. Both the preparation of the hydrochloride in hot solvent and the particular mode of neutralization are critical to the process. By this means, *anti*-benzaldoxime can be prepared conveniently in large quantities in 88% over-all yield from benzaldehyde. The method is described below on a 2-mol scale and has been carried out on a scale many fold larger. Oxime so produced is free of *syn* isomer and has remained stable for several weeks. The nmr spectrum in tetrahydrofuran showed the —CH=N— proton as a singlet at 7.27 ppm relative to TMS, a value identical

(1) *anti*-Benzaldoxime has been referred to as β-benzaldoxime in the older literature. The name (Z)-benzaldoxime has been proposed by *Chemical Abstracts Service* [J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968)].

(2) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).

(3) E. Falco and G. B. Brown, *J. Med. Chem.*, **11**, 142 (1968).

(4) E. Buehler and G. B. Brown, *J. Org. Chem.*, **32**, 265 (1967).

(5) E. Beckmann, *Chem. Ber.*, **23**, 1684 (1890).

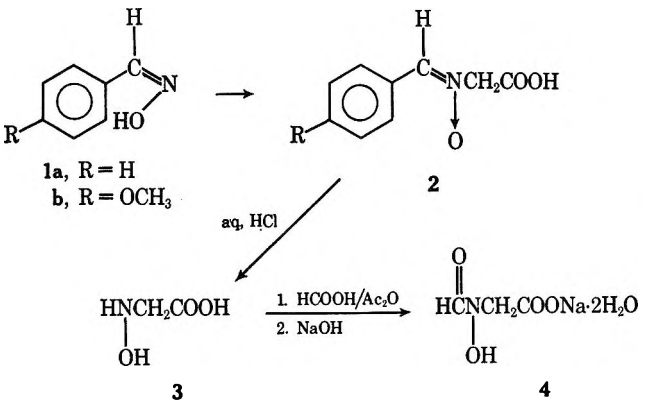
(6) O. Brady and F. Dunn, *J. Chem. Soc.*, 1783 (1923). In this reference, the designations *syn* and *anti* are interchanged.

(7) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed., Longmans, Green and Co., Ltd., London, 1956, p 719.

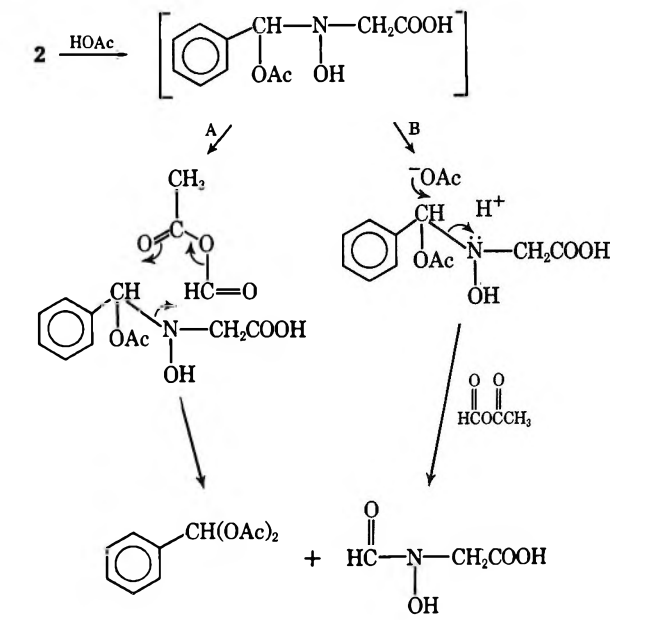
(8) E. A. Kaczka, C. O. Gitterman, E. L. Dulaney, and K. Folkers, *Biochemistry*, **1**, 340 (1962).

with that obtained by interpolation of data[9] relating the chemical shift of this resonance in aromatic oximes to the substituent constant σ. The generality of the method is shown by the conversion of anisaldehyde into *anti*-anisaldoxime (79% yield).

These *anti*-oximes have been converted into the N-(carboxymethyl)-α-arylnitrones (**2**) by known means[10] and have been used for the preparation of hadacidin (**4**, sodium N-formylhydroxyaminoacetate dihydrate) by hydrolysis to N-hydroxyaminoacetic acid[4,10] followed by formylation.[8]



As isolation of N-hydroxyaminoacetic acid from the aqueous hydrolysate is difficult, a more direct conversion of **2** into hadacidin was sought. We have found that these nitrones can be cleaved with concomitant formylation by treatment with formic acetic anhydride at room temperature. This reaction can be best formulated as an initial addition of acetic acid followed by either a concerted formylation cleavage (A) or an acid-catalyzed cleavage followed by formylation (B). The aromatic aldehyde appears as a by-product during work-up.



Experimental Section[11]

β-Benzaldoxime Hydrochloride.—Benzaldehyde (212 g, 2.0 mol) was added with stirring to a solution of 200 g (5.0 mol) of sodium hydroxide in 600 ml of water at room temperature. Hydroxylamine hydrochloride (144 g, 2.06 mol) was added in one portion. The temperature rose to 70°, and a clear solution was obtained. The solution was cooled to 30–35°, and carbon dioxide was passed in until the pH fell to 10. Alizarin yellow (1 mg) can be added during the carbonation to serve as a convenient internal indicator (rose to yellow). The free (*syn*) oxime which separated was extracted with 800 and 400 ml of benzene. The combined extracts were dried ($MgSO_4$) and filtered.

A small sample was evaporated *in vacuo* to constant weight. The ir spectrum ($CHCl_3$) of the resultant oil showed 3570 (s), 3300 (s, br), 1620 (w), 1565 (w), 1480 (m), 1255 (s), and 860 cm^{-1} (vs). The nmr spectrum (tetrahydrofuran) showed the —CH=N— proton singlet at 8.04 ppm relative to TMS.[12] The benzene solution was placed in a 2-l. three-necked flask equipped with a large-bore gas-inlet tube set for subsurface delivery, stirrer, thermometer, distillation head, and heating mantle. The solution was heated with stirring, and about 100 ml of solvent was distilled out to ensure dryness. An efficient condenser with a drying tube was set for reflux; the solution was reheated to boiling; the heating mantle was removed; and a strong flow of anhydrous hydrogen chloride gas was sparged through the vigorously stirred hot solution. The heat of reaction maintained vigorous reflux with a liquid temperature of 77–80°. Addition of hydrogen chloride was continued until the oil which first separated had crystallized and the liquid temperature had fallen to 50°.

The resultant slurry was cooled to 10° and filtered, and the crystalline hydrochloride was washed with two 200-ml portions of benzene and two 500-ml portions of *n*-hexane. Care must be taken to avoid exposure to atmospheric moisture, and air should not be allowed to be drawn through the filter cake. The hydrochloride, wet with solvent, may be stored in a desiccator over potassium hydroxide pellets. No attempt was made to weigh this intermediate.

***anti*-Benzaldoxime.**—Ethyl ether (2.0 l.) and 1.5 l. of an aqueous solution of sodium hydroxide (160 g, 4 mol) were mixed and cooled to 10° with good stirring. Maintaining vigorous agitation, the oxime hydrochloride prepared above was rapidly added. As soon as all solids had dissolved (*ca.* 1 min), a solution of 400 g of ammonium chloride in 1.5 l. of water was added. When the precipitated solids had redissolved (*ca.* 1 min), the stirring was stopped, the layers separated, and the aqueous layer was reextracted with 800 ml of ethyl ether. The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to a very thick slurry. *n*-Hexane (300 ml) was added, and the mixture was again vacuum concentrated to a thick slurry. Another 300-ml portion of *n*-hexane was added, and the *anti*-oxime was filtered, using the mother liquor to aid in transfer. The filter cake was washed liberally with *n*-hexane. The product was air dried to constant weight. The *anti*-oxime, obtained as white needles, mp 129.5–130°, weighed 213 g (88% of theory from benzaldehyde). The ir spectrum ($CHCl_3$) showed 3570 (s), 3240 (s, br), 1630 (w, br), 1565 (w), 1480 (m), 1175 (w), and 840 cm^{-1} (s). The nmr spectrum (tetrahydrofuran) showed a proton as a singlet at 7.27 ppm relative to TMS.

Anal. Calcd for C_7H_7NO: C, 69.41; H, 5.83; N, 11.56. Found: C, 69.80; H, 5.89; N, 11.60.

***anti*-Anisaldoxime.**—The same procedure was used to convert anisaldehyde (68.07 g, 0.5 mol) into β-anisaldoxime hydrochloride which was dried to constant weight *in vacuo* yielding 87.3 g (93.2% of theory), mp 133–133.5° dec. On neutralization as above, there was obtained 59.80 g (79% from anisaldehyde) of *anti*-anisaldoxime, mp 131–137° (lit. mp 130–130.5°[5] and 131.5°[6]).

N-(Carboxymethyl)-α-phenylnitrone.—*anti*-Benzaldoxime was converted into N-(carboxymethyl)-α-phenylnitrone by the procedure of Hantzsch and Wild.[10] The product was obtained in 81% yield, mp 176–179° (lit.[4] mp 178–179°).

Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.51; H, 5.18; N, 8.04.

(9) I. Pejkovic-Tadic, M. Hranisavljevic-Jakovljevic, S. Nesic, C. Pascual, and W. Simon, *Helv. Chim. Acta*, **48**, 1157 (1965).

(10) A. Hantzsch and W. Wild, *Ann.*, **289**, 285 (1896).

(11) All melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer 421 grating spectrophotometer. The nmr spectra were obtained through the use of a Varian Associates Model 4300B high resolution spectrometer and tetramethylsilane (TMS) as an internal standard.

(12) Interpolation of the data of ref 9 gives 8.07 ppm relative to TMS for the chemical shift of this proton in *syn*-benzaldoxime.

N-(Carboxymethyl)-α-(*p*-methoxyphenyl)nitrone.—In a similar fashion, *anti*-anisaldoxime (54.8 g, 0.362 mol) was converted into 53.2 g (70.4%) of the nitrone, mp 165–165.5° dec. A sample which recrystallized from aqueous ethanol had mp 165.5–166° dec.

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.51; H, 5.13; N, 6.98.

Sodium N-Formylhydroxyaminoacetate Dihydrate.[13]—To 65.6 ml (1.7 mol) of 98% formic acid in a three-necked flask maintained at 25–30° was added 87.5 ml (0.925 mol) of acetic anhydride over 30 min with stirring. The solution was aged 15 min at 25° and then treated with 35.0 g (0.195 mol) of N-carboxymethyl-α-phenylnitrone portionwise over 15 min. The resultant slurry was stirred over 25° until the solid dissolved (1.5 hr) and then for an additional hour. Versene (0.2 g) was added;[14] the solution cooled to 5° and partially neutralized, at a temperature kept below 30°, by dropwise addition of 122 ml of 8 *N* aqueous NaOH. The final pH was 3.7. The solution was washed with 50 ml of ethyl ether to remove benzaldehyde. The product was crystallized by slow addition of 720 ml of ethanol, with stirring and seeding. The resulting slurry was cooled to 0–5°, aged at that temperature for 30 min, and filtered. The cake was washed with three 35-ml portions of 95% ethanol, sucked damp dry, and dried under forced air at 35°. There was obtained 24.2 g of sodium N-formylhydroxyaminoacetate dihydrate (70% of theory) mp 191–193° dec.

Anal. Calcd for $C_3H_4NO_4Na \cdot 2H_2O$: C, 20.34; H, 4.55. Found: C, 20.56; H, 4.57.

Very similar results were obtained when N-carboxymethyl-α-(*p*-methoxyphenyl)-nitrone was employed in this reaction.

Registry No.—**1a**, 13830-84-7; **2a**, 3884-90-0; **2b**, 17556-16-0; **4**, 2618-22-6.

Acknowledgments.—We wish to thank Dr. Byron H. Arison and Dr. Nelson R. Trenner for the nmr spectra, Mr. Robert Walker for the infrared spectra, and Mr. Richard N. Boos and his staff for the elemental analyses.

(13) The procedure as originally developed used a larger volume of formic acid and acetic anhydride, and the reaction mixture was evaporated to a syrup at reduced pressure below 40°. Under these conditions a possibly hazardous exotherm was sometimes observed. We are indebted for this modification, in which smaller initial volumes obviate the vacuum concentration, to Mr. William F. Elmendorf and Dr. David F. Hinkley of these laboratories.

(14) Hadacidin forms an intensely colored chelate with iron, and an off-color product may be obtained unless a sequestering agent is used.

Diazomethane and Deuteriodiazomethane by the Base-Catalyzed Reaction of Hydrazine with Chloroform

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The record number of preparations for diazomethane which appear in "Organic Syntheses"[1] accentuates not only its importance to the synthetic organic chemist, but also its lability. Despite its many years in the chemists repertory of reagents, the explosive nature[2] of diazomethane is not understood. In the course of another study,[3] pure deuterated diazomethane was required. Although the best preparative methods[4] avoid concentrated solutions of diazomethane,[2] the solvent-free gas and a procedure easily adaptable for preparation of deuteriodiazomethane was desired for the above mentioned study.

Demore, Pritchard, and Davidson,[5] and others[6,7] report the preparation of deuterated diazomethane by direct exchange with D_2O. An ir spectrum shown by Demore, *et al.*, indicates the presence of approximately 40% CD_2N_2, 40% $CHDN_2$, and 20% CH_2N_2. In the present work, this technique was extended to two 30-min exchanges and resulted in the loss of 95% of the original diazomethane sample due to the reaction of diazomethane with water to produce methyl ether.

Leitch, Gagnon, and Cambron[8] have prepared a relatively pure sample of deuterated diazomethane by decomposing methyl-d_3-nitrosourea in NaOD–D_2O. Although the presence of CH_2N_2 was negligible, the end product contained a large quantity of $CHDN_2$. The rather lengthy procedure required to produce all the deuterated intermediate reactants and solvents illustrated the necessity of having such species deuterated in all positions.

Utilization of the technique of Staudinger and Kupfer[9] to prepare deuterated diazomethane is more straightforward since deuterated hydrazine and chloroform are commercially available, and the preparation of deuterated solvent and potassium hydroxide are moderately simple. The relatively low yields of diazomethane (≈20%) and the impurities produced must be considered before utilizing this technique.

With reaction conditions as formulated by Staudinger and Kupfer[9] (eq 1), ammonia and ethylene are

$$NH_2NH_2 \cdot H_2O + CHCl_3 + 3KOH \xrightarrow{CH_3CH_2OH} CH_2N_2 + 3KCl + 4H_2O \quad (1)$$

gaseous contaminants in diazomethane by ir analysis. If methyl alcohol is substituted for ethyl alcohol as the solvent, methyl ether is an additional gaseous product. With no solvent, chloroacetylene has been identified as a minor product.[10] Variation of the reactants as shown in Table I causes a considerable variation in the products observed.

Although all of the gaseous products probably arise by interesting mechanisms, we were particularly fascinated with the formation of chloroacetylene. It was identified in the following way. Diazomethane

(1) (a) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 165; (b) C. E. Redemann, F. O. Rice, R. Roberts, and H. P. Ward, ref 1a, Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y. 1955, p 244; (c) Th. J. deBoer and H. J. Backer, ref 1a, Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 250; (d) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

(2) Diazomethane is unpredictably dangerous. For leading references and representative warnings concerning its use, see ref 1d and the following: (a) I. T. Millar and H. D. Springall, "Sidgewick's Organic Chemistry of Nitrogen," 3rd ed, Clarendon Press, London, 1966, pp 478–479; (b) P. A. S. Smith, "The Chemistry of Open-Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 212–215.

(3) C. L. Dodson, Ph.D. Thesis, University of Tennessee, 1963.

(4) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, pp 191–195.

(5) W. B. Demore, H. O. Pritchard, and N. Davidson, *J. Amer. Chem. Soc.*, **81**, 5874 (1959).

(6) G. W. Robinson and M. McCarty, Jr., *ibid.*, **82**, 1859 (1960).

(7) T. D. Goldfarb and G. C. Pimentel, *ibid.*, **82**, 1865 (1960).

(8) L. C. Leitch, P. E. Gagnon, and A. Cambron, *Can. J. Res.*, **28B** 256 (1950).

(9) H. Staudinger and O. Kupfer, *Ber.*, **45**, 505 (1912).

(10) We suspect chloroacetylene as a product with solvent also; its solubility may keep it from codistilling with diazomethane. In one experiment a mixture of CH_2N_2 and chloroacetylene was bubbled through ethyl alcohol which removed chloroacetylene, but CH_2N_2 reacted with the solvent to produce methyl ethyl ether.

TABLE I

REPRESENTATIVE EXAMPLES OF THE GASEOUS PRODUCTS FROM REACTION OF $CHCl_3$ AND $NH_2NH_2 \cdot H_2O$

Base	Solvent	% yield of CH_2N_2[a]	Calcd % partial pressure[b]				
			CH_2N_2	$CH_2{=}CH_2$	NH_3	CH_3OCH_3	$HC{\equiv}CCl$
KOH	CH_3CH_2OH	9.18	61	35	4		
KOH	CH_3OH	5.5[c]	79	6	6	9	
KOH	$PhCH_2OH$	4.3	70	Trace	29		
Na	CH_3OH	17	16		20		
KOH	$(n\text{-}C_4H_9)_2O$	6.4	70		25		4
KOH		Not calcd	30	44	22		4

[a] Does not include that amount which is measured as ethylene. [b] Estimated from comparison of ir spectra with spectra of known concentration. [c] Average of duplicate runs.

mixed with ammonia and chloroacetylene was removed by reaction with silicone grease. An ir spectrum of chloroacetylene was obtained with the ammonia in the mixture balanced out by a sample of pure ammonia with appropriate pressure in the reference beam of the spectrometer. All absorption bands present correlate with literature data for chloroacetylene as shown in Table II.

TABLE II

COMPARISON OF IR DATA FOR CHLOROACETYLENE

Assignment	$HC{\equiv}C{-}Cl$ Obsd, cm^{-1}	$HC{\equiv}C{-}Cl$ Lit., cm^{-1}	$DC{\equiv}C{-}Cl$ Obsd, cm^{-1}	$DC{\equiv}C{-}Cl$ Lit., cm^{-1}[b]
C—H stretch (ν_1)	3341	3319,[a] 3340[b]	2611	2612
C≡C stretch (ν_2)	2114	2109,[a] 2110[b]	1977	1980
($2\nu_5$)	1199	1202[a]		941
C—Cl stretch (ν_3)	756	756[a,b]	744	742
C≡C—Cl bend (ν_4)	607	606,[a] 604[b]	491	472
C≡C—Cl bend (ν_5)	323	326[b]		312

[a] W. S. Richardson and J. H. Goldstein, *J. Chem. Phys.*, **18**, 1314 (1950). [b] G. R. Hunt and M. K. Wilson, *ibid.*, **34**, 1301 (1961).

When deuterated diazomethane was prepared, deuterated chloroacetylene was obtained, and again the measured frequencies (Table II) of this species were in agreement with literature values. (Deuterated ammonia[3] was required in this instance in the reference beam of the spectrometer.)

The obvious mechanism for the formation of chloroacetylene involves the stepwise formation of dichlorocarbene[11] by basic hydrolysis of chloroform followed by the reaction of dichlorocarbene with diazomethane (eq 2) to produce 1,1-dichloroethylene. A base-catalyzed dehydrohalogenation of 1,1-dichloroethylene (eq 3) would then complete the sequence for formation of chloroacetylene.

$$:CCl_2 + CH_2N_2 \longrightarrow [\bar{C}Cl_2{-}CH_2{-}\overset{+}{N}{\equiv}N] \xrightarrow{-N_2} CCl_2{=}CH_2 \quad (2)$$

$$CCl_2{=}CH_2 + {}^-OH \longrightarrow Cl{-}C{\equiv}C{-}H + H_2O + Cl^- \quad (3)$$

The suspected path was tested to determine if dichlorocarbene was formed as expected[11] under the reaction conditions employed.[12] When cyclohexene was used as an additive, 7,7-dichlorobicyclo[4.1.0]heptane was identified as a product by comparison of its glpc retention time and ir spectrum with those of a known sample.[13] Reimlinger[14] has recently demonstrated that dihalocarbenes react with diazoalkanes to form dihaloethylene derivatives. His examples, however, were all disubstituted, and no further reaction of the type as shown here was possible. By treating a commercial sample of 1,1-dichloroethylene under conditions present for the reaction depicted by eq 3, chloroacetylene was isolated and identified. This then establishes eq 2 and 3 as the most likely mechanism of formation of chloroacetylene. Despite the low yields obtained,[15] the formation of chloroacetylene here suggests the general use of this one-step process to form certain difficultly prepared acetylenic products.

Of all by-products, ethylene is the most expected. It is assumed to occur by reaction of methylene with diazomethane.[16] If ethyl alcohol is used as a solvent in the reaction between hydrazine and chloroform, ethylene also originates from the alcohol as has been previously demonstrated.[17,18] This was verified in the present work by an experiment which utilized all deuterated materials, except the alkyl portion of the alcohol, and it was observed that 95% of the ethylene obtained was the completely protonated species. The relatively high yield of ethylene obtained when ethyl alcohol is used as a solvent (see Table I) is consequently explained. Methyl ether is a known insertion product[19] between methylene and methyl alcohol.

Ammonia could be derived by more than one feasible process. Hydrazine is known to undergo base-catalyzed air oxidation to form ammonia.[20] We have found that heating hydrazine and chloroform together at 50° for 40 min in a helium atmosphere produces small, but measurable, quantities of ammonia. We were not able to identify any ammonia, however, if sodium methoxide and hydrazine reacted under the above conditions. One explanation for the forma-

(11) J. Hine, *J. Amer. Chem. Soc.*, **72**, 2438 (1950).

(12) In each case either hydrazine or chloroform was intentionally left out to prevent formation of diazomethane[2] while still maintaining a meaningful experiment.

(13) W. von E. Doering and A. K. Hoffmann, *ibid.*, **76**, 6162 (1954).

(14) H. Reimlinger, *Ber.*, **97**, 339, 3503 (1964).

(15) No attempts were made to optimize the yields of chloroacetylene in our experiments.

(16) (a) J. Hine, "Divalent Carbon," Ronald Press Co., New York, N. Y. 1964, p 31; (b) W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, p 11.

(17) J. Hine, E. L. Pollitzer, and Hans Wagner, *J. Amer. Chem. Soc.*, **75**, 5607 (1953).

(18) M. Hermann, *Ann.*, **95**, 211 (1855).

(19) H. Ogoshi and Y. Takezaki, *Bull. Inst. Chem. Res., Kyoto Univ.*, **38**, 299 (1960); *Chem. Abstr.*, **55**, 20913 (1961).

(20) For leading references, see L. F. Audrieth and B. A. Ogg, "The Chemistry of Hydrazine," John Wiley & Sons, Inc., New York, N. Y., 1951, pp 139–145.

tion of ammonia could be the acid–base reaction shown in eq 4 followed by a nucleophilic cleavage (eq 5).

$$CHCl_3 + NH_2NH_2 \longrightarrow \bar{C}Cl_3 + \overset{+}{N}H_3NH_2 \quad (4)$$

$$\overset{+}{N}H_3NH_2 + \bar{C}Cl_3 \longrightarrow NH_3 + CCl_3NH_2 \quad (5)$$

Because of its probable mode of formation and of the contaminating by-products which we have described here and because of other adaptable methods,[1] this method is not a recommended procedure for the preparation of pure protonated diazomethane.[21-24] It is competitive with others[5-7] for the preparation of deuteriodiazomethane since a sample approximately 92% deuterated was obtained when no solvent was used and all starting materials contained 99% of the maximum possible deuterium.

Although there is convincing evidence that diazomethane will explode alone,[2] the presence of previously unknown contaminants may make these mixtures more explosive[25,26] than pure diazomethane from other sources.[4] While we recognize and respect the explosive unpredicability of diazomethane, our experience[27] supports recent evidence[1d] that contrary to previous practice ground-glass apparatus can be used in its preparation without incident. As a result of this study, however, we do not claim to understand the reasons for the unpredictability of the decomposition of diazomethane.

Experimental Section

Infrared measurements were recorded as liquids or gases using a Beckman IR-10, Perkin-Elmer 421, or Perkin-Elmer 237 instrument. The gas chromatographic analysis were performed with a F & M Model 700 gas chromatograph using a flame ionization detector and a 10% diisodecylphthalate on a Chromosorb W column.

Caution: Proper precautions must be taken when working with diazomethane.[2]

Preparation of Diazomethane.—Variations of the procedure of Staudinger and Kupfer[9] were used throughout (see Table I). Ground-glass joints were used throughout.[1d] All gaseous products were collected in a liquid nitrogen trap.

Preparation of Deuteriodiazomethane.—Deuterated chloroform and hydrazine hydrate were purchased from Merck Sharp and Dohme of Canada, Ltd. Potassium hydroxide-*d* was prepared by adding clean potassium directly to D_2O in a dry box using a nitrogen atmosphere. It was then dried over P_2O_5 in a vacuum desiccator. The KOD and $D_2NND_2 \cdot D_2O$ were placed in the reaction flask, while in the dry box. Connection of the reaction flask to the generating assembly and the addition of $CDCl_3$ to a dropping funnel were accomplished while helium flushed out the entire apparatus to prevent exchange with atmospheric moisture. Procedure then followed that of Staudinger and Kupfer.[9] Deuterated diazomethane was collected in a liquid nitrogen cooled trap and was twice distilled under vacuum from −80 to −196°. Ethylene was removed by exposing the sample, maintained at −150° by an isopentane bath, to vacuum pumping for 30 min.

Proof of the Presence of Dichlorocarbene.—From a reaction of 28.0 g (0.50 mol) of potassium hydroxide and 16.9 ml (0.167 mol) of dried ($CaCl_2$) and freshly distilled cyclohexene in 122 ml of methanol with 13.4 ml (0.167 mol) of chloroform, 3 ml of a yellow oil identified by glpc analysis as 7,7-dichlorobicyclo[4.1.0]heptane[13] was obtained. Infrared comparison with a known sample[13] confirmed the glpc analysis.

Isolation of Chloroacetylene from the Dehydrohalogenation of 1,1-Dichloroethylene.—In a three-necked 100-ml flask fitted with a condenser, an additional funnel, and a nitrogen inlet, 4.0 g of potassium hydroxide in 5.6 ml of hydrazine were stirred by a magnetic stirrer and treated dropwise with 1.58 g of 1,1-dichloroethylene. During the addition, the temperature was kept at 5°; the system was swept with dry nitrogen; and all volatile products were collected in a Dry Ice–acetone trap. A noticeable reaction occurred as the solution became yellow and a precipitate formed. After the mixture had been stirred for 1.5 hr, the trap was closed to the system and opened to an evacuated ir cell which was connected through a ballast flask and a drying tube ($CaCl_2$). After the product was allowed to warm to room temperature, the pressure in the cell was 200 mm. The ir spectra clearly revealed the presence of chloroacetylene.

Experiments to Elucidate Ammonia Formation Mechanism. A.—To 15 ml of methyl alcohol was added 1.5 g of sodium and 2.5 ml of anhydrous hydrazine. The resulting solution was heated to 50° for 0.5 hr, and all gaseous products were collected in a liquid nitrogen trap. No ammonia was present by ir analysis.

B.—Approximately 2 g of anhydrous hydrazine and 5.5 g of chloroform were heated together at 50° for 40 min with all gases being trapped in a liquid nitrogen trap. All ir peaks were assigned to chloroform and ammonia with the latter being the minor component.

Registry No.—Diazomethane, 334-88-3; deuteriodiazomethane, 17510-78-0; hydrazine, 302-01-2; chloroform, 67-66-3.

Acknowledgment.—This work was partially supported by a NASA grant, NsG-381, for which we are grateful.

(21) It has been proposed[22,23] that diazomethane is formed with amino isocyanide as intermediate. For rearrangement to diazomethane, another probable intermediate would be isodiazomethane,[22] which explodes at temperatures lower than those of the reaction conditions used here.[24]

(22) I. T. Millar and H. D. Springall, ref 22, p 476.

(23) E. Muller, "Neuere Anschauungen Der Organischen Chemie," 2nd ed, Julius Springer, Berlin, Germany, 1957, pp 452–454.

(24) J. P. Anselme, *J. Chem. Ed.*, **43**, 596 (1966).

(25) (a) Impure CH_2N_2 is said[2a] to be especially dangerous and explodes even at low temperatures. (b) Chloroacetylene is reported to be sensitive to oxygen and is a treacherous explosive.[26]

(26) E. H. Huntress, "Organic Chlorine Compounds," John Wiley & Sons, Inc., New York, N. Y., 1948, p 930.

(27) In the course of this and other work, stopcocks and ground-glass joints were freely used in the apparatus for generating and storing diazomethane. Relatively pure samples of the compound have been passed through medium-porosity, fritted-glass bubblers and chromatographic columns using ground fire-brick as a supporting material and over irregularly shaped KOH and silica gel. No explosions were observed in any of these experiments.

During preparation and manipulation of diazomethane, no explosions have occurred using this or other more conventional procedures.[4] In contrast, an explosion occurred with a spectroscopically pure sample of solid diazomethane following 3 days' storage in liquid nitrogen.

The Preparation of 2-(Substituted amino)-3-phenyl-3H-indol-3-ols

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Received May 17, 1968

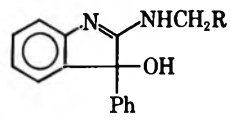
The synthesis of amidines from amides, without formation of intermediates such as imino chlorides or imidate salts, is known, but its preparative usefulness is limited to formamidines[1] or to special cases, such as the preparation of 2,3,4,6,7,8-hexahydropyrrolo[1,2-*a*]-pyrimidine from 1-(3-aminopropyl)-2-pyrrolidinone, where the amine function is held in proximity of the amide carbonyl.[2]

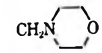
In the preparation of 1-methyl-2-(phenylimino)-pyrrolidine from 1-methyl-2-pyrrolidinone and aniline,

(1) J. B. Shoesmith and J. Haldane, *J. Chem. Soc.*, **123**, 2704 (1923).

(2) H. Oediger, H. J. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

TABLE I

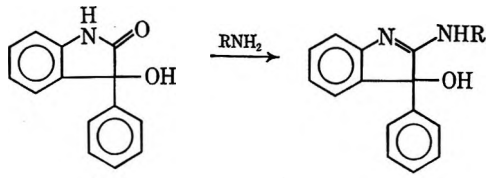


II	R	Mp, °C[a]	Yield, %[b]	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
a	Phenyl	156–157	32	$C_{21}H_{18}N_2O$	80.24	5.77	8.91	80.33	5.74	8.87
b	α-Pyridyl	219–221	71	$C_{20}H_{17}N_3O$	76.16	5.43	13.32	75.95	5.41	13.25
c	CH_2-α-Pyridyl	171–172	39	$C_{21}H_{19}N_3O$	76.58	5.82	12.76	76.45	5.86	12.84
d		187–189	55	$C_{20}H_{23}N_3O_2$	71.20	6.87	12.46	71.04	6.64	12.31
e	$(CH_2)_2N(CH_3)_2$	186–188	80	$C_{19}H_{23}N_3O$	73.74	7.49	13.58	73.55	7.47	13.73
f	$(CH_2)_2N(C_2H_5)_2$	164–165	60	$C_{21}H_{27}N_3O$	74.25	8.07	12.45	74.55	7.96	12.18
g		164–166	65	$C_{22}H_{27}N_3O$	75.45	7.79	12.03	75.15	7.70	12.00
h		157–158	70	$C_{21}H_{25}N_3O_2$	71.78	7.17	11.96	71.51	7.14	11.78
i	$(CH_2)_2N(C_2H_5)(CH)_2OH$	149–150	68	$C_{21}H_{27}N_3O_2$	71.37	7.70	11.90	71.14	7.70	12.01

[a] Melting points were observed on a Fisher-Johns block with a calibrated thermometer. [b] Solvent of recrystallization was 2-propanol.

phosphorus oxychloride is used,[3] and an imino chloride intermediate is first formed.

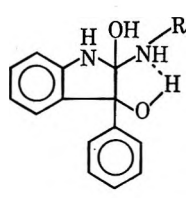
To our surprise, the preparation of the title compounds (II) was accomplished conveniently from 3-hydroxy-3-phenyloxindole (I), and an excess of primary amine in boiling xylene in the presence of a catalytic amount of *p*-toluenesulfonic acid by azeotropic removal of the water formed.



I II

The structure of II was established by infrared data. The oxindole carbonyl band at 1700–1715 cm^{-1} was missing. Instead, three bands at 1620, 1600, and 1580 cm^{-1} appeared, two assignable to phenyl ring vibrations, the remaining one due to C=N stretching vibration. As expected, in KBr the 3200-cm^{-1} region showed intermolecular bonded NH—OH, but in CCl_4 solution the free hydroxyl group was clearly visible at 3600 cm^{-1} and the NH group at 3440 cm^{-1}.

It was found that formation of amidine from I under the conditions used took place only when the 1 position was unsubstituted and free OH in the 3 position was present. It is known that the proton in the 3 position of I is quite readily removed. Hydrogen bridging from the 3-hydroxyl proton to the free electron pair in the addition product (III), necessary for the amidine formation, could block the amine nitrogen effectively, thus allowing protonation merely of the 2-hydroxyl group.



III

(3) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).

Experimental Section

The preparation of the compounds in Table I is demonstrated in the following example.

2-[(3-Morpholinopropyl)amino]-3-phenyl-3H-indol-3-ol.—A mixture of 22.5 g (0.1 mol) of 3-hydroxy-3-phenyloxindole,[4] 28.8 g (0.2 mol) of 4-(3-aminopropyl)morpholine, and a catalytic amount of *p*-toluenesulfonic acid in 400 ml of xylene was boiled with stirring under a Dean–Stark trap for 10–15 hr, after which time 1.8 ml of water was collected. The solvent was evaporated under reduced pressure, and the residue was slurried in isopropyl ether, then recrystallized from 2-propanol to give 24.6 g (70%) of a white crystalline solid.

Registry No.—IIa, 17510-66-6; IIb, 17510-60-0; IIc, 17510-67-7; IId, 17510-61-1; IIe, 17510-62-2; IIf, 17510-63-3; IIg, 17510-64-4; IIh, 17510-65-5; IIi, 17510-59-7.

Acknowledgment.—The authors wish to thank Mr. C. E. Childs and staff for microanalytical data and Dr. J. M. Vandenbelt and Mr. E. J. Schoeb for infrared data.

(4) H. E. Baumgarten and P. L. Creger, *J. Amer. Chem. Soc.*, **82**, 4634 (1960).

Synthesis of β-Hydroxyamides from Phenylacetamides and Ketones or Aldehydes by Means of Alkali Amides and *n*-Butyllithium[1a]

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Until recently,[2] considerable difficulty was encountered in synthesizing β-hydroxyamide 2a from

(1) (a) Supported at the University of Missouri by the Petroleum Research Fund, administered by the American Chemical Society, on Grant 959-G2, and at Duke University by the National Science Foundation; (b) University of Missouri; (c) Duke University.

(2) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3316 (1966).

TABLE I

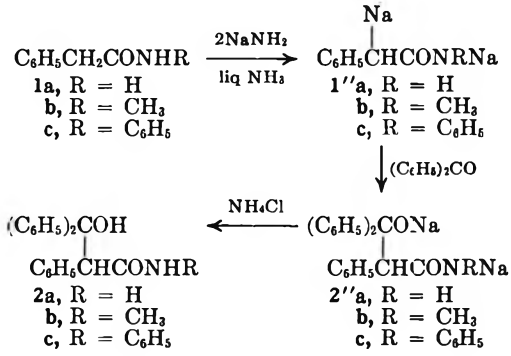
ADDITION REACTIONS OF DIALKALI ARYLACETAMIDES WITH KETONES AND BENZALDEHYDE

R	Carbonyl compound	Adduct	Mp, °C	Yields, %: Method A[a] $NaNH_2$, NH_3	Method A[a] $LiNH_2$, NH_3	Method B[b] n-C_4H_9Li, THF	Method B[b] n-C_4H_9Li, ether
H	Benzophenone	2a	202–203[c,d]	86[c]	23	41 (0)	
CH_3	Benzophenone	2b	194.5–195.5[e]	59[f]	2	45 (0)	
C_6H_5	Benzophenone	2c	202–203[e,g]	85	14	81 (0)	
H	Fluorenone	3	161–163[e]	72			
H	Cyclohexanone	4a	176.5–178.5[h]	17	39		32
CH_3	Cyclohexanone	4b	154–155[i]		33		41
C_6H_5	Cyclohexanone	4c	194.5–196[i]		5		80
H	Cyclopentanone	5a	123–123.5[e]				35
C_6H_5	Cyclopentanone	5c	159–160[h]		13		
H	Benzaldehyde	6a	145–146 184–186[j]	54[j]			20[j]
CH_3	Benzaldehyde	6b	175–176[j]	25[j]			64[j]
C_6H_5	Benzaldehyde	6c	222–224[j]	19[j]			78[j]

[a] At −33°. [b] At 35° or at indicated temperature. [c] See ref 2. [d] Recrystallized from absolute ethanol. [e] Recrystallized from 95% ethanol. [f] Three equivalents of sodium amide and two of benzophenone afforded adduct **2b** in 72% yield. [g] See ref 8. [h] Recrystallized from hexane–ethanol. [i] Recrystallized from hexane–ethyl acetate. [j] In some cases, the adducts consisted of a mixture of diastereoisomers. See D. M. von Schriltz, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, 32, 2610 (1967).

phenylacetamide (**1a**) and benzophenone through the intermediate formation of disodio salts **1''a** and **2''a** (Scheme I). However, with the recognition that the

SCHEME I

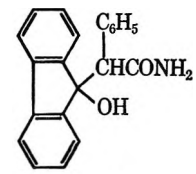


addition reaction of disodio salt **1''a** with the ketone in liquid ammonia is kinetically controlled, the satisfactory synthesis of adduct **2a** was readily achieved. Thus, **2a** was obtained in 86% yield upon inverse neutralization of the reaction mixture[3] after only a few minutes. After a usual reaction period (15 min or longer), the starting materials were recovered since disodio salt **2''a** had then been converted into the sodium amide adduct of benzophenone through a thermodynamically controlled process.[2]

Phenylacetamide (**1a**), N-methylphenylacetamide (**1b**), and phenylacetanilide (**1c**) have now been condensed not only with benzophenone, but also with other ketones and benzaldehyde. Such condensations were effected by means of sodium amide and lithium amide in liquid ammonia (method A) and by *n*-butyllithium in various inert solvents (method B) to afford β-hydroxyamides **2a–6c**.

In Table I are summarized the results obtained by these two methods. This table shows that for phenylacetamide (**1a**), method A employing sodium amide was more satisfactory than method B for benzophenone and benzaldehyde, and method A was also suitable for fluorenone. However, lithium amide (method A)

(3) This mode of neutralization involves pouring the reaction mixture into excess acid.



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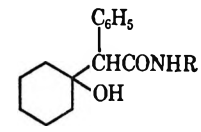
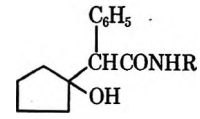
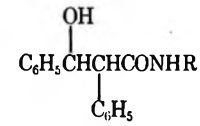


4a, R = H
b, R = CH_3
c, R = C_6H_5



5a, R = H
c, R = C_6H_5



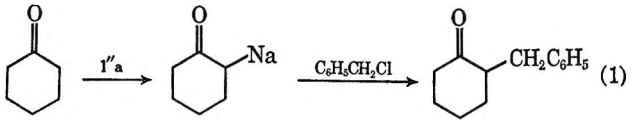
6a, R = H
b, R = CH_3
c, R = C_6H_5

and *n*-butyllithium (method B) (at 0° but not at 25°) were more satisfactory than sodium amide (method A) for cyclohexanone. In addition, methods A (sodium amide) and B were both suitable for the condensations of N-substituted amides **1b** and **1c** with benzophenone; better yields of **2b**, though, were realized by method A upon using a 100% excess each of sodium amide and the ketone. Method B was more satisfactory than method A in the reactions of amides **1b** and **1c** with benzaldehyde and cyclohexanone.

In general, better yields of the β-hydroxyamides were obtained by the use of 10 mol % excess over the required 2 equiv of alkali amide presumably because of a displacement of the equilibria between the starting dianions **1''a–c** toward the intermediate alkoxides, for example, **2''a–c** (see Scheme I). In the case of **1''b**, though, the best yields of **2b** were obtained by a 100% excess of alkali amide apparently because the inductive effect of the N-methyl group of **1b** causes the amido hydrogen to be less acidic than that of phenylacetamide. Thus, formation of the dianion **1''b** is probably incomplete unless a large excess of base is employed to shift the equilibrium toward this dianion. In the reactions effected by method B, a 10 mol % excess over the necessary 2 equiv of *n*-butyllithium could be employed only with the N-substituted amides **1b** and **1c** since the parent phenylacetamide (**1a**) is readily con-

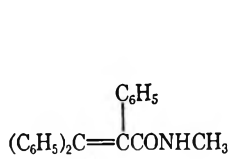
verted into trilithio salt 1‴; this salt undergoes a facile elimination of lithium oxide to afford lithiophenylacetonitrile 7′.[4]

In the condensations of amides 1a–c with enolizable ketones such as cyclohexanone, dilithio rather than disodio salts are recommended since the sodio salts predominately effect ionization of an α hydrogen of the ketone.[5] This was demonstrated in the current investigation in the reaction of cyclohexanone with disodio salt 1″a by treatment of the reaction mixture with benzyl chloride to give 2-benzylcyclohexanone (eq 1).



Incidentally, a temperature effect was observed in the condensations of phenylacetanilide (1c) with benzophenone effected by *n*-butyllithium (method B). Thus, when the ketone was added to 1″c at 0°, the resulting solution refluxed for 1 hr, and inverse neutralization then effected at −80 and 64°, the yield of adduct 2c was 51 and 0%, respectively; inverse neutralization at 25° afforded 2c in 16% yield. That the lower yields of adduct 2c at higher temperatures were not due to reaction of starting dilithio salt 1″c with the THF solvent was demonstrated by a 55% yield of adduct 2c even when 1″c was refluxed in THF–hexane for 60 hr prior to addition of benzophenone at 0°. Furthermore, even dilithiophenylacetamide 1″a was stable to refluxing THF–hexane as evidenced by deuteration after 1–3 hr of reflux to afford recovered phenylacetamide containing 0.43–0.5 α-deuterium atoms per molecule. These results thus imply that alkoxyamides like 2″a–c are relatively more stable at lower temperatures. Examples are known where the stability of compounds such as amine–borane adducts[6] and sterically hindered hydrocarbons[7] are greater at lower temperatures; perhaps anionic compounds could behave similarly.

The structures of the new compounds were supported by elemental analyses and by infrared (ir) spectroscopy (Table II). In some cases, the β-hydroxyamides were dehydrated. Thus, dehydration of 2b gave 8 in 65% yield, while dehydration of adduct 3 by hot polyphosphoric acid afforded unsaturated amide 9 in 80% yield. Hydroxyamides 1a and 1c have previously been dehydrated.[8]



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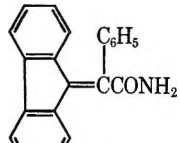

9

(4) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **32**, 3640 (1967).

(5) C. R. Hauser and W. H. Puterbaugh, *J. Amer. Chem. Soc.*, **75**, 4756 (1953).

(6) H. C. Brown, H. I. Schlesinger, and S. Z. Cardon, *ibid.*, **64**, 325 (1942).

(7) J. B. Conant and N. M. Bigelow, *ibid.*, **50**, 2041 (1928).

(8) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Org. Chem.*, **29**, 722 (1964).

TABLE II

INFRARED AND ANALYTICAL DATA OF NEW β-HYDROXYAMIDES

Adduct	Ir, cm^{-1}	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2b	3350, 3160, 1690, 750, 700	79.73	6.39	4.27	79.81	6.28	4.33
3	3450, 3380, 3180, 1675, 740, 730, 690	79.98	5.43	4.44	79.55	5.51	4.40
4a	3350, 3180, 1630, 730, 700	72.07	8.21	6.00	72.24	8.18	5.91
4b	3480, 3280, 1630, 730, 690	72.84	8.56	5.66	73.01	8.68	5.61
4c	3350, 3190, 1660 750, 690	77.64	7.49	4.53	77.57	7.61	4.69
5a	3440, 3180, 1675 770, 730	71.20	7.82	6.39	70.88	8.02	6.40
5c	3460, 3230, 1660, 740, 690	77.26	7.17	4.74	77.42	7.31	4.71

Experimental Section[9]

Addition Reactions of Arylacetamides with Carbonyl Compounds.—In Table I are summarized the results of the condensation reactions of arylacetamides with various ketones and benzaldehyde. General procedures are described below.

I. **Alkali Amides in Liquid Ammonia (Method A).**—To a stirred suspension of 0.11 mol of alkali amide in 300 ml of commercial anhydrous liquid ammonia[10] was added 0.05 mol of the solid arylacetamide. After 15 min for sodium amide and 30 min for lithium amide, the reaction mixture was assumed to contain 0.05 mol of the corresponding dialkali arylacetamide. Such salts were then treated during 5 min with a solution of 0.05 mol of the appropriate ketone or benzaldehyde in 50 ml of ether. After 5 min, the resulting suspension was poured into 200 ml of ammonia containing excess ammonium chloride (inverse neutralization), and the ammonia was allowed to evaporate. The solid residue remaining was hydrolyzed by 100 ml of 3 *N* hydrochloric acid, and the products were extracted by three 50-ml portions of ether. Drying ($CaSO_4$ or $MgSO_4$) and concentration afforded the crude product which was recrystallized from a suitable solvent.

II. ***n*-Butyllithium in Inert Solvents (Method B).**—To 0.05 mol of the arylacetamide in 62.5–69 ml of anhydrous THF or ether at an appropriate temperature under nitrogen was added, during 3–5 min, 62.5–69 ml (0.10–0.11 mol) of 1.6 *M* *n*-butyllithium in hexane.[11] After 5–30 min, the resulting mixture was treated during 5–10 min with a solution of 0.05 mol of the carbonyl compound in 50 ml of THF or ether. After 15 min more, the mixture was poured into ice water–hydrochloric acid. Work-up, isolation, and purification of products were then accomplished as described above.

Benzylation of Disodiophenylacetamide–Cyclohexanone Reaction Mixture.—Cyclohexanone (4.9 g, 0.05 mol) was condensed with disodio salt 1″a as described in I, except that after 5 min, the reaction mixture was treated with 6.33 g (0.05 mol) of benzyl chloride instead of effecting the inverse neutralization. After 45 min, the resulting solution was poured into ammonia containing excess ammonium chloride, and the ammonia was allowed to evaporate as it was replaced by ether. The ethereal solution was concentrated, and the crude product was analyzed by vpc; the major product exhibited the same retention time as an authentic sample of 2-benzylcyclohexanone. Distillation of a portion of the crude product afforded pure 2-benzylcyclohexanone, bp 164–166° (17 mm) [lit.[12] bp 162–165° (17 mm)].

Dehydration of β-Hydroxyamide 2b.—Solid adduct 2b (1.0 g) was added in small portions to 20 ml of magnetically stirred concentrated sulfuric acid maintained at 0°. After most of the solid had dissolved, the reaction mixture was poured into 60 g of ice water, and the resulting yellow solid was extracted into 200 ml of ether. The combined extracts were washed with water, then

(9) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer as potassium bromide disks. Vapor phase chromatograms were obtained on a F & M Model 500 Chromatograph using a 5-ft silicon oil column. Analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and Triangle Chemical Laboratories, Chapel Hill, N. C.

(10) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(11) Supplied by the Foote Mineral Co., Exton, Pa.

(12) A. Tiffeneau and M. Porcher, *Bull. Soc. Chim. Fr.*, **31**, 329 (1922).

with saturated aqueous sodium bicarbonate. After drying ($CaSO_4$) and concentrating, the resulting crude product was recrystallized from 95% ethanol to afford 0.6 g (65%) of N-methyl-2,3,3-triphenylpropenamide hemihydrate (**8**): mp 172.5-174°; ir 3250 (NH), 1620 (C=O), 770 (C=C), and 685 (ArH).

Anal. Calcd for $C_{44}H_{40}N_2O_3$: C, 81.96; H, 6.25; N, 4.34. Found: C, 82.32; H, 6.55; N, 4.27.

Dehydration of β-Hydroxyamide 3.—Solid adduct **3** (2.0 g) was added in small portions to 45.6 g of polyphosphoric acid maintained at a sufficiently high temperature to allow magnetic stirring. After 5 min, the brown-green solution was treated with 50 g of ice, and the cold solution was extracted several times with a total of 400 ml of ether. After work-up as in the dehydration of adduct **2b**, the resulting residue was recrystallized from benzene to give 1.47 g (80%) of 2-(9-fluorenyl)-2-phenylacetamide (**9**), mp 229–231°.

Anal. Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.09; N, 4.71. Found: C, 84.52; H, 5.25; N, 4.48.

Registry No.—*n*-Butyllithium, 109-72-8; **2b**, 2683-62-7; **3**, 17510-68-8; **4a**, 17510-69-9; **4b**, 17510-70-2; **4c**, 17510-71-3; **5a**, 17510-72-4; **5c**, 17510-73-5; N-methyl-2,3,3-triphenylpropenamide, 2683-63-8; **9**, 17510-75-7.

Metalation at Methyl Group of N-Substituted o-Toluenesulfonamides by Excess *n*-Butyllithium. Condensation with Benzophenone[1]

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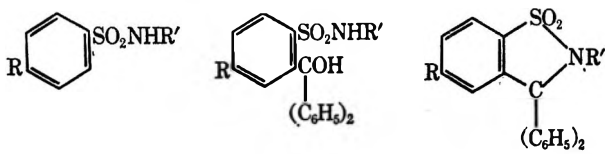
Received May 20, 1968

N-Substituted benzenesulfonamides **1** (R = H; R′ = CH_3 or C_6H_5) and also *p*-toluenesulfonanilide (**1**, R = CH_3; R′ = C_6H_5) have previously[2] been shown to undergo *ortho* metalation, as well as N metalation, with excess *n*-butyllithium, as evidenced by condensations of the resulting dilithiosulfonamides with benzophenone to form *ortho* derivatives **2**; these products underwent thermal cyclodehydration to give the sultams **3**.

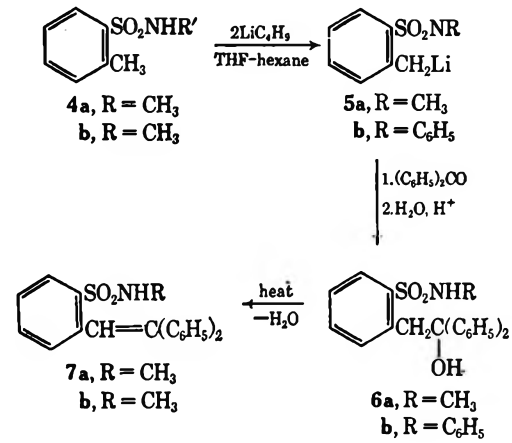


1 **2** **3**

N-Substituted *o*-toluenesulfonamides **4a**, **b** have now been found to undergo metalation at the methyl group, as well as N metalation, with excess *n*-butyllithium to form dilithiosulfonamides **5a**, **b**, as evidenced by condensation with benzophenone to give carbinol sulfonamides **6a**, **b**; these products underwent thermal dehydration to afford unsaturated sulfonamides **7a** and **b**, respectively (Scheme I).

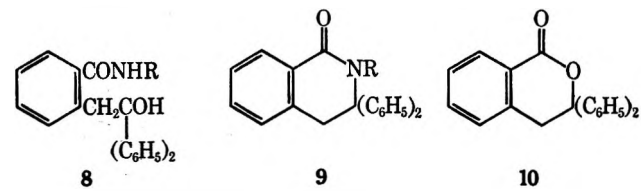
The carbinol sulfonamides **6a**, **b** and their dehydration products **7a**, **b** were obtained in high yields (73–96%). Their structures were supported by analyses and absorption spectra. Surprisingly, carbinol sulfonamide **6b** appeared to undergo a change in structure on standing at room temperature, especially in the presence of polyphosphoric acid, as evidenced by a change in the nmr spectrum. That the second structure was still essentially carbinol sulfonamide **6b** was supported, not only by analysis and absorption spectra, but also by dehydration to form the unsaturated sulfonamide **7b** (see Experimental Section).

SCHEME I



The difference in the courses of metalation of the *o*- and *p*-toluenesulfonamides appears to be due to initial coordination of the lithium of the *n*-butyllithium with the nitrogen of the monolithio intermediate to form a complex in which the potential *n*-butyl carbanion is directed to a methyl hydrogen in the 2-methyl compounds **4a**, **b** but to an *ortho* hydrogen in the 4-methyl compound **1** (R = CH_3; R′ = C_6H_5). Thus, although a nucleophilic mechanism probably operates to form a weaker base in both cases, the lithium cation also plays an important role especially in the latter case where an *ortho* hydrogen rather than the probably more acidic 4-methyl hydrogen is ionized.[3]

The difference in the courses of thermal dehydration of the benzophenone adducts of the *o*- and *p*-toluenesulfonamides is evidently due to the presence of methylene hydrogen β to the hydroxyl group in the former compounds, but not in the latter. Thus, whereas the carbinol sulfonamides **2** can undergo only cyclodehydration, the carbinol sulfonamides **6a**, **b** can, and do, exhibit linear dehydration involving their methylene hydrogen. Although **6a**, **b** also underwent linear dehydration with acid catalysts in refluxing acetic acid or benzene, they might possibly exhibit cyclodehydration with acids at lower temperatures since the corresponding carbinol carboxamides **8**, which have methylene hydrogen, have recently been observed to undergo cyclodehydration with cold sulfuric acid to form **9**.[4] Unfortunately, cold sulfuric acid has now been found



8 **9** **10**

(1) Supported by Army Research Office (Durham).

(2) H. Watanabe, R. L. Gay, and C. R. Hauser, *J. Org. Chem.*, **33**, 900 (1968).

(3) See K. P. Klein and C. R. Hauser, *ibid.*, **32**, 1479 (1967); also see A. A. Morton, "Solid Organoalkali Reagents," Gordon and Breach, Inc., New York, N. Y., 1964.

(4) I. T. Barnish, C. L. Mao, and C. R. Hauser, *Chem. Commun.*, 564 (1968).

to convert carbinol sulfonamides **6a, b** into water-soluble products under similar conditions.

Incidentally, the courses of the thermal reactions of carbinol sulfonamides **6a, b** and **2** differ, not only from each other, but also from that of carbinol carboxamides **8** which undergo thermal deamination to form lactone **10**.[5]

Experimental Section[6]

Metalations of 4a, b with *n*-Butyllithium to Form Dilithiosulfonamides 5a, b.—A solution of 0.020 mol of N-methyl- or N-phenyl-o-toluenesulfonamides (**4a** and **4b**, respectively) in 70 ml of tetrahydrofuran[7] in a dry flask under nitrogen was cooled to 0°, and 30 ml of (0.046 mol) of a solution of 1.6 *M* *n*-butyllithium in hexane[8] was added during 4–5 min. After stirring for 30 min at 0°, the clear, deep orange solution from **4a** and the clear, dark red solution from **4b** were considered to contain 0.020 mol of the dilithiosulfonamides **5a** and **5b**, respectively. These solutions were employed at 0° described below.

Condensations of Dilithiosulfonamides with Benzophenone to Form Carbinol Sulfonamides. A. Condensation of 5a to Form 6a.—To the stirred, cold solution of dilithiosulfonamide **5a** was added under nitrogen with stirring, during 4–5 min, a solution of 4.74 g (0.026 mol) of benzophenone in 30 ml of tetrahydrofuran,[7] and the stirring continued for 1 hr at 0°. To the resulting clear, yellow solution (at 0°) was added with stirring 30 ml of distilled water and then 35–40 ml of 5% hydrochloric acid. The two layers were separated. After saturation with sodium chloride, the aqueous layer was extracted three times with ether, and the extracts were combined with the organic layer. After washing twice with a saturated solution (30 ml) of sodium chloride and drying ($MgSO_4$), the solvent was removed under reduced pressure on the steam bath to give a slightly yellow, viscous liquid, which was stirred with a little methanol and then left to stand in a current of air under a hood for a few hours. The resulting crystals were collected, washed with a little cold methanol, and dried in air; more crystals were recovered from the filtrate to which the washings had been added. The combined crystals were recrystallized from methanol, giving 6.64 g (91%) of carbinol sulfonamide **6a** (prismatic crystals): mp 161–163°, and mp 163.5–164.5° after further recrystallization; ir 3495 (OH), 3315 (NH), 1295 (SO_2), 1145 (SO_2), 840, 780, 756, 740, and 695 cm^{-1}; nmr (acetone-d_6) δ 8.13–6.26 (m, 15.40, aromatic H and OH or NH), 5.04 (s, 0.7, NH or OH), 4.20 (s, 1.8, CH_2), and 2.55 ppm (d, 2.8, J = 5.3 cps, N–CH_3).

Anal. Calcd for $C_{21}H_{21}NSO_3$: C, 68.64; H, 5.76; N, 3.81. Found: C, 69.00; H, 5.51; N, 3.64.

B. Condensation of 5b to Form 6b.—This condensation was effected essentially as described above under A to give a clear, yellow-orange solution which, on work-up, afforded 7.06 g (82%) of carbinol sulfonamide **6b**, mp 149–151.5°. Recrystallization from methanol gave 5.73 g (67%) (large prismatic crystals, sample A): mp 152–153°; ir 3500, 3400 and 3265 (OH, broad), 3160 (NH), 1312 and/or 1290 (SO_2), 1150 and/or 1140 (SO_2), 934, 778, 757, 740, 690 cm^{-1}; nmr (acetone-d_6) δ 9.27 (s, 0.9, OH or NH), 8.67–6.42 (m, 19.4, aromatic H), 5.05 (s, 0.9, NH or OH), 4.21 ppm (s, 2.0, CH_2). After standing at room temperature for 3 months, the ir spectrum was unchanged; the nmr spectrum (acetone-d_6) showed δ 7.50–6.00 (m, 20.4, aromatic H and OH), 4.56 (broad, NH), and 3.73 ppm (s, 1.8, CH_2).

Anal. Calcd for $C_{26}H_{23}NSO_3$: C, 72.70; H, 5.40; N, 3.26. Found: C, 72.81; H, 5.24; N, 3.17.

A 1-g sample of this compound was mixed well with 40 g of polyphosphoric acid. After standing at room temperature (25–30°) for 24 hr the mixture was poured, with stirring, onto 100 g of ice–water. The resulting solid was collected and recrystallized from methanol to give 0.96 g of recovered carbinol sulfonamide **6b** (fine crystals, sample B): mp 156–157.5°; with sample A, mmp 156–157°; ir 3500 (OH), 3265 (NH), 1315 and/or 1285 (SO_2), 1150 (SO_2), 918, 777, 753, 740, and 696 cm^{-1}; nmr (acetone-d_6) δ 8.00–6.33 (m, 21.4, aromatic H, OH and NH), and 4.17 ppm (s, 1.9, CH_2); nmr ($CDCl_3$) δ 8.03–6.80 (m, 18.7, aromatic H), 6.27 (broad, 0.9, NH), 4.05 (s, 2.2 CH_2), and 3.35 ppm (s, 1.0, OH). After standing at room temperature for 6 months, the ir spectrum was unchanged; the nmr spectrum (acetone-d_6) showed δ 7.50–6.00 (m, 20.0, aromatic H and OH), 4.50 (broad 0.6, NH), and 3.73 ppm (s, 2.1, CH_2).

Anal. Calcd for $C_{26}H_{23}NSO_3$: C, 72.70; H, 5.40; N, 3.26. Found: C, 72.90; H, 4.97; N, 3.15.

Dehydration of Carbinol Sulfonamides to Form o-Sulfamyltriphenyl ethylenes. A. Thermal Method.—A 1-g sample of carbinol sulfonamide **6a** was heated under a slow stream of nitrogen in a round-bottomed flask on a Wood's metal bath (220–230°) for 5 hr. The flask was removed from the bath, and the molten mass was allowed to come to room temperature. The resulting solid was recrystallized from methanol to give 0.77 g (81%) of **7a** (fine prismatic crystals): mp 107.5–109.5°; ir 3300 (NH), 1315 (SO_2), 1155 (SO_2), 843, 777, 764, 759, 744, and 695 cm^{-1}; nmr ($CDCl_3$) δ 8.17–6.88 (m, 14.2, aromatic H), 7.57 (s, 1.0, vinyl H), 4.53 (broad, 0.7, NH), and 2.57 ppm (d, 2.6, J = 5.1 cps, N–CH_3).

Anal. Calcd for $C_{21}H_{19}NSO_2$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.38; H, 5.37; N, 3.89.

Similarly, a 1-g sample of carbinol sulfonamide **6b** (sample A) was dehydrated at 235–245°. The resulting mass was recrystallized from methanol to give 0.92 g (96%) of **7b** (fine needles): mp 128.5–130°; ir 3240 (NH), 1315 (SO_2), 1150 (SO_2), 920, 829, 779, 757, 751, 738, 725, and 690 cm^{-1}; nmr ($CDCl_3$) δ 8.28–7.65 and 7.45–6.50 (m, 20.0, aromatic H and NH) and 7.25 ppm (s, 0.7, vinyl H).

Anal. Calcd for $C_{26}H_{21}NSO_2$: C, 75.88; H, 5.14; N, 3.40. Found: C, 75.76; H, 5.27; N, 3.45.

B. Acetic–Sulfuric Acid Method.—A solution of a 1-g sample of carbinol sulfonamide **6a** in 30 ml of glacial acetic acid containing 0.015 ml of concentrated sulfuric acid was refluxed for 24 hr and then cooled to room temperature. The clear, colorless solution was poured onto 100 ml of ice–water. The mixture was made basic with sodium carbonate. The resulting white solid was collected and dissolved in hot methanol. After separation of insoluble material (0.14 g), the filtrate was evaporated to give 0.69 g (73%) of **7a** (fine prismatic crystals): mp 106.5–108°; mixture melting point with **7a** obtained under A, 106–108°; the ir spectra of the two samples were identical.

C. *p*-Toluenesulfonic Acid Method.—A solution of 0.60 g of carbinol sulfonamide **6b** (sample B) in 30 ml of benzene containing 0.03 g of *p*-toluenesulfonic acid (hydrate) was refluxed for 10 hr, during which a Dean–Stark water trap was used to remove water as an azeotrope of benzene–water. The hot, colorless, clear solution was allowed to evaporate in a current of air under a hood. The resulting sticky liquid was scratched to solidify. The solid was washed with dilute sodium carbonate solution and water, and then recrystallized from methanol to give 0.56 g (89%) of **7b** (fine needles): mp 128.5–130°; mixture melting point with **7b** obtained under A, 128.5–130°; ir spectra of the two samples were identical.

Registry No.—*n*-Butyllithium, 109-72-8; benzophenone, 119-61-9; **6a**, 17510-55-3; **6b**, 17510-56-4; **7a**, 17510-57-5; **7b**, 17510-58-6.

(5) R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, **29**, 3514 (1964).

(6) Melting points are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Ir spectra (KBr method) were produced on Perkin-Elmer Infracord Model 137 and Model 237. Nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane (δ 0 ppm) as an internal standard.

(7) Freshly distilled from lithium aluminum hydride.

(8) Foote Mineral Co., Exton, Pa.

Fluorination of Methyl Isobutyrate with Perchloryl Fluoride[1]

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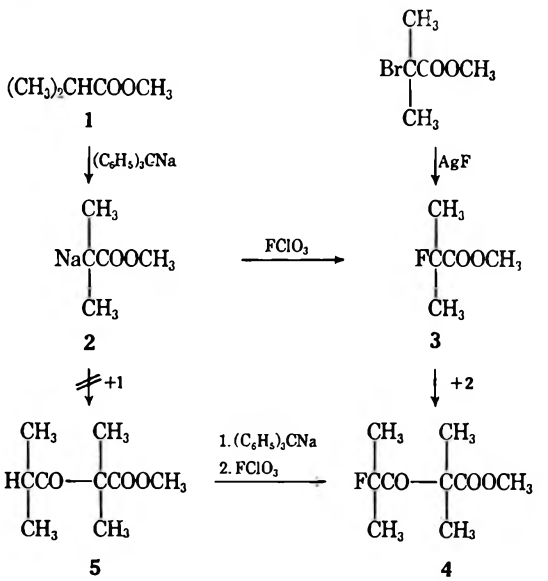
Enolates react with perchloryl fluoride to give α-fluoro carbonyl derivatives. This kind of fluorination

(1) This work has been supported by National Cancer Institute through Research Grants CA 02891 and CA 10529.

generally makes use of 1,3-dicarbonyl compounds, so that the position undergoing substitution is activated by two groups.[2] We wish to report evidence for fluorination at a position activated by only a single carbonyl group.

When perchloryl fluoride was bubbled into an ethereal solution of the sodioenolate 2 of methyl isobutyrate, methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4)



was isolated as the only pure product. The assigned structure of 4 is consistent with the presence of two carbonyl absorption maxima in its infrared absorption spectrum and of three kinds of proton signals in its nmr spectrum. Product 4 could arise either from condensation of the first-formed fluorination product 3 with a second mole of sodio derivative 2, or it could arise by fluorination of the Claisen condensation product 5 from methyl isobutyrate. The fact that methyl α-fluoroisobutyrate (3)[3] condensed smoothly with methyl sodioisobutyrate (2) to give methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4) makes the 2 → 3 → 4 sequence admissable in the perchloryl fluoride action. Fluorination of the sodio derivative of methyl 3-oxo-2,2,4-trimethylpentanoate (5)[4] also gave methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4), so that on this basis the alternate 2 → 5 → 4 sequence could not be excluded. However, failure to isolate Claisen product 5 from reactions designed to furnish 5 suggested that it could not be an intermediate and thereby speaks against the latter sequence.

Whether fluorinations on singly activated positions will be successful only with tertiary H's as in methyl isobutyrate (1) or methyl 3-oxo-2,2,4-trimethylpentanoate (5) remains to be seen.

Experimental Section

General.—Boiling points are uncorrected. Ultraviolet spectra were taken with a Beckman DK spectrophotometer; infrared spectra were taken with Perkin-Elmer Infracords. Nmr spectra were determined on a Varian 60-MHZ instrument;[5] the chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Gas–liquid partition chromatographic analysis made use of an ionization detector and a column with diethylene glycol succinate or neopentyl glycol succinate as stationary phases. Analyses for elements were reported by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Galbraith Laboratories, Inc., Knoxville, Tenn.

Methyl 4-Fluoro-3-oxo-2,2,4-trimethylpentanoate (4) from the Sodio Derivative 2 of Methyl Isobutyrate and Perchloryl Fluoride.—Methyl isobutyrate (1, 0.89 g or 8.7 mmol) was added to 8 mmol of triphenylmethylsodium[6] as a 0.13 *M* solution in ether at 0°. Enough additional triphenylmethylsodium was introduced to produce a persistent red color (total reagent, 9.0 mmol). Perchloryl fluoride[7] was passed through a tube packed with anhydrous calcium sulfate and then into the cold reaction mixture. The gas flow was adjusted to be rapid at first and then slow. The red color disappeared within 1 min; a precipitate was evident after 5 min. After 20 min, a drop of the mixture on wet pH paper showed pH 5. Dry nitrogen was then bubbled through the solution for about 20 min to remove excess perchloryl fluoride. The solids were separated and washed with ether. The combined ether filtrate and washings were concentrated, and the residue was distilled to give 0.25 g (30%) of water-white methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4), bp 80° (15 mm). This product was homogeneous to the extent of 97% according to glpc.

Anal. Calcd for $C_9H_{15}FO_3$: C, 56.83; H, 7.95; F, 9.99. Found: C, 57.01; H, 8.01; F, 10.17.

As a 2.5×10^{-3} *M* solution in absolute ethanol, the product 4 showed λ_{max} 214 mμ (ε 420) and 273.5 (104). The ir absorption spectrum taken with neat material showed carbonyl peaks at 1720 (ketone) and 1760 cm^{-1} (ester) but no hydroxyl or carboxyl absorption above 3000 cm^{-1}. The liquid tended to become yellow on standing.

Methyl α-Fluoroisobutyrate (3).—Methyl α-bromoisobutyrate, bp 31–32° (0.4 mm),[8] was obtained in 80% yield by allowing a solution of α-bromoisobutyryl bromide in anhydrous methanol to stand for 5 hr. The nmr spectrum of the bromo ester in deuteriochloroform showed peaks at 1.89 [6 H, s, $BrC(CH_3)_2$] and 3.71 ppm (3 H, s, OCH_3). A stirred mixture of bromo ester (21.0 g or 0.116 mol) and dry powdered silver fluoride (30.0 g or 0.236 mol; gray, used as received) was held for 3 hr in a bath at 140–145° under a reflux condenser. The cooled reaction mixture, diluted with 30 ml of ether, was filtered, and the solids were washed with ether. The ether solutions were washed with water, dried, and passed through an 80-g column of silica gel. Another 25 ml of ether was passed through the column. After removal of solvent from the combined ether solutions, fractionation of the residue through a 16-in. spinning-band column gave 2.8 g (20%) of methyl α-fluoroisobutyrate (3), bp 43–45° (75 mm), and 2.0 g of liquid, bp 35–39° (1 mm), identical with methyl α-bromoisobutyrate according to glpc and ir absorption comparisons.

The desired methyl α-fluoroisobutyrate (3) showed ir absorption peaks at 1753 (carbonyl) and 1145 cm^{-1} (C–F). In deuteriochloroform, the material gave nmr signals at 1.52 (6 H, d, J = 21.5 Hz, CH_3 groups) and 3.70 ppm (3 H, s, OCH_3).

Anal. Calcd for $C_5H_9FO_2$: C, 50.00; H, 7.49; F, 15.83. Found: C, 50.30; H, 7.68; F, 16.10.

(2) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling, and F. L. Scott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling, E. A. Tyczkowski, *J. Amer. Chem. Soc.*, **80**, 6533 (1958); H. M. Kissman, A. M. Small, M. J. Weiss, *ibid.*, **82**, 2312 (1960); H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 973 (1966); A. H. Nathan, J. C. Babcock, and J. A. Hogg, *ibid.*, **24**, 1395 (1959); A. H. Nathan, B. J. Magerlein, and J. A. Hogg, *ibid.*, **24**, 1517 (1959); S. A. Fuqua and R. M. Silverstein, *ibid.*, **29**, 395 (1964); J. Edwards and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 5262 (1959); A. S. Kende, *Tetrahedron Lett.*, No. 14, 13 (1959); C. H. Robinson, N. F. Bruce, E. P. Oliveto, S. Tolksdorf, M. Steinberg, and P. L. Perlman, *J. Amer. Chem. Soc.*, **82**, 5256 (1960); and S. Nakanishi, K. Morita, E. V. Jensen, *ibid.*, **81**, 5259 (1959). The last article has an example of an attack on an α position activated by one carbonyl and two fluorine groups. If the carbonyl compound is a ketone, α fluorination may be effected indirectly *via* the enamine, the enol ether, or the enol acetate. [*Cf.* J. W. Chamberlin, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p 164.]

(3) *Cf.* B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 1773 (1948).

(4) *Cf.* R. Levine and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1768 (1944).

(5) We wish to acknowledge the help of National Science Foundation in providing funds for the purchase of a Varian A-60 nmr spectrometer (Research Equipment Grant GP 3618).

(6) W. B. Renfrow, Jr., and C. R. Hauser, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 607.

(7) The information on perchloryl fluoride provided by the manufacturer, Pennsalt Chemicals Corp., Philadelphia, Pa., in its booklet DC-1819 should be carefully noted.

(8) *Cf.*, C. C. Price and E. C. Coyner, *J. Amer. Chem. Soc.*, **62**, 1306 (1940).

An earlier preparation according to this method[3] gave impure fluoro ester, bp 24–30° (24 mm), in unspecified yield.

Methyl 4-Fluoro-3-oxo-2,2,4-trimethylpentanoate (4) from the Claisen Condensation of Methyl Sodioisobutyrate (2) and Methyl α-Fluoroisobutyrate (3).—Ethereal triphenylmethylsodium (100 ml, 9.7 mmol) was added slowly and with stirring to 0.80 g (7.8 mmol) of methyl isobutyrate (1) freshly distilled from calcium hydride. A stream of pure nitrogen was passed through the flask before and during the reaction. The red color was quickly discharged; only at the end of the addition did a persistent (15 min) red develop. To this enolate (2) solution, 0.90 g (7.5 mmol) of methyl α-fluoroisobutyrate (3) was added over a period of 5 min, and the mixtue was stirred at room temperature for 24 hr. A solution of acetic acid (1 ml) plus water (15 ml) was added; the aqueous layer was discarded; and the ether layer was first shaken with 10% aqueous sodium carbonate solution and then dried. Removal of solvent left a residue which on distillation afforded 0.73 g (51%) of water-white methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4), bp 77–79° (14 mm). The ir absorption curve for this material and that for the same material described above, both taken with neat liquids, were identical. The condensation product dissolved in deuteriochloroform showed nmr signals at 1.35 (6 H, s, 2,2-dimethyl), 1.48 [6 H, d, J = 21.5 Hz, $FC(CH_3)_2$], and 3.67 ppm (3 H, s, OCH_3).

Attempted Self-Condensation of Methyl Isobutyrate (1) with Methyl 3-Oxo-2,2,4-trimethylpentanoate (5). A. With Sodium Hydride.—A mixture of dry, freshly distilled methyl isobutyrate (46.3 g or 0.45 mol) and commercial sodium hydride (5.84 g or 0.24 mol) was boiled in an atmosphere of nitrogen for 4 hr. Hydrogen was evolved during the early stages of the reaction. The cooled mixture was poured over a mixture of concentrated sulfuric acid (20 ml) and crushed ice (100 g). The mixture was extracted with ether, and the ether solution was washed free of acid, dried, and warmed to remove solvent. Fractional distillation afforded 16 ml of unchanged starting material followed by about 11 ml of liquid, bp 80–110° (110–120 mm). Glpc revealed the presence of eight components. This product was not examined more closely.

B. **With Triphenylmethylsodium.**—Methyl isobutyrate (0.80 g or 7.8 mmol) was converted into its sodio derivative 2 exactly as described above in the condensation with methyl α-fluoroisobutyrate. Then, instead of the fluoro ester, 0.80 g of methyl isobutyrate (1) was added. The same treatment as before produced 1.3 g (81%) of unchanged starting material, bp 85–89°. The ir and the nmr spectra of the recovered material were the same as those from pure methyl isobutyrate.[9]

Other attempts at forming methyl 3-oxo-2,2,4-trimethylpentanoate (5) by Claisen condensation of methyl isobutyrate also failed.

Methyl 3-Oxo-2,2,4-trimethylpentanoate (5).—Diisopropyl ketone (10 ml of 0.091 mol) that had been distilled from calcium hydride was treated with 555 ml of a 0.138 M ethereal solution of triphenylmethylsodium (0.076 mol) until the red color persisted. The solution was poured over 50 g of solid carbon dioxode. The ether layer, rinsed with water and dried, was treated with excess ethereal diazomethane. Removal of solvent followed by two distillations of the residue gave 7.3 g (47%) of methyl 3-oxo-2,2,4-trimethylpentanoate (5), bp 93–94° (25 mm). By glpc this material contained less than 2% impurities.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 63.08; H, 9.35.

The neat liquid showed ir absorption peaks at 1720 and 1748 cm^{-1}.

Levine and Hauser, who employed the same method, but with sodium amide in place of triphenylmethylsodium, reported bp 93° (27 mm).[4]

Perchloryl Fluoride Fluorination of Methyl 3-Oxo-2,2,4-trimethyl pentanoate (5).—Methyl 3-oxo-2,2,4-trimethylpentanoate (5, 7.0 ml of 0.039 mol) was added in an atmosphere of nitrogen to 350 ml of a 0.10 M ethereal solution of triphenylmethylsodium (0.035 mol). The red color persisted for 10 min. An additional quantity of reagent was admitted (0.004 mol), and the mixture was allowed to stand for 30 min. Dry perchloryl fluoride was then bubbled through the orange solution. After 45 min, a drop of the reaction mixture in contact with water showed pH 5. Further treatment similar to that in the fluorination starting with methyl isobutyrate afforded 1.5 ml of distillate, bp 71° (6 mm), which by glpc contained at least 70% of methyl 4-fluoro-3-oxo-2,2,4-trimethylpentanoate (4). The fluorine content of the mixture was low (7.84 instead of 9.99%) and the carbon content was high (58.76 instead of 56.83%). The ir absorption curve of this material was practically identical with that obtained before for 4.

Registry No.—1, 547-63-7; 3, 338-76-1; 4, 17555-86-1; 5, 918-71-8; perchloryl fluoride, 7616-94-6.

(9) Interestingly, Claisen condensation does occur when *ethyl* isobutyrate is treated with triphenylmethylsodium. *Cf.* C. R. Hauser and W. B. Renfrow, Jr., *ibid.*, **59**, 1824 (1937). Also *cf.* M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950).

Cyclization and Rearrangement of Substituted Glyoxal Aldoxime Semicarbazones to 6-Substituted *as*-Triazine-3,5(2H,4H)-diones

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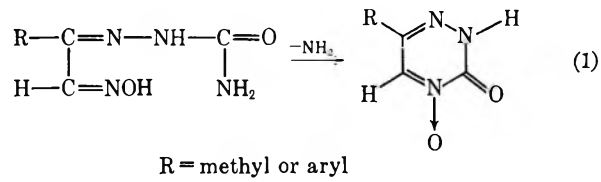
Cyclization of benzil monoxime guanylhydrazone nitrate to 2-imino-5,6-diphenyl-*as*-triazine 4-oxide, according to Scott and Reilly,[1] and the synthesis of 2-aminopyrazine 1-oxides by condensation of aminonitriles with substituted glyoxal aldoximes[2] are examples of the preparation of N-oxides from hydroximino compounds.

As a result of our attempts to prepare *as*-triazine derivatives (azapyrimidines) of pharmacological interest, it has been found that pyruvaldehyde aldoxime semicarbazone and arylglyoxal aldoxime semicarbazones undergo cyclization with loss of ammonia in boiling aqueous alkaline solutions.

From simple structural considerations the expected product would be 6-methyl- (or aryl-) *as*-triazine-3(2H)-one 4-oxide according to eq 1.



(1)

R = methyl or aryl

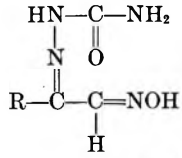
Physical properties and chemical reactions showed, however, that the compounds obtained are in fact the *as*-triazine-3,5(2H,4H)-diones identical with samples prepared by other methods.[3–5] Small amounts of nitriles (5–10%) and acids (10–20%) related to the starting materials were found as by-product. Thus benzonitrile was separated by steam distillation of the reaction mixture, and benzoic acid was extracted from the crude 6-phenyl-*as*-triazine-3,5(2H,4H)-dione.

(1) F. L. Scott and J. Reilly, *Chem. Ind.* (London), 907 (1952).
(2) W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951).
(3) J. Thiele and J. Bailey, *Ann.*, **303**, 75 (1898).
(4) S. Rossi, *Gazz. Chim. Ital.*, **83**, 133 (1953).
(5) J. Bougault, *Compt. Rend.*, **159**, 83 (1914).

TABLE I
PHENYLGLOXAL ALDOXIMES

Formula	No.	% yield	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
p-$FC_6H_4C(=O)CH=NOH$	1	60	128	57.48	57.12	3.59	3.66	8.38	8.18
p-$CH_3OC_6H_4C(=O)CH=NOH$	2	65	118	60.33	60.44	5.02	4.97	7.82	8.18
p-$CH_3C_6H_4C(=O)CH=NOH$	3	68	142	55.38	55.80	4.61	4.57	7.17	7.23

TABLE II
PHENYLGLYOXAL ALDOXIME SEMICARBAZONES



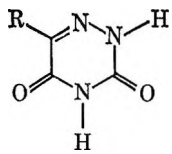
R	No.	% yield	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
p-FC_6H_4	1	95	181	$C_9H_9FN_4O_2$	48.21	48.36	4.01	3.91	25.00	25.25
p-ClC_6H_4	2	88	192	$C_9H_9ClN_4O_2$	44.90	45.11	3.73	3.63	23.28	23.41
p-BrC_6H_4	3	93	186	$C_9H_9BrN_4O_2$	42.18	42.25	3.15	3.20	19.64	19.92
p-$CH_3C_6H_4$	4	89	186	$C_{10}H_{12}N_4O_2$	54.54	54.60	5.45	5.41	25.45	25.19
p-$CH_3OC_6H_4$	5	85	180	$C_{10}H_{12}N_4O_3$	50.84	50.71	5.08	5.06	23.72	23.69
p-$CH_3SC_6H_4$	6	93	190	$C_{10}H_{12}N_4O_2S$	47.61	47.32	4.76	4.71	22.22	22.09
p-$NO_2C_6H_4$	7	86	223	$C_9H_9N_5O_4$	43.02	42.95	3.56	3.66	27.88	27.61

TABLE III
6-ARYL-*as*-TRIAZINE-3,5(2H,4H)-DIONES[a]

Aryl	No.	% yield	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
p-FC_6H_4	1	55	291	$C_9H_6FN_3O_2$	52.17	52.80	2.89	3.01	20.28	19.90
p-ClC_6H_4	2	48	279	$C_9H_6ClN_3O_2$	48.32	48.08	2.68	2.90	18.79	19.01
p-BrC_6H_4	3	45	298	$C_9H_6BrN_3O_2$	40.29	41.01	2.23	2.26	15.67	15.82
p-$CH_3C_6H_4$	4	67	275	$C_{10}H_9N_3O_2$	59.11	60.02	4.43	4.62	20.68	21.05
p-$OCH_3OC_6H_4$	5	54	273	$C_{10}H_9N_3O_3$	54.79	54.80	4.10	4.21	19.17	19.19
p-$CH_3SC_6H_4$	6	64	283	$C_{10}H_9N_3O_2S$	51.06	51.12	3.82	3.91	17.87	17.98
p-$NO_2C_6H_4$	7	65	293	$C_9H_6N_4O_4$	46.15	46.20	2.56	2.55	23.93	23.63

[a] All *as*-triazine derivatives prepared were subjected to infrared spectroscopy and show broad absorption in the region of 3–3.5 μ. C=O stretchings appear in the region of 5.75–5.95 μ as sharp strong doublets.

The reaction seems to be quite general. The following *as*-triazinediones have been prepared.



R = CH_3, C_6H_5, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *p*-$NO_2C_6H_4$

It seems probable that formation of 6-methyl- (or aryl-) *as*-triazine-3(2H)-one 4-oxide is the first step of this cyclization and the oxygen atom of the N-oxide is transposed to the neighboring carbon atom to form a more stable product. The Wallach rearrangement[6] of azoxybenzenes to *p*-hydroxyazobenzenes is one of the earliest examples of transposition of N-oxide oxygen to form a hydroxyl group.

It has been shown recently[7] that 3-amino-*as*-triazine, treated with hydrogen peroxide, in acetic acid, "specific reagent for preparation of amine oxides," afforded 3-amino-5-hydroxy-*as*-triazine. 3-Amino-5,-6-dimethyl-*as*-triazine, under the same conditions, was oxidized to 3-amino-5-hydroxy-6-methyl-*as*-triazine, as a minor product. 3-Amino-5,6-dimethyl-*as*-triazine N-oxide was the major product.

We have successfully repeated the former reaction. 3-Amino-5-hydroxy-*as*-triazine was diazotized and gave *as*-triazine-3,5(2H,4H)-dione (azauracil) in 70% yield. This compound was also prepared by cyclization of glyoxylic acid semicarbazone[5] for comparison studies.

Attempts to prepare 3-hydroxy-6-alkyl- (or aryl-) *as*-triazine with no substitution at the 5 position, for further oxidation, failed.

Experimental Section[8]

Substituted Glyoxal Aldoximes.—Commercially available pyruvaldehyde aldoxime was used after recrystallization from aqueous methanol.

(6) O. Wallach and L. Belli, *Ber.*, **13**, 525 (1880).

(7) T. Sazaki and K. Minamoto, *Chem. Pharm. Bull.* (Tokyo), **12**, 1329 (1964).

(8) Melting points are corrected and were determined on a Kofler hot table microscope. The infrared spectra were determined with a Leitz Model III spectrograph, using potassium bromide disks.

New phenylglyoxal aldoximes were prepared following procedures for the known compounds in this series.[9,10] The properties of the new phenylglyoxal aldoximes are described in Table I.

We have observed that in all cases different amounts of corresponding substituted benzoic acids appeared as by-products. The crude compounds were washed with an excess of 5% cold solution of sodium bicarbonate, which dissolved all free acid present. Analytical samples were prepared by recrystallization in diluted ethyl alcohol.

Substituted Glyoxal Aldoxime Semicarbazones.—Pyruvaldehyde aldoxime semicarbazone[11] and phenylglyoxal aldoxime semicarbazone[12] are known compounds. New phenylglyoxal aldoxime semicarbazones were prepared according to the Dey procedure[12] by interaction of corresponding phenylglyoxal aldoximes with equimolecular quantities of semicarbazide hydrochloride and sodium acetate dissolved in a minimum quantity of 50% ethyl alcohol at 50°. The solvent of recrystallization was also 50% ethyl alcohol. The physical data of semicarbazones obtained are summarized in Table II.

***as*-Triazine-3,5(2H,4H)-dione (Azauracil).**—3-Amino-5-hydroxy-*as*-triazine,[7] 2.25 g (0.02 mol) in 10 ml of concentrated hydrochloric acid and 10 ml of water, was treated with a concentrated solution of 1.5 g (0.022 mol) of sodium nitrite, below 5°. The solution was shaken occasionally during 3 hr standing at room temperature, after which pure azauracil crystallized out. A further quantity can be obtained by concentration of the mother liquor. The yield was 70%, mp 283° (water) (lit.[8] mp 272°). Mixture melting point with a specimen of the same compound prepared with a 15% yield by cyclization of glyoxylic acid semicarbazone[5] was not depressed.

6-Methyl-*as*-triazine-3,5(2H,4H)-dione (Azathymine).—A suspension of pyruvaldehyde aldoxime semicarbazone, 7.20 g (0.05 mol) in 40 ml of water, was refluxed for 20 hr with 7 g (0.05 mol) of anhydrous potassium carbonate. Ammonium bicarbonate accumulated in the refrigerator was removed each 3 hr by circulating water through it. Finally, the solution was charcoaled, acidified with hydrochloric acid, and evaporated until dry on a steam bath. The dry residue was extracted in a Soxhlet apparatus with ethyl acetate. The solvent was distilled off, and the residue was recrystallized in water to give 2.1 g (36%), mp 216° (lit.[13] mp 212°). The infrared spectrum of the compound obtained was identical with the spectrum of a specimen prepared by another method.[13]

6-Phenyl-*as*-triazine-3,5(2H,4H)-dione.—Phenylglyoxal aldoxime semicarbazone,[12] 2 g (0.01 mol) in 25 ml of water, was refluxed for 8 hr with 2.76 g (0.02 mol) of the anhydrous potassium carbonate. Ammonium bicarbonate accumulated in the course of reaction in the condenser was removed occasionally by washing the condenser. The solution was charcoaled and acidified with concentrated hydrochloric acid to give a white crystalline powder. The yield was 1.2 g (64%), mp 262° (from diluted alcohol) (lit.[5] mp 262°).

When the same reaction was conducted with sodium bicarbonate instead of potassium carbonate a 25% yield was obtained.

Substituted 6-phenyl-*as*-triazine-3,5(2H,4H)-diones were prepared by cyclization of the corresponding phenylglyoxal aldoxime semicarbazones according to the above method. The properties of the compounds obtained are summarized in Table III.

Registry No.—Table I—1, 17628-74-9; 2, 1823-76-3; 3, 17628-76-1; Table II—1, 17628-77-2; 2, 17628-78-3; 3, 17628-79-4; 4, 17628-80-7; 5, 17628-81-8; 6, 17628-82-9; 7, 17628-83-0; Table III—1, 17629-10-6; 2, 17629-11-7; 3, 17629-12-8; 4, 17629-16-2; 5, 17629-17-3; 6, 17629-18-4; 7, 17629-19-5.

Acknowledgment.—The author wishes to thank Professor N. Sharghi for his constant encouragement and the Central Treaty Organization for provision of essential materials.

(9) L. Claisen, *Ber.*, **20**, 655 (1887).
(10) W. Borsche, *ibid.*, **62**, 1360 (1929).
(11) H. Rupe and S. Kessler, *ibid.*, **42**, 4715 (1909).
(12) B. B. Dey, *J. Chem. Soc.*, **105**, 1039 (1914).
(13) K. Chang Pauline, *J. Org. Chem.*, **23**, 1951 (1958).

Fischer Indole Synthesis. Direction of Cyclization of Isopropylmethyl Ketone Phenylhydrazone

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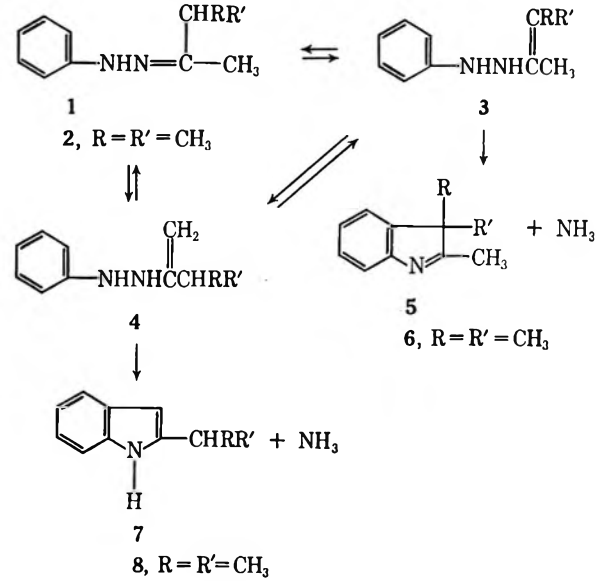
Plancher obtained 2,3,3-trimethylindolenine (2,3,3-trimethylpseudoindole) (**6**) by treating isopropylmethyl ketone phenylhydrazone (**2**) with zinc chloride in alcohol.[1] After observing the reactions of other phenylhydrazones (**1**), he established the rule that ketone arylhydrazones containing the group —NHN=C(CH$_3$)CH< cyclize exclusively at the tertiary carbon atom to give 2-methylindolenines (**5**).[2] More recent reports have shown that the direction of ring closure of unsymmetrical methyl ketone phenylhydrazones is dependent on the nature of the acid catalysts.[3-5] This dependence has been attributed to shifts in the equilibrium (**3** ⇌ **4**)[4] and, more specifically, to steric interactions in the transition state which are affected by the size of the acid.[5] See Scheme I.

SCHEME I



We wish to report another interesting exception to Plancher's rule. The phenylhydrazone **2** cyclizes to give both the indolenine **6** and 2-isopropylindole **8**, with the product ratio depending on the strength and amount of acid catalyst. Thus, the product ratio (**6**:**8**) decreases from 95:1 with dilute H_2SO_4 to 0.15:1 with 6 mol of 78% H_2SO_4. This is the first recorded case in which both directions of cyclization have been obtained by varying the concentration and amount of one catalyst. Weak acids give **6** exclusively. The results are given in Tables I and II. Samples of 2,3,3-tri-

(1) G. Plancher, *Ber.*, **31**, 1496 (1898).
(2) G. Plancher and A. Bonavia, *Gazz. Chim. Ital.*, **32**, 418 (1902).
(3) For a thorough review of the Fischer indole synthesis, see B. Robinson, *Chem. Rev.*, **63**, 387 (1963).
(4) N. P. Buu-Hoi, P. Jacquignon, and D. Perin-Roussel, *Bull. Soc. Chim. Fr.*, 2849 (1965).
(5) R. E. Lyle and L. Skarlos, *Chem. Commun.*, **18**, 644 (1966).

SCHEME II

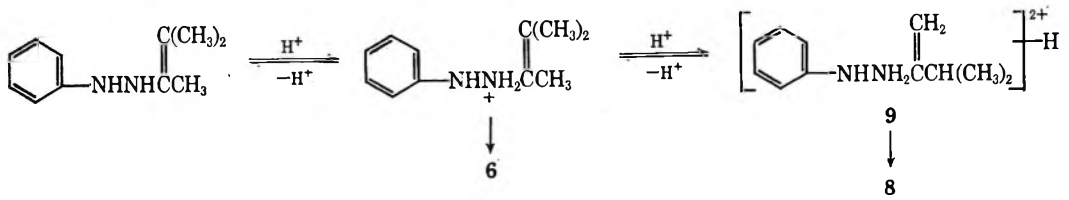


TABLE I
EFFECT OF CONCENTRATION AND AMOUNT OF H_2SO_4 ON YIELD IN THE CYCLIZATION OF 2 AT 90°

% H_2SO_4	$-H_0$[a]	Mole ratio of H_2SO_4: hydrazone	% 2,3,3-trimethyl-indolenine[b]	% 2-isopropyl-indole[b]
10	0.31	1:1	94.8	1.1
		5:1	88.5	2.1
20	1.01	1:1	93.9	1.4
		5:1	93.0	1.8
30	1.72	1:1	97.7	<1.0
		5:1	91.4	<1.0
40	2.41	1:1	96.4	1.0
		5:1	91.2	<1.0
50	3.38	1:1	97.8	<1.0
		5:1	85.3	4.4
60	4.46	1:1	98.1	<1.0
		5:1	56.1	30.3
70	5.65	1:1	96.5	<1.0
		5:1	27.1	67.1
78	6.71[c]	1:1	91.5	2.1
		5:1	20.2	79.0
		6:1	12.9	84.0

[a] All H_0 values are taken from M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [b] Analysis by gas chromatography. [c] Determined graphically from values in footnote *a*.

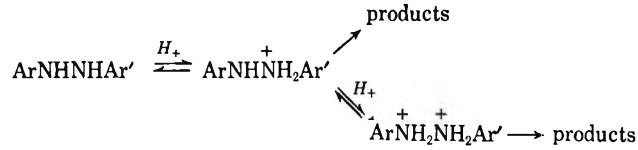
TABLE II
EFFECT OF CATALYST ON YIELD IN THE CYCLIZATION OF 2 AT 90°

Catalyst	$-H_0$[a]	Mole ratio of catalyst: hydrazone	% 2,3,3-trimethyl-indolenine[b]	% 2-isopropyl-indole[b]
$ZnCl_2$[c]		1:1	87.3	
		5:1	90.4	
100% HOAc		6:1	90.3	
50% $KHSO_4$	−0.4[d]	5:1	98.0	
75% $KHSO_4$	−0.4[d]	5:1	95.2	
85% H_3PO_4	3.7[d]	5:1	97.2	
PPA[e]	4.80[f]	1:1	73.5	14.3
PPA[e]	4.80[f]	5:1	8.4	72.2
10% HCl	1.00	1:1	59.0[g]	
		5:1	91.5	2.1
37% HCl	4.41	1:1	81.2[g]	
		2:1	95.4	
		5:1	81.7	10.1
		17:1	69.9	23.8

[a] See Table I, footnote *a*. [b] Analysis by gas chromatography. [c] Toluene was the solvent. [d] Determined graphically from values given in footnote *a*. [e] PPA = polyphosphoric acid. Toluene was the solvent. [f] Value for 100% H_3PO_4. [g] The reaction was incomplete.

methylindolenine (6) which were treated with an excess of 78% sulfuric acid gave no indication of isomerization to 8.

These data indicate that the direction of cyclization of 2 is affected by the acidity of the reaction medium. For instance, only the strong acids (H_2SO_4, HCl, and H_3PO_4) give 8 and, even then, only when sufficiently concentrated. In fact, H_3PO_4 gives 8 only when anhydrous. This necessity of a minimum acidity for the formation of 8 can be explained if we compare the mechanisms of the Fischer indole synthesis and the benzidine rearrangement.[3,6] The benzidine rearrangement can be either first or second order with respect to hydrogen ion concentration, depending on the nature of the hydrazo compound and the acidity of the reaction medium. In fact, some such rearrangements are first order at low acidity values and become second order as the acidity is increased.[6] The accepted mechanism of the Fischer



indole synthesis involves a single protonation step, although the possibility of a second protonation has been considered.[3-6]

Our results indicate that double protonation may occur, initiating a new mechanism which leads to the formation of compound 8. See Scheme II above. This hypothesis receives additional support from the observation that 8 forms only if more than 2 mol of HCl or H_2SO_4 is used. Thus, 1 mol is needed for the first protonation, another mole for the second protonation, and an additional amount is required to bind with the NH_3, which is a by-product. Protons from the second ionization of H_2SO_4 lack the activity to effect the second protonation; this is demonstrated by the failure of $KHSO_4$ to form any 8. Unfortunately, the data do not indicate the point of attachment of the second proton, although strict comparison with the benzidine rearrangement would place the second proton on the other nitrogen of the enehydrazine (9). The acidity dependence could also mean that the two-proton mechanism is really one with one less base molecule in the activated complex. In this case the second proton would be removing an electron donor, such as a nitrogen-containing species, instead of adding to the enehydrazine as in 9.[7] Kinetic studies are being conducted to determine the specific role of the second proton in the mechanism.

A convenient measure for the acidity of this system is the Hammett acidity function. Actually, H_0 should be used for the first protonation and H_+ for the second; however, Bonner and Lockhart[8] have shown that, in aqueous H_2SO_4, H_0 and H_+ either differ by a small constant or are identical. The data in Table I show that H_2SO_4 solutions must have a $-H_0$ value of at least 3.38 in order to produce significant amounts of 8. A comparison with Table II indicates that H_2SO_4 of a given $-H_0$ value gives more 8 than does H_3PO_4 or HCl having

(6) The similarity between these mechanisms has been discussed by H. J. Shine, "Aromatic Rearrangements," Elsevier Publishing Co., New York, N. Y., 1967, p 190.

(7) We wish to thank Dr. Edward S. Lewis for this and other valuable suggestions.

(8) T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 364 (1957).

the same value. Weak acids do not effect the second protonation because their acidity does not increase sufficiently with concentration.[9]

Experimental Section

All melting and boiling points are uncorrected. Infrared absorption spectra were determined on a Perkin-Elmer Model 421. Gas chromatography was conducted on an F & M Model 500 (thermal conductivity detector) using a 15 ft × 0.25 in. column containing 15% methyl silicone stationary phase on a support of 60–80 mesh diatomaceous earth. Elemental analyses were determined by Galbraith Laboratories and by our analytical department on a Perkin-Elmer Model 210 elemental analyzer.

Isopropylmethyl Ketone Phenylhydrazone (2).—Phenylhydrazine (324 g, 3 mol) and isopropylmethyl ketone (258 g, 3 mol) were heated together at 70° for 4 hr. Distillation under vacuum gave 477 g (90% theory) of **2**, bp 85–87° (11 mm).

Cyclization of 2. A. with $ZnCl_2$.—Isopropylmethyl ketone phenylhydrazone (**2**) (17.6 g, 0.1 mol) was dissolved in 30 ml dry toluene, and anhydrous zinc chloride (13.6 g, 0.1 mol) was added. The mixture was heated at 90° for 3 hr and drowned into 200 ml of water. The toluene layer was collected, and the solvent was evaporated under vacuum.

B. With Protonic Acids.—Isopropylmethyl ketone phenylhydrazone (**2**, 1.67 g, 0.1 mol) was added to the acid at 25°, heated at 90° for 3 hr, cooled to 25°, and neutralized with sodium carbonate. The organic layer was extracted with ether and dried over magnesium sulfate, and the solvent was evaporated.

Analysis of Products.—The mixture of reaction products was analyzed by gas chromatography. The peaks for **6** and **8** were compared with those for known samples. For identification purposes, **6** was separated by distillation, an ether solution was treated with hydrogen chloride gas, and the white hydrochloride was recrystallized from ethyl acetate: mp 188–189°.

Anal. Calcd for $C_{11}H_{14}ClN$: C, 67.5; H, 7.21; N, 7.16. Found: C, 67.4; H, 7.3; N, 7.1.

2-Isopropylindole (**8**) was recrystallized from methanol and water. Ir spectra and mixture melting point (73–74°) showed the reaction product to be identical with the known sample.

Anal. Calcd for $C_{11}H_{13}N$: C, 83.0; H, 8.17; N, 8.80. Found: C, 82.96; H, 8.37; N, 8.52.

2-Isopropylindole (8).—Isobutyryl chloride (52.2 g, 0.5 mol) was added dropwise to *o*-toluidine (107 g, 1.0 mol) in 100 ml of ether. The mixture was heated at reflux (35°) for 1 hr; 200 ml H_2O was added; and the ether was evaporated on a steam bath. Ethanol was added at 65° until the white solid dissolved and the solution was allowed to cool. The N-isobutyryl-*o*-toluidine (**10**) was collected by filtration to yield 81 g (0.45 mol), mp 115–116°.

A mixture of 35.4 g (0.2 mol) of **10** and 19 g (0.49 mol) of $NaNH_2$ was heated to 250° for 10 min and then cooled. Ethanol (10 ml) and then 50 ml of H_2O were added dropwise. 2-Isopropylindole (**8**) was removed by steam distillation and recrystallized from water and methanol to yield 16.4 g (0.103 mol), mp 73–74°.

Anal. Calcd for $C_{11}H_{13}N$: C, 83.0; H, 8.17; N, 8.80. Found: C, 83.0; H, 8.5; N, 9.0.

Registry No.—**2**, 6243-71-6; **6** HCl, 17790-92-0; **8**, 17790-93-1.

(9) See Table I, footnote *a*.

Kinetics of the Thermal Rearrangement of Ascaridole

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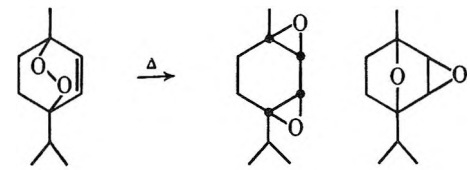
Received May 20, 1968

Ascaridole (I), the main constituent of chenopodium oil and one of the best known anthelmintics, is converted into an isomeric material when heated in an inert solvent.[1] The isomeric product can be isolated in pure form in yields up to 80% from the thermal rearrangement.[2] As a result of several investigations[1,3-6] two structures had been suggested for the rearrangement product: namely, 1,2:3,4-diepoxy-*p*-menthane (II) and 1,4:2,3-diepoxy-*p*-menthane (III). In 1956 a report[2] on the steriochemistry of products resulting from the acid hydrolysis of the isomeric material firmly established the 1,2:3,4-diepoxy structure (II).



I II III

Although the thermal rearrangement of ascaridole has been known since 1911,[1] no kinetic study of the reaction has been reported. The present work was undertaken to obtain rate data with a view toward evaluating the kinetic parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$. Specific rate constants for the isomerization of ascaridole have been obtained at a series of temperatures in the range 100 to 150°. Changes in concentration of the peroxide were followed by measurement of the ascaridole C-2 and C-3 proton area in the nmr spectra. An internal standard of toluene was utilized. Spectra of samples heated for varying lengths of time showed only peaks which could be attributed to toluene, ascaridole, or the diepoxide (II). The results of our measurements appear in Table I. Specific rate constants at each temperature were obtained using the *method of least squares*. The energy of activation (E_a) and the frequency factor (A) were evaluated from the Arrhenius equation, $\ln k_1 = -E_a/RT + \ln A$, and the kinetic parameters ($\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and $\Delta S^{\ddagger}$) were calculated from the equations

$$\Delta H^{\ddagger} = E_a - RT;\ k_1 = \frac{h}{kT} e^{-\Delta G^{\ddagger}/RT};\ \Delta S^{\ddagger} = \frac{\Delta G^{\ddagger} - \Delta H^{\ddagger}}{T}$$

Figure 1 shows a typical plot of the rate equation, whereas Figure 2 gives the Arrhenius plot from which E_a and A were evaluated.

TABLE I

SUMMARY OF KINETIC DATA FOR THE THERMAL REARRANGEMENT OF ASCARIDOLE[a]

Temp, °C	$k_1 \times 10^5$, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
98.5	2.14 ± 0.02	30.7	31.4	1.88
111.0	6.67 ± 0.01	30.6	31.6	2.60
132.0	74.1 ± 0.3	30.6	31.5	2.20
151.0	417. ± 3	30.6	31.6	2.36

[a] $E_a = 31.4 \pm 0.1$ kcal; $A = 6.6 \times 10^{12}$ sec^{-1}.

The simplest mechanism consistent with the values obtained, involves a homolytic cleavage of –O–O– bond

(1) (a) E. K. Nelson, *J. Amer. Chem. Soc.*, **33**, 1404 (1911); (b) E. K. Nelson, *ibid.*, **35**, 84 (1913).

(2) O. A. Runquist, Ph.D. Thesis, University of Minnesota, July 1956, p 20–46; *Dissertation Abstr.*, **16**, 2313 (1956).

(3) H. Thoms and W. Dohke, *Arch. Pharm.* (Weinheim), **268**, 128 (1930).

(4) F. Richter and W. Presting, *Ber.*, **64**, 878 (1931).

(5) T. A. Henry and H. Paget, *J. Chem. Soc.*, **119**, 1722 (1921).

(6) (a) M. Matic and D. A. Sutton, *ibid.*, 349 (1953); (b) M. Matic and D. A. Sutton, *ibid.*, 2679 (1952).

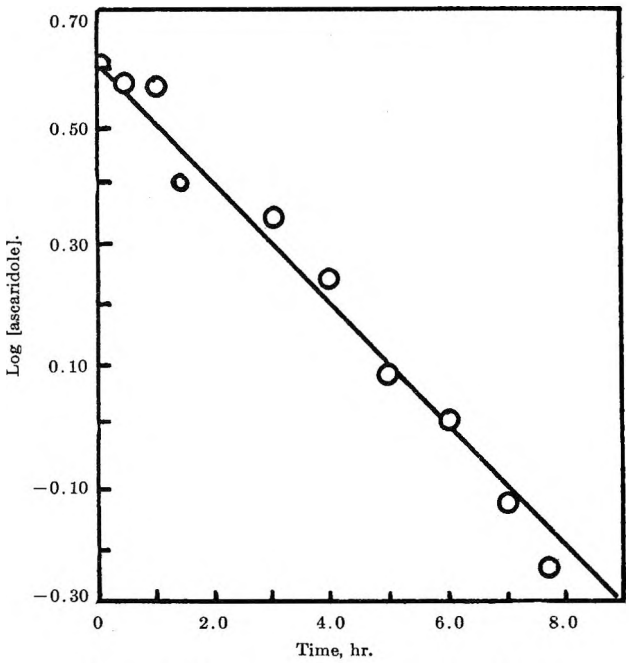


Figure 1.—Isomerization of ascaridole at 131°.

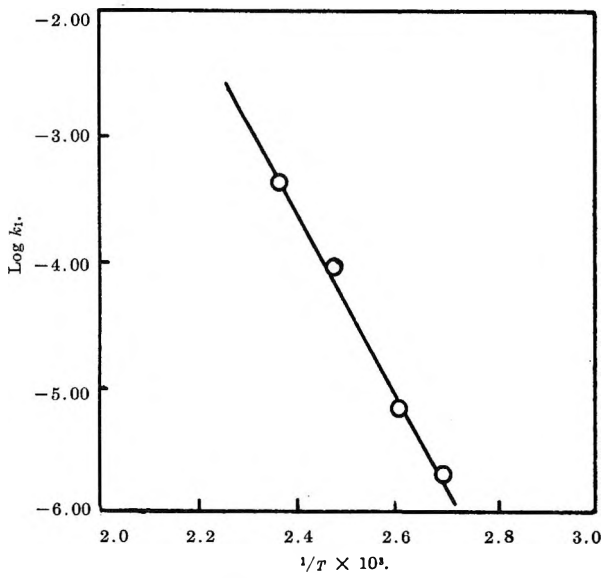
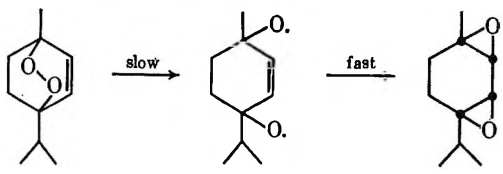


Figure 2.—Arrhenius plot for the thermal isomerization of ascaridole.

in a slow step followed by rapid addition of oxygens to the double bond. The value of $\Delta H^{\pm}$ is entirely consistent with this mechanism. Bond strengths of acyclic peroxides are in the range of 33 kcal/mol,[7] and, because of strain, the peroxide bond of ascaridole would be expected to be weaker by several kcal/mol. The entropy of activation for a unimolecular cleavage, as proposed, would be expected to be small.[8]



(7) "Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards Circular 500, U. S. Government Printing Office, Washington, D. C., 1950.

Experimental Section

Materials.—Ascaridole was obtained from chenopodium oil by fractional vacuum distillation and further purified on an aluminum oxide column. Toluene was purified by distillation.

Sample Preparation.—Stock solutions of toluene and ascaridole were made up gravimetrically. After mixing, aliquots were sealed into vials made from 5-mm soft-glass tubing. Sets of sample tubes were immersed in a suitable refluxing solvent, and tubes were periodically removed, cooled, and analyzed. Initial concentrations of ascaridole in separate kinetic runs were 4.14 and 4.60 *M*.

Analysis.—Analysis of samples were performed on a Varian A-60 A spectrometer. Peak integrations of the aromatic protons of toluene (τ 3.1) and the C-2, C-3 protons in ascaridole (τ 3.9) were made. The peak areas of the C-2 and C-3 protons in the isomerized product (τ 7.2) and the methyl protons of toluene were also recorded. The isomerization was followed to about 80% completion in each run. The moles of ascaridole and rearrangement product present in each sample were calculated from the following equations.

$$[\text{ascaridole}] = {}^5/_2(\tau\ 3.9\ \text{area}/\tau\ 3.1\ \text{area})\ (\text{moles of toluene})$$

$$[\text{rearrangement product}] = {}^3/_2(\tau\ 7.2\ \text{area}/\tau\ 7.9\ \text{area})\ (\text{moles of toluene})$$

Calculations.—Rate constants were determined both from the concentration of ascaridole present in the samples and the concentration of diepoxide formed. The rate constants determined from the concentration of starting material and product were consistent with each other. Because of the proximity of absorbtion of other protons, the ratio of peak areas for the C-2 and C-3 protons of the diepoxide and methyl protons of toluene could not be established as precisely as the ratio between the C-2 and C-3 protons of ascaridole and the aromatic protons of toluene. The data listed in Table I was calculated from the ascaridole/toluene ratios.

Registry No.—I, 512-85-6.

(8) Several examples of first-order isomerization and first-order decompositions with small entropies of activation are listed and discussed in A. A. Frost and R. G. Pierson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, pp 109–112.

The Thermal Decomposition of o-Azidodiphenylmethane Leading to Azepino[2,1-*a*]-1*H*-indole

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The thermal decomposition of *ortho*-substituted phenyl azides, where possible, generally leads to five-membered-ring structures. Examples of such thermolyses are *o*-azidobiaryls,[2] *o*-azidobenzylidenamines,[3] benzylidene-*o*-azidoanilines,[4] *o*-azidobenzophenone,[5] and diazidoazobenzene.[6] On the other hand, the

(1) International Minerals and Chemical Corp., Growth Sciences Center, Libertyville, Ill.

(2) (a) P. A. S. Smith and J. H. Boyer, *J. Amer. Chem. Soc.*, **73**, 2626 (1951); (b) P. A. S. Smith and J. H. Hall, *ibid.*, **84**, 480 (1962); (c) B. Coffin and R. F. Robbins, *J. Chem. Soc.*, 1252 (1965).

(3) L. Krbechek and H. Takimoto, *J. Org. Chem.*, **29**, 1150 (1964).

(4) (a) L. Krbechek and H. Takimoto, *ibid.*, **29**, 3630 (1964); (b) J. H. Hall and D. R. Kamm, *ibid.*, **30**, 2092 (1965).

(5) P. A. S. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *J. Amer. Chem. Soc.*, **75**, 6335 (1953).

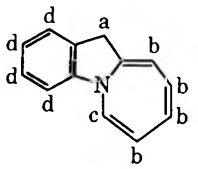
(6) (a) R. A. Carboni and J. E. Castle, *ibid.*, **84**, 2453 (1962); (b) R. A. Carboni, J. C. Kauer, W. R. Hatchard, and R. J. Harder, *ibid.*, **89**, 2626 (1967).

formation of six-membered-ring structures is also reported[5] in the *o*-azidobiaryl systems where the two aryl groups are separated by O, S, or SO_2. The yields in the latter cases, however, are much lower than the former. In the cases where cyclization is not possible, the ring enlargement of the phenyl to form seven-membered azepine structures have also been reported. Thus, 2-anilino-7H-azepine[7] is formed from the decomposition of phenyl azide in aniline. The present report describes the thermal decomposition of *o*-azidodiphenylmethane, where the aryl groups are separated by a methylene group, resulting in a ring enlargement.

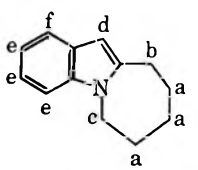
Thermolysis of *o*-azidodiphenylmethane in decalin at 160° resulted in a hydrogen-abstraction reaction with the formation of *o*-aminodiphenylmethane. However, the decomposition of this azide, in 1,2,4-trichlorobenzene at 160°, resulted in a loss of nitrogen and yielded a compound (66%) having the empirical formula $C_{13}H_{11}N$ (I), mp 91–95.5°. This compound was not dihydroacridine, the product that would result from six-membered-ring closure during the decomposition of *o*-azidodiphenylmethane. The ultraviolet spectrum of I in ethanol exhibited absorption bands at 314 mμ (log ε 3.79), 272 (4.23), and 227 (4.40). Hydrogenation of I with 10% Pd–C in ethanol resulted in an uptake of 2 mol of hydrogen to yield (79.5%) a second compound, $C_{13}H_{15}N$ (II). Absorptions at 292 mμ (log ε 3.83), 283 (3.92), 277 (3.89) shoulder, and 224 (4.62) were observed for II in ethanol.

The nmr spectrum of I in CCl_4 exhibited absorptions at δ 3.33 (2 H, a), 5.93–5.40 (4 H, b), 7.32 (1 H, c), and 7.10–6.78 (4 H, d). Compound II, also in CCl_4, had absorptions at δ 1.74 (6 H, a), 2.76 (2 H, b), 3.97 (2 H, c), 6.08 (1 H, d), 6.98 (3 H, e), 6.32 (1 H, e), and 7.32 (1 H, f).

Based on the above information, the following structures were assigned.



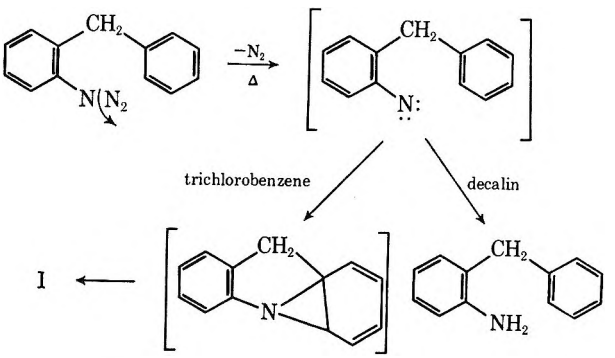
I



II

The ultraviolet absorptions for I at 227 and 272 mμ are attributed to the nitrogen attached to a benzene ring similar to that found in aniline. The latter compound has absorptions at 230 mμ (log ε 3.93) and 280 (3.16)[8] in water. The absorption at 314 mμ for I is attributed to the azepine structure, since many azepines exhibit bands at approximately 300 mμ. For example, 2-diethylamino-3H-azepine has an absorption maximum at 297 mμ (log ε 3.90),[9] 2-benzylamino-7H-azepine shows absorptions at 210 mμ (log ε 4.32) and 287 (3.88),[7b] 2-(*o*-tolylamino)-7H-azepine exhibits maxima at 205 mμ (log ε 4.37) and 290 (4.03),[7c] and 2-(diisopropylamino)-7H-azepine has maxima at 213 mμ (log ε 4.45) and 297 (4.28).[7c] The reduction of I by the uptake of 2 mol of hydrogen resulted in the saturation of the azepine and the shift of one of the unsaturated bonds into conjugation with the benzene ring to form the indole structure. Thus, the longer wavelength absorption of I assigned to the azepine disappeared, and the spectrum of II is consistent with the indole structure. Indole has absorptions at 287 mμ (log ε 3.6), 280 (3.7), 265 (4.4) broad band, in cyclohexane.[10]

The decomposition of *o*-azidodiphenylmethane in 1,2,4-trichlorobenzene appears to proceed by the elimination of nitrogen and the attack of the nitrene (univalent uncharged nitrogen) on the neighboring phenyl group. The elimination of nitrogen and the attack may occur either *via* a concerted or a stepwise reaction. The stepwise reaction is favored since *o*-aminodiphenylmethane was obtained in decalin by the hydrogen abstraction from the solvent by the nitrene.[11] The decalin, being a better donor of hydrogen than trichlorobenzene, traps the nitrene and prevents the azepine formation. The rearrangement of the resulting intermediate leads to I.



The formation of I leading to ring enlargement of the phenyl group is similar to the decomposition reaction of 2-(β-phenylethyl)-phenyldiazomethane reported by Gutsche, *et al.*[12] In this case the phenyls are separated by two methylene groups, and a carbene is generated instead of a nitrene. The addition of the carbene to the phenyl followed by rearrangement, leads to the product 6,6a-dihydro-5H-cyclohepta[*a*]naphthalene.

Experimental Section[13–15]

***o*-Azidodiphenylmethane.**—A solution of 3.6 g (0.02 mol) of *o*-aminodiphenylmethane was diazotized[16] in 8 ml of concentrated hydrochloric acid and 80 ml of water cooled to −10°. To the cold solution, 1.4 g (0.02 mol) of sodium nitrite in 10 ml of water was slowly added. A solution of 1.5 g of sodium azide in 10 ml of water was added to the diazonium salt. The solution was extracted twice with 100 ml of ether. The ethereal extract was washed with 5% sodium hydroxide solution and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was chromatographed on alumina. Petroleum

(7) (a) R. Huisgen, D. Vossius, and M. Appl, *Angew. Chem.*, **67**, 756 (1955); (b) R. Huisgen, D. Vossius, and M. Appl, *Ber.*, **91**, 1 (1958); (c) M. Appl and R. Huisgen, *ibid.*, **92**, 2961 (1959).

(8) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold Ltd., London, 1957, p 140.

(9) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966).

(10) R. A. Friedel and M. Orchin, "Ultraviolet Spectron of Aromatic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1951, Spectra No. 192.

(11) The preference of the nitrene mechanism was suggested by one of the referees.

(12) C. D. Gutsche, E. F. Jason, R. C. Coffey, and H. E. Johnson, *J. Amer. Chem. Soc.*, **80**, 5756 (1958).

(13) All melting points are uncorrected.

(14) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(15) The nmr spectra were taken and interpreted by Wilbur Simon, Simon Research Laboratory, Elgin, Ill., on a Varian A-60 MC instrument with tetramethylsilane as an internal standard.

(16) C. L. Hewett, L. J. Lermit, H. T. Oppenshaw, A. R. Todd, A. H. Williams, and F. N. Woodward, *J. Chem. Soc.*, 292 (1948).

ether (bp 60–90°) eluted 3.8 g (92%) of *o*-azidodiphenylmethane.

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.61; H, 5.30; N, 20.09. Found: C, 74.84; H, 5.37; N, 19.96.

Decomposition of *o*-Azidodiphenylmethane. A.—To 150 ml of decalin preheated to 160°, 4.5 g of *o*-azidodiphenylmethane was added. After 5 hr at 160–165°, all gas evolution had ceased. A total of 480 ml of gas at standard conditions were collected (theoretical, 475 ml). The solvent was removed at <5-mm pressure. The residue was dissolved in a mixture of benzene and petroleum ether and put on an alumina chromatographic column. Petroleum ether eluted the first fraction. This fraction yielded 1.6 g (41%) of *o*-aminodiphenylmethane upon distillation. No other products were isolated.

B.—A solution of 2.0 g of *o*-azidodiphenylmethane in 100 ml of 1,2,4-trichlorobenzene was heated to 160° and maintained at this temperature for 4 hr. The solvent was removed at <5-mm pressure, and the residue subjected to steam distillation. The steam distillate was extracted twice with 150 ml of ether. The etheral extracts were dried with sodium sulfate. Removal of the ether at reduced pressure left 1.1 g (66%) of crude azepino-[2,1-*a*]-11H-indole (I), mp 80–87°. This solid was recrystallized from hexane to yield white crystals, mp 91°. An analytical sample was sublimed at 80° (0.1 mm), mp 91–91.5°.

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.05; H, 6.20; N, 7.62.

1,2,3,4,5-Pentahydroazepino[2,1-*a*]indole (II).—A solution of 0.8 g of I in 200 ml of ethanol was catalytically hydrogenated with 0.4 g of 10% palladium on charcoal on a Parr shaker. The sample was filtered free of catalyst, and the solvent was removed at reduced pressure. The solid residue was recrystallized from a hexane–cyclohexane mixture to yield 0.65 g (79.5%) of 1,2,3,4,5-pentahydroazepino[2,1-*a*]indole, mp 82–88°. An analytical sample was prepared by sublimation at 80° (0.1 mm) to yield white crystals, mp 88°.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.27; H, 8.16; N, 7.56. Found: C, 84.29; H, 8.00; N, 7.59.

Registry No.—I, 17691-63-3; II, 17691-64-4; *o*-azidodiphenylmethane, 17691-65-5.

Acknowledgments.—The authors are deeply indebted to Dr. L. Schieler and Professor P. A. S. Smith for their helpful interest in this work and to Mr. S. Hotta for spectral measurements and valuable preparative assistance.

Synthesis of New Chlorine-Substituted Derivatives of 2-Tetralone[1,2]

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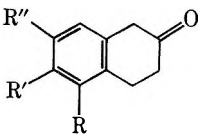
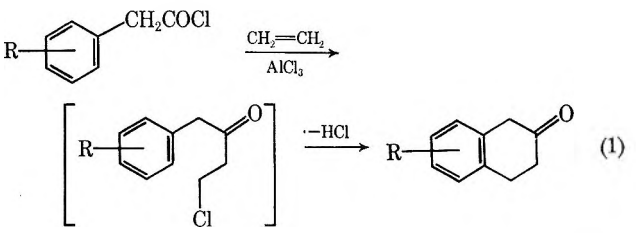
2-Tetralones containing one or more chlorine substituents on the aromatic ring have not been described in the chemical literature to date. Such compounds are of interest, in this laboratory, as points of departure for the synthesis of various chlorine-substituted condensed ring systems of potential biological interest. In the present Note, we should like to report the preparation of 6-chloro-2-tetralone (**1**), 7-chloro-2-tetralone (**2**), 5,7-dichloro-2-tetralone (**3**), and 6,7-dichloro-2-tetralone (**4**) *via* the Darzens reaction,[3] as modified by Burckhalter and Campbell.[4]



1, R = R″ = H; R′ = Cl
2, R = R′ = H; R″ = Cl
3, R = R″ = Cl; R′ = H
4, R = H; R′ = R″ = Cl

Methods of synthesis of 2-tetralone and its substituted analogs have been reviewed recently.[5] The approach favored by most workers during the past 25 years has involved reduction of substituted 2-methoxynaphthalene derivatives with sodium in alcohol. Catalytic, electrolytic, and sodium–liquid ammonia reductions have also been reported. This general plan appeared to be unsuitable for the synthesis of chlorinated 2-tetralones because of (1) the possibility of base-catalyzed dehalogenation, and (2) the relative inaccessibility of the required 2-methoxynaphthalene intermediates. Multistep sequences have been devised to transform substituted 1-tetralones into the corresponding 2-tetralones. However, such methods offer no particular advantage in this case because chlorinated 1-tetralones are themselves not readily obtained. The condensation of substituted phenylacetyl chlorides with ethylene under the influence of aluminum chloride (eq 1), according to the convenient



(1)

one-step procedure of Burckhalter and Campbell,[4] appeared to be an attractive alternative to the use of preformed naphthalene precursors. 2-Tetralones containing alkyl substituents in the saturated ring were prepared as early as 1947 by this approach in a two-step procedure.[6] However, little work has been done to define either the precise mechanism or the synthetic scope of this interesting reaction.

(1) This investigation was supported in part by Research Contract DA-49-193-MD-3008 from the U. S. Army Medical Research and Development Command, Office of the Surgeon General, and by Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is publication number 342 from the Army Research Program on Malaria.

(2) Presented in part before the Division of Medicinal Chemistry at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 4, 1968.

(3) L. F. Fieser and M. Fieser, "Topics in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1963, p 548.

(4) J. H. Burckhalter and J. R. Campbell, *J. Org. Chem.*, **26**, 4232 (1961).

(5) V. F. Schner and N. M. Przhiyalgovskaya, *Russ. Chem. Rev.*, **35**, 523 (1966).

(6) J. Colonge and J. Chambion, *Compt. Rend.*, **224**, 128 (1947); J. Colonge and J. Chambion, *Bull. Soc. Chim. Fr.*, 1002 (1947).

The substituted phenylacetic acids employed in this work were all known previously[7-9] and were prepared essentially according to the literature, with the exception of 3,5-dichlorophenylacetic acid, which we chose to prepare *via* 3,5-dichlorobenzyl chloride instead of 3,5-dichlorobenzyl bromide as reported.[8] The bromide is less accessible than the chloride and is inconvenient to use on a large scale because of its strong lachrymatory properties. Condensation of the acid chlorides with ethylene was conducted essentially as described by Burckhalter and Campbell,[4] except that the reaction was allowed to proceed overnight in order to compensate for the expected deactivating effect of halogen substituents.

p-Chlorophenylacetyl chloride and 3,5-dichlorophenylacetyl chloride gave single products **1** and **3**, respectively, upon reaction with ethylene. Reaction with 3,4-dichlorophenylacetyl chloride produced only one of the two possible 2-tetralone derivatives, as evidenced by glpc analysis. The nmr spectrum of this compound showed two isolated singlets at τ 2.76 and 2.86, in agreement with the 1,4 aromatic proton substitution pattern in structure **4**. The sterically less favored isomer, 5,6-dichloro-2-tetralone, would be expected to show a pair of doublets corresponding to 1,2 aromatic proton substitution. The reaction of *m*-chlorophenylacetyl chloride, on the other hand, was found to be somewhat less selective than that of the 3,4-dichloro analog. Glpc analysis of material purified by routine vacuum distillation revealed the presence of two products, in the ratio of approximately 3:1. The nmr spectrum of the mixture likewise indicated that one isomer, presumably **2**, was preponderant. A strong singlet at τ 6.56 was observed, which was assigned to the $ArCH_2CO$ protons in **2**. A small second peak at τ 6.53 was also seen, which was assumed to be caused by the presence of a minor quantity of 5-chloro-2-tetralone.

On the basis of the failure of *p*-nitrophenyl- and diphenylacetyl chloride to yield substituted 2-tetralones, Burckhalter and Campbell[4] proposed that electron-withdrawing substitution in the aromatic ring retards the reaction by hindering ionization to an intermediate carbonium ion–aluminum chloride complex of unspecified structure. In the present investigation, the condensation of mono- and dichlorophenylacetyl chlorides with ethylene has been found to proceed in yields averaging 55–60%. The yields do not differ greatly from the values given for 2-tetralone (75%) and 6-methoxy-2-tetralone (56%), the only 2-tetralone derivatives reported by Burckhalter and Campbell. Thus our data suggest that electron-withdrawing halogen substituents may retard the condensation to a small extent. However, as with other Friedel–Crafts reactions involving halogen-substituted aromatic compounds,[10] the effect is not strong enough to negate the obvious preparative advantages of this reaction.

(7) R. C. Elderfield and K. L. Burgess, *J. Amer. Chem. Soc.*, **82**, 1975 (1960).

(8) M. B. Pybus, R. L. Wain, and F. Wightman, *Ann. Appl. Biol.*, **47**, 593 (1959); *Chem. Abstr.*, **54**, 12052 (1960).

(9) (a) S. Chiavarelli and M. A. Jorio, *Gazz. Chim. Ital.*, **86**, 1054 (1956); *Chem. Abstr.*, **52**, 3832 (1958).

(10) For a discussion of the Friedel–Crafts alkylation of aromatic compounds with alkyl halides, see F. A. Drahowzal in "Friedel–Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 4.

Experimental Section[11]

Materials.—*p*-Chlorophenylacetonitrile and 3,5-dichlorobenzoic acid were purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis. *m*-Chlorophenylacetonitrile and 3,4-dichlorobenzyl chloride were obtained from Columbia Organic Chemicals Co., Inc., Columbia, S. C., and from K & K Laboratories, Inc., Plainview, N. Y. *p*-Chlorophenylacetic acid, mp 104–106° (lit.[7] mp 106–106.5°), and *m*-chlorophenylacetic acid, mp 76–77° (lit.[7] mp 77–77.5°), were prepared from the corresponding nitriles in 94 and 71% yield, respectively, by hydrolysis with a refluxing mixture of aqueous acetic and sulfuric acids as prescribed in the literature.[7] *p*-Chlorophenylacetyl chloride, bp 94° (0.5 mm) [lit.[12] bp 119° (14 mm)], and *m*-chlorophenylacetyl chloride, bp 87–88° (0.25 mm) [lit.[12] bp 121° (17 mm)], were obtained by reaction of the acids with excess thionyl chloride on the steam bath, the yields of distilled acid chlorides being 76 and 58%, respectively. 3,4-Dichlorophenylacetonitrile, bp 130–135° (0.5–1.0 mm) [lit. bp 150–151° (6 mm),[9] 167–169° (15 mm)[13]], was synthesized in 88% yield by treatment of the benzyl chloride derivative with sodium cyanide in refluxing aqueous ethanol.[9] Hydrolysis of the nitrile with the standard aqueous acetic–sulfuric acid reagent[7,9] afforded 3,4-dichlorophenylacetic acid, mp 79–85° (lit.[9] mp 84°), in 81% yield. Overnight reaction of the crude acid with thionyl chloride in refluxing benzene gave a 77% yield of 3,4-dichlorophenylacetyl chloride, bp 123–126° (0.5–1.0 mm). The acid chlorides were used as soon as possible after distillation, in order to minimize decomposition during storage.

6-Chloro-2-tetralone (1).—A solution of *p*-chlorophenylacetyl chloride (46 g, 0.24 mol) in carbon disulfide (500 ml) was added dropwise with vigorous mechanical stirring to a suspension of anhydrous aluminum chloride (61.2 g, 0.46 mol) in carbon disulfide (700 ml) at 5°. When addition was complete, ethylene gas was introduced through a sintered-glass inlet tube for a period of 5 hr, with the temperature being kept at 5–10°. The mixture was stirred overnight at room temperature, and then poured into a large beaker of crushed ice. The aqueous layer was separated and washed with dichloromethane (two 900-ml portions). The dichloromethane extracts and carbon disulfide layer were combined, dried, and concentrated to dryness under reduced pressure. The dark oily residue was treated with a solution of sodium bisulfite (100 g) in water (180 ml) and ethanol (60 ml), and the mixture was shaken vigorously and allowed to stand overnight.[14] The crystalline bisulfite adduct was filtered, washed with alcohol, and rinsed with ether to yield 66.5 g (97%). The bisulfite adduct was suspended in water (350 ml), and sodium carbonate (80 g) was added. The basic mixture (pH 9) was stirred for 3 hr, and then extracted with ether (three 250-ml portions). The combined ether extracts were washed with 1 *N* hydrochloric acid (90 ml), rinsed to neutrality with water, dried, and evaporated to dryness: yield 30 g (70%); mp 60–62.5°; ν_{max}^{KCl} 1720 cm^{-1} (C=O); positive "tetralone blue" test.[4,15] The analytical sample, prepared in a separate small-scale run, had mp 68–70°.

Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02; Cl, 19.63. Found: C, 66.30; H, 5.04; Cl, 19.64.

The **semicarbazone** of **1** had mp 195–197° (EtOH).

(11) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in potassium chloride disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Nmr spectra were determined in carbon tetrachloride solution on a Varian A-60 instrument, with tetramethylsilane as the internal reference. Glpc analyses were performed on an F & M Model 720 instrument, using 6 ft × 1/4 in. 10% silicone rubber (SE-30) columns and helium as the carrier gas. Analytical samples were dried over phosphorus pentoxide at 70–100° (0.05 mm). Melting points were measured in Pyrex capillary tubes in a modified Wagner–Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938)] at a heating rate of 2°/min and are corrected wherever possible. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(12) P. D. Bartlett and C. Rüchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960).

(13) S. Chiavarelli and M. A. Jorio, German Patent 1,109,700 (June 29, 1961); *Chem. Abstr.*, **56**, 12802 (1962).

(14) M. D. Soffer, M. P. Bellis, H. E. Gellerson, and R. A. Stewart, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 904.

(15) (a) H. W. Wanzlich, M. Lehmann-Hrochler, and S. Mohrmann, *Ber.* **90**, 2521 (1957); (b) A. C. Baillie and R. H. Thomson, *J. Chem. Soc.*, 2184 (1966). In this test an alcoholic solution of the compound is basified with dilute sodium hydroxide and shaken vigorously; the appearance of a deep blue color indicates a 2-tetralone.

Anal. Calcd for $C_{11}H_{12}ClN_3O$: C, 55.58; H, 5.09; Cl, 14.92; N, 17.68. Found: C, 55.57; H, 5.08; Cl, 14.69; N, 17.37.

7-Chloro-2-tetralone (2).—The procedure described above for the synthesis of **1** was repeated with *m*-chlorophenylacetyl chloride. Vacuum distillation was used to purify the oily ketone recovered after base treatment of the crystalline bisulfite adduct: yield 47%; bp 145° (0.6 mm); mp 43–46° (solid formed in the receiver); ν_{max}^{KCl} 1720 cm^{-1}. Analysis of this material by glpc (150°)[11] showed two peaks with retention times of 3.6 and 6.4 min, respectively. The ratio of peak areas was approximately 3:1. The nmr spectrum indicated the presence of two compounds in unequal proportions. The principal isomer, assumed to be **2**, showed a singlet at τ 6.56 ($ArCH_2CO$). A smaller singlet at τ 6.53 was also observed, suggesting the probable presence of some 5-chloro-2-tetralone.

Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02; Cl, 19.63. Found: C, 66.66; H, 5.28; Cl, 19.93.

5,7-Dichloro-2-tetralone (3).—3,5-Dichlorobenzoic acid was reduced in 78% yield with lithium aluminum hydride in refluxing ether,[16] with formation of 3,5-dichlorobenzyl alcohol, mp 78° (lit.[16] mp 78–79°). A mixture of this alcohol (125 g, 0.71 mol) and thionyl chloride (113 g, 0.95 mol) was refluxed 3 hr to give 94 g (68%) of 3,5-dichlorobenzyl chloride,[17] bp 83° (1.8 mm) [lit. bp 60° (0.35 mm),[16] 115–123° (10 mm)[18]]. To a stirred suspension of sodium cyanide (13 g, 0.27 mol) in dry dimethyl sulfoxide (50 ml) was added dropwise under nitrogen at 50° a solution of the above benzyl chloride (45 g, 0.23 mol) in dry dimethyl sulfoxide (150 ml). After being stirred overnight at room temperature, the mixture was diluted with water (400 ml), and extracted with chloroform (three 300-ml portions). The combined extracts were washed with water (100 ml), dried, and evaporated to dryness. Distillation of the residue gave 28 g (66%) of 3,5-dichlorophenylacetonitrile, bp 101–103° (0.1 mm) [lit.[8] bp 165–168° (17 mm)]. The dinitrile was heated for 6 hr under reflux with a mixture of concentrated sulfuric acid (28 ml), glacial acetic acid (28 ml), and water (28 ml). The hydrolysis mixture was cooled, and the precipitate was filtered and washed thoroughly with ice-cold water to give 24 g (78%) of 3,5-dichlorophenylacetic acid, mp 110–112° (lit.[8] mp 112–115°). This acid (139 g, 0.68 mol) was allowed to react overnight with thionyl chloride (100 g, 0.84 mol) in refluxing benzene (200 ml). Removal of the solvent and unreacted thionyl chloride under reduced pressure and distillation of the residue gave 99 g (66%) of 3,5-dichlorophenylacetyl chloride, bp 114–118° (2 mm).[19] The general procedure used in the preparation of **1** was repeated with this acid chloride to give a 58% yield (best run) of **3**: mp 76–78°; ν_{max}^{KCl} 1730 cm^{-1} (C=O); positive "tetralone blue" test.

Anal. Calcd for $C_{10}H_8Cl_2O$: C, 55.84; H, 3.75; Cl, 32.97. Found: C, 56.04; H, 3.97; Cl, 33.10.

The **2,4-dinitrophenylhydrazone** of **3** had mp 172.5–174° (EtOH).

Anal. Calcd for $C_{16}H_{12}Cl_2N_4O_4$: C, 48.12; H, 3.06; Cl, 17.94; N, 14.17. Found: C, 48.44; H, 3.29; Cl, 18.03; N, 14.01.

6,7-Dichloro-2-tetralone (4).—The general procedure used for the synthesis of **1** was repeated with 3,4-dichlorophenylacetyl chloride to give a 58% yield (best run) of **4**. Glpc analysis (200°)[11] showed a single peak with a retention time of 4.75 min. For microanalysis, a portion of the crude crystalline product was recrystallized from 1:2 carbon tetrachloride–petroleum ether (bp 60–80°): mp 97–98°; ν_{max}^{KCl} 1720 cm^{-1}.

Anal. Calcd for $C_{10}H_8Cl_2O$: C, 55.84; H, 3.75; Cl, 32.97. Found: C, 55.57; H, 3.80; Cl, 32.87.

The **semicarbazone** of **4** had mp 224–225° (EtOH).

Anal. Calcd for $C_{11}H_{11}Cl_2N_3O$: C, 48.55; H, 4.08; Cl, 26.06; N, 15.44. Found: C, 48.72; H, 4.16; Cl, 26.34; N, 15.16.

Registry No.—**1**, 17556-18-2; **1** semicarbazone, 17605-22-0; **2**, 17556-19-3; **3**, 17556-20-6; **3** 2,4-dinitrophenylhydrazone, 17556-21-7; **4**, 17556-22-8; **4** semicarbazone, 17556-23-9; 2-tetralone, 530-93-8.

(16) R. Fuchs and D. M. Carlton, *J. Amer. Chem. Soc.*, **85**, 104 (1963).

(17) 3,5-Dichlorobenzyl chloride has also been prepared from the alcohol by reaction with phosphorus pentachloride [F. Asinger and G. Lock, *Monatsh. Chem.*, **62**, 344 (1933)], and also from 3,5-dichlorotoluene by direct photocatalytic chlorination at 180° (see ref 18).

(18) British Patent 923,128 (April 10, 1963); *Chem. Abstr.*, **60**, 1048 (1964).

(19) A 79% yield of acid chloride was obtained in a subsequent experiment, in which the acid was added in small portions to an equal weight of thionyl chloride on the steam bath, and the mixture was refluxed for 3 hr.

Base-Catalyzed Conversion of Thiolcarbonate Esters into Sulfides. Reactions of Xanthate Esters

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Contribution No. 1456 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received May 16, 1968

Thiolcarbonate and xanthate esters are well known to be readily solvolized by protonic solvents under basic conditions,[1] but little is known of their base-catalyzed reactions under aprotic conditions. This Note described our study of such reactions of representative thiolcarbonates and xanthates.

Thiolcarbonate esters.—We have found that certain aprotic Lewis bases strongly catalyze conversion of thiolcarbonates into sulfides with loss of CO_2. In favorable cases, the reaction goes under mild conditions in quantitative yields. For example, liquid O-methyl-S-phenyl thiolcarbonate (**1**) is converted into methyl phenyl sulfide (**2**) and CO_2 in high yield at 35° by solutions containing fluoride ion (eq 1). Without a catalyst **1** is thermally stable to about 180°, where slow (0.25%/hr) conversion into **2** occurs (eq 2). An analogous reaction of cyclic ethylene thiolcarbonate was reported to give ethylene sulfide.[2]

$$\underset{\mathbf{1}}{C_6H_5S\overset{\overset{O}{\|}}{C}OCH_3} \xrightarrow[35°,\ 64\ hr]{Et_4N^+F^-,\ MeCN} \underset{\mathbf{2}\ (97\%)}{C_6H_5SCH_3} + CO_2 \quad (1)$$

$$\mathbf{1} \xrightarrow[180°,\ 64\ hr]{neat} \mathbf{2}\ (12\%) + CO_2 \quad (2)$$

A number of bases were tested as catalysts for conversion of **1** into **2** in nitrobenzene (Table I). Mixtures of solvent, **1**, and catalyst in a 40:10:1 ratio by weight was heated at 85 ± 1° for 1.0 hr. Yields were estimated by nmr analysis.

TABLE I

CATALYSTS FOR CONVERSION OF 1 INTO 2

Catalyst	Conversion, %	Catalyst	Conversion, %
$Et_4N^+F^-$	100	$(Me_2NCH_2^-)_2$	100
$Bu_4N^+Br^-$	9	Pyridine	52
Et_3P	99	Quinoline	2
$(C_8H_{17})_3P$	94	Imidazole	2
$(C_6H_5)_3P$	18	$(C_6H_5)N{=}N(C_6H_5)$	Trace
Et_3N	100	$(C_6H_5)_3PS$	Trace
$(C_6H_5)CH_2NMe_2$	86	None	Trace

These data show that tertiary phosphines, tertiary amines, and soluble fluorides are good catalysts. Similar tests at 35° revealed that fluoride ion is far more active than pyridine; fluoride appears to be the best catalyst for difficult cases. Trioctylphosphine is also a useful catalyst, being nonvolatile, easily handled, and

(1) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, pp 137, 165–167.

(2) (a) D. D. Reynolds, *J. Amer. Chem. Soc.*, **79**, 4951 (1957). (b) D. D. Reynolds, U. S. Patent 2,828,318 (1958); *Chem. Abstr.*, **52**, 14651*f* (1958).

fairly active. Tertiary amines are active but cause darkening during the reaction.

Similar experiments demonstrated a strong solvent effect on the reaction. Mixtures of solvent, **1**, and triphenylphosphine in a 40:5:1 ratio were heated at 85° for 1 hr. In solvents of relatively low polarity (chloroform, benzene, *o*-dichlorobenzene) the conversion into **2** was 1.6 to 2%. Increasing polarity gave higher conversions into **2**: acetonitrile (5%), nitrobenzene (9%), dimethyl sulfoxide (~45%), and N,N-dimethylformamide (55%).

The scope of the reaction as a synthetic method was examined in representative cases (Table II).

TABLE II

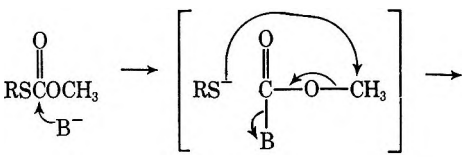
SYNTHESIS OF SULFIDES FROM THIOLCARBONATES

$$RSCOR' \xrightarrow{\text{base}} RSR' + CO_2$$

R	R′	Base	Solvent	Temp, °C	Time, hr	Yield, %
C_6H_5	CH_3	$(C_8H_{17})_3P$	None	100	20	100
C_6H_{13}	CH_3	$(C_8H_{17})_3P$	None	100	18	97
C_6H_5	C_2H_5	$(C_8H_{17})_3P$	None	100	17	26
C_6H_5	C_2H_5	$Et_4N^+F^-$	CH_3CN	70	20	98
C_6H_5	$CH(CH_3)_2$	$Et_4N^+F^-$	DMF	153	10	24
C_6H_5	C_6H_5	$Et_4N^+F^-$	DMF	145	15	0

These results show that branching at R′ strongly impedes the reaction. No reaction occurs when R′ is phenyl.

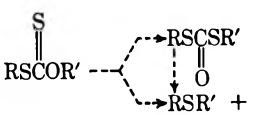
A reasonable mechanism for sulfide formation involves initial attack of the catalyst on the carbonyl carbon (eq 3). This mechanism is consistent with the



$$RSCH_3 + B^- \cdots CO_2 \quad (3)$$

strong solvent effect and with the fact that the rates apparently parallel the ease of nucleophilic substitution at R′. This mechanism suggests that the nature of group R is relatively unimportant, in agreement with the limited experimental data. We have not determined whether the reaction is intra- or intermolecular.

Xanthate Esters.—Xanthate esters could potentially react analogously to give sulfides and COS. A competing reaction, isomerization to dithiolcarbonates, is also possible (eq 4). Bond energy data indicate that isomerization is exothermic by about 24 kcal/mol.[3]



(4)

Scattered reports of thermal reactions of xanthate esters which cannot undergo Chugayev elimination suggest that isomerization predominates.[4,5] Internally catalyzed isomerization of tertiary amino[5] and allylic[6] xanthate esters to dithiolcarbonate esters occurs in high yields.

We briefly examined thermal and base-catalyzed reactions of S-benzyl O-methyl xanthate (**3**) (Table III). We found that isomerization and elimination occur readily and at competitive rates (eq 5).

$$\underset{\mathbf{3}}{C_6H_5CH_2SCOCH_3} \xrightarrow[\text{base}]{\text{solvent}} \underset{\mathbf{4}}{C_6H_5CH_2SCSCH_3} + \underset{\mathbf{5}}{C_6H_5CH_2SCH_3} + COS + \text{other products} \quad (5)$$

TABLE III

PRODUCT COMPOSITION FROM REACTION OF **3**

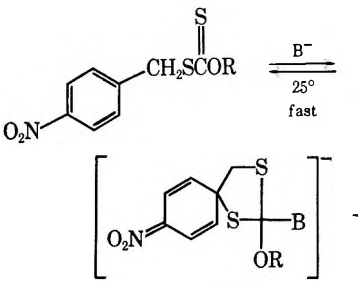
Catalyst	Solvent	Temp, °C	Time, hr	Product composition, % 4	5	Others
None	None	176	18	66	10	24
$(C_8H_{17})_3P$	$CDCl_3$	60	19	40	40	10
$(C_8H_{17})_3P$	C_6H_{12}[a]	60	19	44	32	20
$Et_4N^+F^-$	MeCN	25	24	50	15	
$Et_4N^+F^-$	MeCN	60	24	73	19	8

[a] C_6H_{12} = cyclohexane.

These results suggest that usable syntheses of sulfides and dithiolcarbonates from xanthate esters could be developed, but further reactions of the products during work-up make this route unattractive. For example, when xanthate **3** was treated with $Et_4N^+F^-$ and the product was distilled at low pressure, further equilibration of thiomethyl and thiobenzyl groups occurred to give a gross mixture of products, including trithiocarbonates.

These base-catalyzed reactions could occur during synthesis of xanthate esters, particularly with reactive alcohols. Xanthate esters should be synthesized under the mildest possible conditions (*e.g.*, in acetone at 0° or in CH_2Cl_2–H_2O at 25°). Some "xanthate esters" reported in the older (preinfrared) literature are probably dithiolcarbonates.

S-(4-Nitrobenzyl) O-methyl and O-ethyl xanthates gave intensely violet solutions when treated with fluoride, cyanide, or azide salts. The color may be caused by fast, reversible cyclization as indicated in eq 6. Neutral nucleophiles give little or no color. The



slow → mixed products (6)

(3) E. S. Kooyman in "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience Publishers, New York, N. Y., 1967, Chapter 1.

(4) D. H. Rawers and D. S. Tarbell, *J. Amer. Chem. Soc.*, **78**, 70 (1956); H. R. Al-Kazimi, D. S. Tarbell, and D. Plant, *ibid.*, **77**, 2479 (1955); P. V. Laasko, *Suomen Kemistilehti B*, **16**, 19 (1943); *Chem. Abstr.*, **40**, 4687[6]; D. L. Vincent and C. B. Purves, *Can. J. Chem.*, **34**, 1302 (1956); G. E. Risinger, *Nature*, **198**, 382 (1963); V. S. Etlis, *Zh. Obshch. Khim.*, **34**, 2996 (1964); *J. Gen. Chem. USSR*, **34**, 3032 (1964).

(5) T. Taguchi and S. Kasnga, *Chem. Pharm. Bull.* (Tokyo), **13**, 241 (1965); T. Taguchi, Y. Kawazoe, K. Yoshihira, H. Kanayama, M. Mori, K. Tobata, and K. Harano, *Tetrahedron Lett.*, 2117 (1965); T. Taguchi and M. Nakao, *Tetrahedron*, 245 (1962); T. Taguchi, Y. Kawazoe, and M. Nakao, *Tetrahedron Lett.*, 131 (1963).

(6) D. L. Garmaise, A. Uchiyama, and A. F. McKay, *J. Org. Chem.*, **27**, 4509 (1962).

colored intermediates react slowly at 25° to give a mixture of 20 or more products.

Experimental Section[7]

Synthesis of Thiolcarbonates.—S-Phenyl O-isopropyl thiocarbonate was prepared by stirring a mixture of 32 g (0.27 mol) of O-phenylthiocarbonyl chloride (K and K Laboratories), 30 g of potassium carbonate, and 210 g of 2-propanol overnight at 25° and for 5 hr at 85°. Gas evolution was noted at 85°. Filtration and fractionation through a spinning-band column gave 9 g (17%) of product: bp 77–80° (0.3 mm); nmr δ 7.44 (m, 5), 5.11 (septet, 1), 1.28 (d, 6).

Anal. Calcd for $C_{10}H_{12}O_2S$: C, 60.94; H, 6.54; S, 16.26. Found: C, 61.00; H, 6.23; S, 16.06.

The other thiolcarbonates were prepared by treating tetrahydrofuran solutions of phenyl or hexyl mercaptans first with an equimolar amount of butyllithium in hexane and then with chloromethyl, chloroethyl, or chlorophenyl carbonates. Data are in Table IV.

TABLE IV
THIOLCARBONATES

RSCOOR′	Yield, %	Bp (mm) or mp, °C	Lit. bp (mm) or mp, °C
$C_6H_5SCOOCH_3$[a] (1)	69	88–89.5 (2.4)	
$H_{13}C_6SCOOCH_3$[b]	67	70–71 (2.0)	
$C_6H_5SCOOC_2H_5$	80	69.5–70 (0.3)	130 (16)[c]
$C_6H_5SCOOC_6H_5$	47	50–60	56[c]

[a] *Anal.* Calcd for $C_8H_8O_2S$: C, 57.13; H, 4.79. Found: C, 57.63; H, 4.96. [b] *Anal.* Calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15. Found: C, 54.70; H, 9.25. [c] H. Rivier, *Bull. Soc. Chim. Fr.*, (4) 1, 733 (1907).

Nmr Tube Experiments.—Mixtures of solvent, 1, and catalyst in the ratio 40:10:1 by weight (Table I) and 40:5:1 (solvent-effect experiments) were prepared. Samples were placed in nmr tubes and heated in an oil bath thermostatically controlled at 85 ± 1° for 1.0 hr. The compositions of the resulting mixtures were estimated from the integrals of the methyl peaks of 1 at δ 3.78 and 2 at δ 2.37. Other products were seldom detected, never in amounts exceeding 2%.

Similarly, a solution of 0.20 g of 1 and 0.02 g of tetraethylammonium fluoride in 0.78 g of acetonitrile-d_3 were heated at 35° for 64 hr; nmr analysis showed 97% conversion into 2. A solution of 0.20 g of 1 in 0.80 g of pyridine gave 72% conversion into 2 and 28% unreacted 1 under these conditions.

Thermal Stability of O-Methyl S-Phenyl Thiocarbonate (1).—An nmr tube containing 1 was heated in an oil bath at 154° for 4 hr. The nmr spectrum was unchanged. When a sample was heated for 3 days at 180°, nmr analysis showed 12% conversion into $C_6H_5SCH_3$, 88% unchanged starting material.

Methyl Phenyl Sulfide (2).—A mixture of 1.00 g of trioctylphosphine in 5.00 g (0.030 mol) of 1 was heated at 100 ± 1° for 19 hr in a Schlenck tube. Slow evolution of gas was noted. Flash distillation at 1 μ gave 3.72 g (100%) of colorless 2. Glpc at 125° on a 2-m column of 20% Triton X-305® on Gas Chrom R® showed 99.6% purity.

Hexyl Methyl Sulfide.—This reaction was run similarly using 8.82 g (0.05 mol) of S-hexyl O-methyl thiocarbonate. Flash distillation gave 6.50 g (98% of *n*-hexyl methyl sulfide, 97% pure by glpc on a 1-m column of 20% Triton X-305® on Gas Chrom R® with linear programming from 100 to 250°.

Ethyl Phenyl Sulfide.—A mixture of 11.1 g (0.061 mol) of O-ethyl S-phenyl thiocarbonate and 0.3 g of tetraethylammonium fluoride was heated and stirred at 70°. No gas evolved. Acetonitrile (11.6 g) was added to give a homogeneous solution. Heating at 70° was continued for 20 hr as gas slowly evolved. Glpc on a 0.6-m column of 10% Apiezon L® on Gas Chrom R® with linear programming from 100 to 250° showed 98% conversion into product and 2% conversion into an unidentified by-product. Distillation gave 7.48 g (89%) of ethyl phenyl sulfide, bp 81–83° (8.6 mm) [lit.[8] bp 86–87° (14 mm)].

(7) Melting and boiling points are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were produced on a Varian Model A-60 device using 49:1 $CDCl_3$–Me_4Si as solvent, except as noted.

(8) H. Brintzinger and M. Langheck, *Ber.*, **87**, 325 (1954).

Isopropyl Phenyl Sulfide.—A solution of 8.0 g of O-isopropyl S-phenyl thiocarbonate and 0.23 g of tetraethylammonium fluoride in 20 g of N,N-dimethylformamide was stirred at 130° for 16 hr. Little or no gas evolved. The solution was heated at reflux for 10 hr. Gas evolved slowly. The solution was poured into water. The oil was extracted with methylene chloride, dried, and concentrated. Analysis by glpc and nmr showed approximately 24% conversion into product (nmr δ 3.33) and 50% unchanged starting material.

S-Benzyl O-Methyl Xanthate (3).—To a solution of 43.4 g (0.33 mol) of sodium methyl xanthate in 300 ml of acetonitrile was slowly added 57.1 g (0.33 mol) of benzyl bromide at 10–20°. The solution was concentrated under high vacuum and filtered, always keeping the product at 25° or lower. The residue was 67 g (100%) of product, 99% pure by nmr [δ 7.29 (5), 4.35 (2), 4.12 (3)]. Distillation gave 28 g of 3, bp 107–109° (0.4 mm), containing several per cent isomer 4 and sulfide 5.

Rapid addition of benzyl bromide to an equimolar amount of sodium methyl xanthate in warm methanol gave a fast, exothermic reaction. A 42% yield of benzyl methyl sulfide, bp 72° (2.4 mm), was obtained by fractionation of the product.

Reactions of 3.—These reactions were performed in nmr tubes or the equivalent as described above. The methyl and methylene peaks of isomer 4 were at δ 2.36 and 4.35, respectively. The corresponding peaks of sulfide 5 were at δ 1.93 and 3.62.

O-Methyl S-(*p*-Nitrobenzyl) Xanthate.—A solution of 16.6 g (0.013 mol) of sodium methyl xanthate and 27.4 g (0.013 mol) of *p*-nitrobenzyl bromide in 300 ml of acetonitrile was kept at 25° for 3 hr. Solvent removal and recrystallized from toluene–methanol gave 21.7 g (70%) of product: mp 76.5–77.5°; nmr δ 7.88 (q, 4), 4.48 (2), 4.20 (3); ir no C=O peak.

Anal. Calcd for $C_9H_9NO_3S_2$: C, 44.43; H, 3.73; N, 5.76; S, 26.36. Found: C, 44.54; H, 3.90; N, 5.70; S, 26.38.

O-Ethyl S-(*p*-Nitrobenzyl) Xanthate.—This ester, mp 62–63° (lit.[9] mp 65–66°), was prepared as described above for the methyl ester in 83% yield. The product was recrystallized from toluene–pentane: nmr δ 7.84 (4), 4.65 (q, 2), 4.43 (2), 1.40 (t, 3); ir no C=O peak.

Anal. Calcd for $C_{10}H_{11}NO_3S_2$: C, 46.67; H, 4.27; N, 5.44; S, 24.92. Found: C, 46.85; H, 4.26; N, 5.44; S, 24.91.

Reactions of S-(*p*-Nitrobenzyl) Xanthates.—Treatment of these xanthates with soluble F^-, CN^-, or N_3^- salts gave intensely violet colors which slowly faded during several days. Acetonitrile solutions containing equimolar quantities of the O-methyl xanthate and Et_4NF had λ_{max} 520 mμ (ε 2500), 303 (11,000), 277 (12,800); aging caused these peaks to shift in wavelength and intensity. Nmr study of such solutions showed that mixtures were present at all times. Chromatography of a week-old solution gave more than 20 colored fractions.

Registry No.—1, 3186-52-5; 3, 17659-13-1; 5-phenyl O-isopropyl thiocarbonate, 17659-14-2; $H_{13}C_6SCOOCH_3$, 17659-15-3; O-methyl S-(*p*-nitrobenzyl) xanthate, 15183-56-9; O-ethyl S-(*p*-nitrobenzyl) xanthate, 17659-17-5.

Acknowledgment.—We are indebted to Mr. Jake Graff and Mr. Paul Sanders for technical assistance and to Dr. R. A. Clement for helpful discussions.

(9) A. L. Morrison and F. R. Atherton, British Patent 675,779 (1952).

The Specific Debenzylation of Alkylated Carbohydrates *via* Bromination–Hydrolysis

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Received May 8, 1968

We wish to report a new method for the debenzylation of carbohydrates. This method has been used successfully with hexopyranosides, an acyclic hexose,

oligosaccharides, and a polysaccharide. The method appears to be specific for debenzylation, *i.e.*, appended hydroxyl and methoxyl groups as well as heterooxygen bonds remain intact.

Recently, in this laboratory, tri-*O*-benzylamylose was prepared and subjected to methanolysis; the products were then methylated to give a homologous series of perbenzylated methyl terminal 4-*O*-methylmaltooligosaccharides.[1] Debenzylation of these oligosaccharides was unsuccessful when the usual procedures were followed.

Benzylation is frequently used to protect hydroxyl groups during carbohydrate reactions because the resulting benzyl ethers are stable to acids and bases, oxidizing agents, and reducing agents such as sodium borohydride and lithium aluminum hydride. For the most part, hydroxyl groups are subsequently easily regenerated, usually by catalytic hydrogenolysis.[2] Benzylated monosaccharides, for example, are easily debenzylated this way. On the other hand, only slight debenzylation of oligo-[3] and polysaccharides is effected when they are treated by the same methods because of their lower solubility and because they coat the catalyst, making it inaccessible to other molecules.[4]

We have now worked out an apparently general scheme whereby carbohydrate derivatives can be debenzylated rapidly, specifically, and with retention of configuration. The scheme consists of free-radical bromination in chloroform, carbon tetrachloride, benzene, or Sulfolane[5] at 0–25° followed by hydrolysis in saturated sodium carbonate or calcium hydroxide solutions. By this reaction sequence, carbohydrate derivatives can be debenzylated rapidly and with retention of configuration. The experimental procedure is illustrated by several examples in the Experimental Section. A critical discussion of the reaction mechanism is being prepared.

This method was also successfully applied to the debenzylation of perbenzylated methyl terminal 4-*O*-methylmaltooligosaccharides. Tlc analysis of the products revealed a homologous series of compounds identical with that obtained by hydrogenolysis using an excess of Raney nickel.[1] Acid-catalyzed hydrolysis of the products yielded only D-glucose and 4-*O*-methyl-D-glucose which were not present originally. There was no evidence of glycosidic bond cleavage; *i.e.*, there was no indication of the formation of D-glucose, 4-*O*-methyl-D-glucose, methyl D-glucopyranoside, or D-gluconic acid or its lactones during either the bromination or the work-up. Likewise, debenzylation of tri-*O*-benzylamylose was accomplished in one treatment (infrared analysis) with no breakdown of the polymer chain (chromatographic analysis).

By using an incandescent lamp the reaction proceeds slowly enough that hydrogen bromide is released to the atmosphere before its concentration effects degradations. Flushing the beaker with dry air or nitrogen is often helpful. With compounds devoid of acid-labile groups, temperature, moisture, and hydrogen bromide concentration need to be less carefully controlled. For example, pure D-glucitol was obtained in very high yield when a solution of hexa-*O*-benzyl-D-glucitol in chloroform was treated with bromine, irradiated with an ultraviolet lamp, then shaken with lime water.

This new procedure should be useful in removing benzyl ether groups from molecules which contain groups that are reduced or cleaved by catalytic hydrogenation but cannot be used in the presence of triphenylmethyl ethers because of their facile cleavage by hydrogen bromide nor in the presence of benzylidene cyclic acetals. Both methyl 6-*O*-triphenylmethyl-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside are converted into methyl α-D-glucopyranoside when allowed to react under the conditions described in the examples given.

Experimental Section

Procedure. A.—Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside was prepared according to the method of Bell and Lorber.[6] In an open beaker a solution of 0.500 g (1.34×10^{-3} mol) of this substance in 50 ml of Sulfolane was maintained at 20–25° by the use of an acetone–Dry Ice bath.[7] Bromine (0.14 ml, 2.70×10^{-3} mol; 1.0 mol per mole of benzyl ether group) was added all at once and the stirred reaction mixture was irradiated for 3 hr from above with a 60-W incandescent bulb. An additional 0.14 ml of bromine was added, and irradiation was continued for an additional 1.5 hr. The reaction mixture was then shaken with 100 ml of a saturated sodium carbonate solution for 15 min. Several extractions of this mixture with chloroform removed the Sulfolane. The remaining water layer was treated with a mixed anion-cation-exchange resin and evaporated to dryness to yield 0.253 g (97%). Tlc of this syrup revealed only one component which corresponded to methyl α-D-glucopyranoside. Crystallization of the syrup from absolute ethanol converted it into a white solid, mp 164–165°, which was identical with that of standard methyl α-D-glucopyranoside and of a mixture of the two.

B.—Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside was prepared by the method of Tate and Bishop.[8] This substance (1.659 g, 3.0×10^{-3} mol) was dissolved in 50 ml of Sulfolane maintained at 20–25° in an open beaker. Bromine (0.28 ml. 5.40×10^{-3} mol; 0.45 mol per mole of benzyl ether group) was added, and the mixture was irradiated directly with a 60-W incandescent bulb. After 1.5, 3.0, and 4.5 hr, respectively, additional 0.28-ml portions of bromine were added. After a total of 6 hr, the reaction was worked up as described above to yield 0.426 g (73%) of a syrup which by tlc was proved to be identical with an authentic sample of methyl α-D-glucopyranoside.

The above reactions were also effected in benzene, chloroform, or carbon tetrachloride in place of Sulfolane and sodium bicarbonate or calcium hydroxide in place of sodium carbonate. Similar yields of methyl α-D-glucopyranoside were obtained.

C.—Hexa-*O*-benzyl-D-glucitol (0.500 g, 6.92×10^{-3} mol; containing trace impurities of partially benzylated D-glucitol as shown by tlc), prepared by the procedure of Tate and Bishop,[8] was dissolved in 50 ml of chloroform. To the solution, maintained at room temperature in an open beaker, bromine (1.0 ml, 1.93×10^{-2} mol; 2.3 mol per mole of benzyl ether) was added, and the reaction mixture was irradiated for 80 min with a long-wavelength ultraviolet lamp. A precipitate formed during the reaction when chloroform was used as the solvent which has tentatively been identified as an α-bromo ether. (These results will

(1) J. N. BeMiller and R. E. Wing, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. C45; R. E. Wing, Ph.D. Dissertation, Southern Illinois University, 1967; J. N. BeMiller and R. E. Wing, *Carbohyd. Res.*, **6**, 197 (1968).

(2) Debenzylation methods have been reviewed by W. H. Hartung and R. Simonoff, *Org. Reactions* **7**, 263 (1953), and by G. M. McCloskey, *Advan. Carbohyd. Chem.*, **12**, 137 (1957).

(3) R. J. Rebhahn, Ph.D. dissertation, Rutgers—The State University, New Brunswick, N. J., 1966.

(4) Debenzylation of oligosaccharides has been accomplished with amounts of Raney nickel far in excess of what is normally considered to be catalytic.[1]

(5) A trademark of the Shell Chemical Co. for tetramethylene sulfone. Commercial samples normally contain up to 5% water and were used as received.

(6) D. Bell and J. Lorber, *J. Chem. Soc.*, 453 (1940).

(7) This bath was used to control the temperature so as not to expose the open beaker to extra water vapor.

(8) M. E. Tate and C. T. Bishop, *Can. J. Chem.*, **41**, 1801 (1963).

be reported in the critical discussion being prepared.) The reaction mixture was then stirred for 30 min with 100 ml of a saturated calcium hydroxide solution. The precipitate which had formed during the reaction disappeared during this treatment with base. Carbon dioxide was bubbled through the solution until it was neutral, and the calcium carbonate was removed by filtration. The layers were separated and evaporated under reduced pressure. Chromatographic examination of the chloroform layer revealed no carbohydrates. The water layer was stirred with a mixed ion-exchange resin and, after filtration and evaporation, a syrup was obtained [0.125 g (100%)]. Analysis of the syrup by tlc and glpc showed the product to be identical with an authentic sample of D-glucitol.

D.—Methyl terminal 4-*O*-methylmaltooligosaccharides have been prepared in this laboratory.[1] A homologous series (0.100 g) was dissolved in 50 ml of chloroform maintained at 0–10° in an open beaker. Bromine (0.28 ml, 5.40×10^{-3} mol) was added dropwise over a 15-min period, while the stirred mixture was irradiated with a 60-W incandescent bulb. After 1.5 and 3.0 hr, respectively, additional 0.28-ml portions of bromine were added. After a total of 6.0 hr, the reaction mixture, which contained a precipitate, was worked up as described for the D-glucitol reaction to yield 0.04 g. Tlc analysis of the resulting syrup showed the components to be identical with the products obtained when the same compounds were treated with excess Raney nickel.[1] The syrup was hydrolyzed with 30 ml of 2 *N* sulfuric acid for 36 hr. After neutralization (resin) and evaporation, the products were converted into their per(trimethylsilyl) derivatives and analyzed by glpc. Only D-glucose and 4-*O*-methyl-D-glucose were indicated to be present.

E.—Tri-*O*-benzylamylose has been prepared in this laboratory.[1] This substance (0.172 g) was dissolved in 50 ml of chloroform maintained at 0–10° in an open beaker. Bromine (0.2 ml, 3.86×10^{-3} mol) was added all at once, while the stirred reaction mixture was irradiated with a 60-W incandescent light. After 1.5 and 3.0 hr, respectively, additional 0.2-ml portions of bromine were added. After a total of 4.5 hr, the reaction mixture, which contained a precipitate, was worked up as described for the D-sorbitol reaction to yield 0.08 g. Tlc analysis of this product showed no degradation products (D-glucose, D-gluconic acid, or D-gluconolactone). Infrared analysis showed the absence of benzyl ether groups. The product gave a blue color on treatment with iodine solution, indicating that amylose (DP >20) was present.

Registry No.—Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside, 17791-36-5; methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside, 17791-37-6; hexa-*O*-benzyl-D-glucitol, 17791-38-7.

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Steroid Tetrazoles[1]

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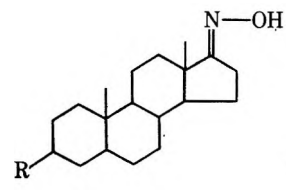
Tetrazoles are known to be formed when an excess of azide is used in the Schmidt reaction,[2,3] and by the reaction of oximes with sodium azide in the presence of sulfuric acid or chlorosulfonic acid.[3,4]

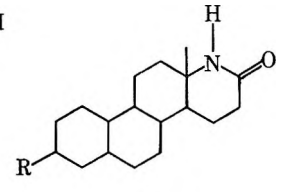
In this Note we wish to report the reaction of sodium azide with steroidal C-17 oximes, which proceeds with concomitant ring D rearrangement, to yield pentacyclic steroid tetrazoles.

Reaction of hydrazoic acid (generated by the action of sodium azide on chlorosulfonic acid) with 5α-androstan-17-one oxime (**1a**) afforded a mixture of lactam **2a** and tetrazole **3a**. The nuclear magnetic resonance (nmr) spectrum of this compound (**3a**), as well as that of the other tetrazoles described here, is characterized by the strong deshielding of the 18-methyl protons (1.36 ppm) by the tetrazole ring.

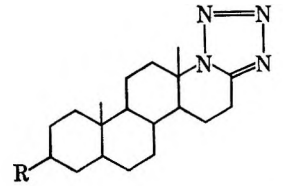
The same reaction with the 3β-acetoxy 17-oxime (**1b**)[5] provided a mixture containing 48% lactam **2b** and 9.5% the expected tetrazole (**3b**). Alkaline hydrolysis of the 3-acetoxyl group in **3b**, gave the corresponding alcohol (**3c**) which was oxidized with chromic acid in acetone[6] to the 3 ketone (**3d**). The latter was

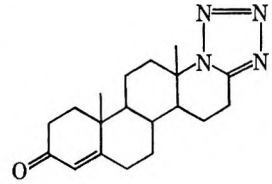


1a, R = H
b, R = AcO



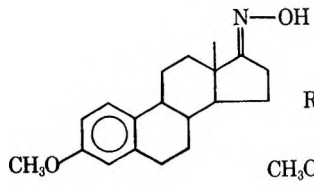
2a, R = H
b, R = AcO





3a, R = H
b, R = AcO
c, R = OH
d, R = ketone
e, 2,4-dibromo; R = ketone

4



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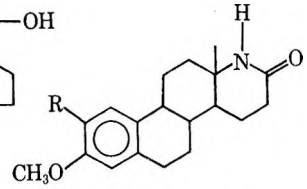
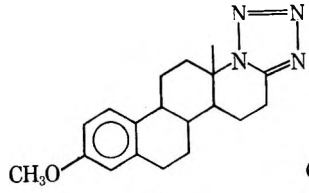


6a, R = H
b, R = SO_2Cl



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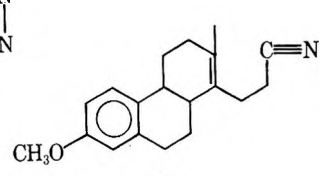


8

(1) Publication no. 332 from the Syntex Institute of Steroid Chemistry. For no. 331, see P. Crabbé, H. Carpio, A. Cervantes, J. Iriarte, and L. Tökes, *Chem. Commun.*, **2**, 79 (1968).

(2) M. A. Spielman and F. L. Austin, *J. Amer. Chem. Soc.*, **59**, 2658 (1937).

(3) For a leading reference, see H. Wolff, *Org. Reaction*, **3**, 307 (1946).

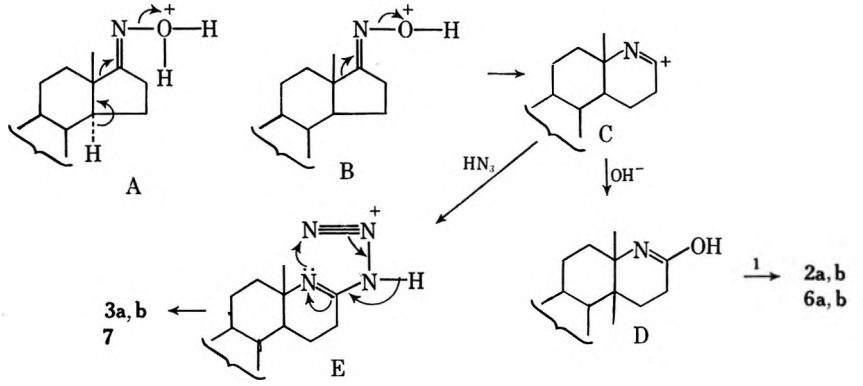
(4) See also (a) K. F. Schmidt, German Patent 855,711 (Nov 17, 1952); *Chem. Abstr.*, **52**, 15592g (1958); (b) Fr. R. Benson, *Chem. Rev.*, **41**, 1 (1947).

(5) R. Anliker, M. Müller, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **38**, 1404 (1955).

(6) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(7) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

SCHEME I



converted to the dibromide (**3e**) and then, by conventional methods,[7] to the Δ^4-3-ketotetrazole (**4**).

Treatment of the oxime **5**[8] with sodium azide and chlorosulfonic acid afforded three compounds, the tetrazole **7** and the lactam **6a**,[8] isolated in 2 and 38% yield, respectively, as well as 9% D-secocyano derivative **8**. Furthermore, a fourth substance, *i.e.*, the chlorosulfonated steroid **6b**, was isolated in 14% yield when the reaction was run at higher temperature (see Experimental Section).

Structure **8**, assigned to the cyano compound, is supported by the C≡N absorption at 2230 cm^{-1}, as well as by the vinylic 13-methyl protons resonance at 1.73 ppm. The location of the newly introduced chlorosulfonyl group at C-2 in the lactam **6b** is inferred from the absence of C-2 aromatic proton in the nmr spectrum.

The fragmentation leading to the seco steroid **8**, is reminiscent of the reported cleavage of oximes by treatment with *p*-toluenesulfonyl chloride,[9] and probably proceeds by concerted fragmentation of the protonated oxime, as indicated in A. Since the lactams (**2a**, **2b**, and **6a**) were recovered unchanged on attempted reaction with HN_3, one may assume that both the lactams and the tetrazoles are formed by action of hydrazoic acid on an azomethine cation intermediate of type C, formed by rearrangement of the oxime and elimination of OH^-, as indicated in B (Scheme I).

Experimental Section[10]

5α-Androstan-17-one Oxime (1a).—A solution of 2 g of 5α-androstan-17-one in 75 ml of ethanol was refluxed for 2 hr with a mixture of 0.9 g of hydroxylamine hydrochloride, 1.07 g of sodium acetate, and 28 ml of ethanol.

Evaporation of the solvent and extraction with ethyl acetate gave 1.5 g of crude 5α-androstan-17-one oxime. Purification by recrystallization from acetone provided the analytical sample: mp 173–175°; $[\alpha]_D$ +14°; ν_{max} 3250 cm^{-1}; nmr 0.77 (19 H), 1.14 (18 H), 5.95 ppm (C=N—OH).

Anal. Calcd for $C_{19}H_{31}ON$: C, 78.84; H, 10.80; N, 4.84. Found: C, 79.19; H, 10.76; N, 5.19.

17a-Aza-D-homo-5α-androstane-17,17a-e-tetrazole (3a).—To 585 mg of sodium azide suspended in 10 ml of ethylene chloride 2.7 ml of chlorosulfonic acid was slowly added. The mixture was stirred for 1 hr, and an additional 585 mg of sodium azide was then added. After 15 min a solution of 1.5 g of 5α-androstan-17-one oxime (**1a**) in 20 ml of ethylene chloride was slowly added, and the reaction mixture was stirred at room temperature for 2 hr. Addition of water and extraction with ethyl acetate gave a dark oil which was chromatographed over 150 g of Florisil. By elution with a mixture of hexane–ethyl acetate (8:2), 280 mg of tetrazole (**3a**) was isolated. After three crystallizations from methylene chloride–hexane, 140 mg of pure tetrazole (**3a**) was obtained. The analytical sample showed mp 185–187°; $[\alpha]_D$ +67°; ν_{max} 3350 cm^{-1}; nmr 0.81 (19 H), 1.36 ppm (18 H).

Anal. Calcd for $C_{19}H_{30}N_4$: C, 72.56; H, 9.62; N, 17.82. Found: C, 72.35; H, 9.93; N, 18.02.

Further elution with hexane–ethyl acetate (2:3) furnished 600 mg of 13α-amino-13,17-seco-5α-androstan-17-oic acid lactam (**2a**). Purification by recrystallization from methylene chloride–ether provided 430 mg of pure lactam (**2a**): mp 314–315°; $[\alpha]_D$ +14°; ν_{max} 3110, 3025, 1675, 1610 cm^{-1}; nmr 0.80 (19 H), 0.90 (18 H), 5.50 ppm (NH).

Anal. Calcd for $C_{19}H_{31}ON$: C, 78.84; H, 10.80; N, 4.84. Found: C, 78.54; H, 10.93; N, 5.04.

17a-Aza-3β-hydroxy-D-homo-5α-androstane-17,17a-e-tetrazole Acetate (3b).—To a stirred suspension of 6 g of sodium azide in 100 ml of ethylene chloride, 18 ml of chlorosulfonic acid was added dropwise. After 1 hr an additional 6 g of sodium azide was added; 16 min later a solution of 10 g of 3β-acetoxy-17-oximino-5α-androstane (**1b**)[6] in 150 ml of ethylene chloride was slowly added. The reaction mixture was stirred at room temperature for 2 hr and then worked up by addition of water and extraction with methylene chloride. The product was filtered through Florisil, with hexane–ethyl acetate (65:35), yielding 1 g of tetrazole (**3b**). Repeated crystallizations from methylene chloride–ether provided the pure sample: mp 254–256°; $[\alpha]_D$ +40°; ν_{max} 1738, 1527, 1455 cm^{-1}; nmr 0.86 (19 H), 1.36 (18 H), 2.0 ppm (3β OAc).

Anal. Calcd for $C_{21}H_{32}O_2N_4$: C, 67.71; H, 8.66. Found: C, 67.42; H, 8.61.

Further elution with ethyl acetate gave 4.8 g of 13α-amino-3β-acetoxy-13,17-seco-5α-androstan-17-oic acid lactam (**2b**). Crystallization from methylene chloride–methanol gave the pure product (**2b**): mp 263–265°; $[\alpha]_D$ −9°; ν_{max} 3130, 3020, 1740, 1680, 1610 cm^{-1}; nmr 0.81 (19 H), 1.13 (18 H), 2.01 (3 OAc), 4.50–4.83 (3α H), 6.81 ppm (–NH–).

Anal. Calcd for $C_{21}H_{33}O_3N$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.44; H, 9.91; N, 4.17.

17a-Aza-D-homo-5α-androstan-3-one-17,17a-e-tetrazole (3d).—3-Acetoxytetrazole **3b**, 3.1 g, was hydrolyzed at room temperature with 90 ml of 1% solution of potassium hydroxide in methanol for 18 hr under nitrogen. Dilution with water and extraction with methylene chloride gave 3 g of the crude alcohol (**3c**) which, without further purification, was dissolved in 200 ml of acetone and treated with stirring at 8° with 3 ml of 8 *N* chromic acid,[6] for 45 min. Aqueous sodium bisulfite was added, and the

(8) B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, **78**, 639 (1956).

(9) See (a) R. M. Carman and D. Cowley, *Aust. J. Chem.*, **18**, 213 (1965); (b) J. Klinot and A. Vystrčil, *Collect. Czech. Chem. Commun.*, **27**, 377 (1962); (c) J. A. Marshall and N. H. Andersen, *Tetrahedron Lett.*, 1219 (1967); (d) E. S. Olson and J. H. Richards, *J. Org. Chem.*, **33**, 434 (1968).

(10) Microanalyses were done by Dr. A. Bernhardt, Mülheim, Germany. Melting points were determined in capillary tubes with a Mel-Temp apparatus; they are corrected. Rotations were taken between 16 and 22°, in chloroform solution, with a 1-dm tube at sodium D line. Infrared spectra were taken with a Perkin-Elmer Model 21 spectrophotometer with a NaCl prism in KBr pellets. Ultraviolet absorption spectra were obtained with a Beckman spectrophotometer, Model DU. The nmr spectra were recorded at 60 Mcps using 5–8% w/v solutions of steroid in chloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies are quoted as parts per million downfield from the TMS reference and are accurate to ±0.01 ppm; coupling constants, *J*, in cycles per second, are accurate to ±0.5 cps. Mass spectra (MS) were determined on an Atlas CH-4 spectrometer by direct insertion of the sample into the ion source; the ionizing energy was 70 eV, and a 3-kV accelerating potential was used. We are indebted to Dr. L. Throop and his staff for nmr and MS measurements.

mixture was extracted with methylene chloride to yield 2.25 g of an homogeneous product. Recrystallization from methylene chloride–hexane gave the pure sample of (3d): mp 262–264°; $[\alpha]D$ +71°; ν_{max} 1705, 1520, 1450 cm^{-1}; nmr 1.06 (19 H), 1.39 ppm (18 H).

Anal. Calcd for $C_{19}H_{28}ON_4$: C, 69.47; H, 8.59; N, 17.06. Found: C, 69.58; H, 8.75; N, 16.90.

17a-Aza-D-homoandrost-4-en-3-one-17,17a-e-tetrazole (4).—A solution of 2 g of the 3 ketone (3d) in 75 ml of acetic acid was treated dropwise with 1.92 g of bromine in 6.2 ml of acetic acid. Three drops of a saturated solution of hydrogen bromide in acetic acid was added, and the mixture was stirred for 18 hr. The reaction mixture was then poured into water, and the precipitated solid was extracted with methylene chloride. The extract was washed to neutrality, dried, and evaporated *in vacuo* to yield 2.6 g of the corresponding 2,4-dibromo compound 3e which, without further purification, was treated with chromous acetate as follows.[7]

Zinc dust (10 g) was amalgamated by shaking with a solution of 0.8 g of mercuric chloride, 10 ml of water, and 0.5 ml of hydrochloric acid for 5 min and decanting the supernatant. Addition of a solution of 5 g of chromic chloride in 20 ml of water and 2 ml of hydrochloric acid under an atmosphere of carbon dioxide gave a dark blue solution of chromous chloride which was immediately transferred to a three-necked flask (under a rapid stream of carbon dioxide) provided with gas inlet and outlet tubes, a dropping funnel, and a sintered-glass filtering stick tube which could be lowered or raised through a rubber stopper. This filter tube was connected to the vacuum line.[7]

A solution of 9.2 g of sodium acetate in 18 ml of deoxygenated water was added through the dropping funnel without stirring. The blue solution turned to crystals of deep red chromous acetate. The suspension was stirred; the filter was lowered and the liquid phase was withdrawn; and the precipitate was washed with two portions of ethanol, and finally with ether. To the dry powder was added with stirring 2.6 g of the dibromo compound 3e dissolved in 75 ml of acetic acid and 18 ml of chloroform. After 8 min, air was blown through the flask to oxidize the excess of chromous acetate. The mixture was then poured into cold water, extracted with methylene chloride, washed several times with water, dried and evaporated *in vacuo*. There was obtained 1.9 g of an oily product which was dissolved in 6 ml of dimethylacetamide and added to a boiling suspension of 0.8 g of calcium carbonate in 18 ml of dimethylacetamide under a stream of nitrogen. After 30 min the mixture was cooled, poured into water, and extracted with methylene chloride, then washed with a 2% solution of hydrochloric acid and finally with water to neutrality.

The residue was purified by preparative thin layer chromatography to yield 630 mg of 4. Recrystallization from methylene chloride–ether yielded 450 mg of the analytical sample: mp 236–238°; $[\alpha]D$ +120°; λ_{max} 240 mμ (log ε 4.15); ν_{max} 3350, 1665, 1615, 1520, 1455 cm^{-1}; nmr 1.25 (19 H), 1.43 (18 H), 5.73 ppm (4 H).

Anal. Calcd for $C_{19}H_{26}ON_4$: C, 69.90; H, 8.03; N, 17.17. Found: C, 69.95; H, 8.07; N, 17.41.

17a-Aza-3-hydroxy-D-homoestra-1,3,5(10)-triene-17,17a-e-tetrazole,3-Methyl Ether (7).—Chlorosulfonic acid (13 ml) was added dropwise with stirring to a suspension of 6 g of sodium azide in 100 ml of ethylene chloride. After 1 hr, more sodium azide (6 g) was added, and, 15 min later, a solution of 10 g of estrone methyl ether 17-oxime (5)[8] was added slowly. The mixture was stirred for 2 hr and then poured into water, and the product extracted with methylene chloride. The residue was dissolved in methylene chloride and filtered through a column on Florisil. Elution with hexane–ethyl acetate (95:5) afforded 1 g of the cyano derivative 8, which after two crystallizations from methanol–water showed mp 68–69°; $[\alpha]D$ −84°; λ_{max} 278, 287 mμ (log ε 3.31, 3.27); ν_{max} 2230, 1605, 1580 cm^{-1}; nmr 1.73 (18 H, vinylic methyl), 3.75 (3 OCH_3), 6.67 (4 H), 6.67, 6.80 (2 H), 7.16, 7.31 ppm (1 H); MS 281 (M^+).

Anal. Calcd for $C_{19}H_{23}ON$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.83; H, 8.19; N, 5.35.

Further elution with 30% ethyl acetate in hexane, gave 200 mg of 7. Crystallization from methylene chloride–ether gave the analytical sample: mp 245–247°; $[\alpha]D$ +107°; λ_{max} 278, 287 mμ (log ε 3.21, 3.17); ν_{max} 1610, 1580, 1500 cm^{-1}; nmr 1.4 (18 H), 3.75 (3 OCH_3), 6.6 (4 H), 6.8 (2 H), 7.1–7.3 ppm (1 H, doublet, J_H = 8 cps).

Anal. Calcd for $C_{19}H_{24}ON_4$: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.12; H, 7.68; N, 17.10.

Elution with ethyl acetate–hexane (1:1) provided 3.8 g of 3-methoxy-13α-amino-13,17-seco-1,3,5(10)-estratrien-17-oic acid 13,17-lactam (6a): mp 222–224°; $[\alpha]D$ +93°; λ_{max} 278, 287 mμ (log ε 3.25, 3.25). Regan and Hayes[8] report mp 222–224°; $[\alpha]D$ +95°; λ_{max} 279, 286 mμ (log ε 3.30, 3.26).

2-Chlorosulfonyl-3-methoxy-13α-amino-13,17-secoestra-1,3,5(10)-trien-17-oic Acid 13,17-Lactam (6b).—The above reaction was carried out with 2 g of estrone methyl ether oxime (5),[8] with larger amounts of chlorosulfonic acid, first heating at 35° for 1 hr and then at 50° for a second hour. After cooling, the reaction mixture was poured into water and extracted with methylene chloride. The organic layer was washed, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The slightly soluble compound 6b was recrystallized from methylene chloride–ether. There was obtained 400 mg of pure sulfonated lactam 6b: mp 258–260°; $[\alpha]D$ +76°; λ_{max} 306 mμ (log ε 3.47); nmr 1.2 (18 H) 4.01 (3 OCH_3), 6.87 (4 H), 7.85 ppm (1 H).

Anal. Calcd for $C_{19}H_{24}O_4NSCl$: C, 57.34; H, 6.08; N, 3.52; S, 8.06. Found: C, 57.26; H, 6.17; N, 3.95; S, 7.83.

Registry No.—1a, 1035-62-7; 2a, 17556-10-4; 2b, 2232-15-7; 3a, 17556-03-5; 3b, 17556-04-6; 3d, 17556-05-7; 4, 17556-06-8; 6b, 17556-11-5; 7, 17556-07-9; 8, 17556-08-0.

Acknowledgment.—We wish to thank Dr. J. Fried for helpful discussions.

Fluoronitroaliphatics. III. Preparation of Some Negatively Substituted Halonitromethanes[1]

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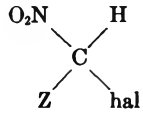
Received May 22, 1968

For a recent study of the effect of α-fluorine on C–H acidities,[3] the negatively substituted monofluoronitromethanes, Ia–IIIa, and the corresponding monochloro derivatives, Ib–IIIb, were required. We wish now to record the syntheses and some properties of these materials.



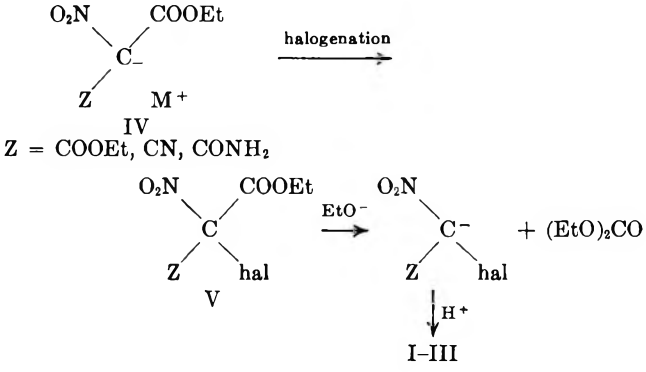
Ia, Z = COOEt; hal = F Ib, hal = Cl
IIa, Z = $CONH_2$; hal = F IIb, hal = Cl
IIIa, Z = Cl; hal = F IIIb, hal = Cl

Direct halogenation of the parent compounds, $Z-CH_2NO_2$, did not appear to be a promising route to I–III in view of the fact that dihalogenation, in particular difluorination, had frequently been observed with such systems. Thus, Inman and coworkers had reported the difluoro derivatives as the only products of the fluorination of the sodium salts of diethyl malonate, ethyl acetoacetate, and 2,4-pentanedione with

(1) Part II: M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).
(2) Deceased.
(3) H. G. Adolph and M. J. Kamlet, *J. Amer. Chem. Soc.*, **88**, 4761 (1966).

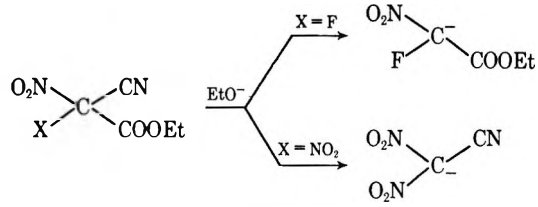
perchloryl fluoride.[4] Shechter and Roberson recorded a similar observation with primary nitroalkane salts; perchloryl fluoride fluorination gave mixtures of mono- and difluoro derivatives in low yields.[5]

Since we were interested only in the monofluorination products and wished to avoid the problems encountered by the earlier workers, the use of an easily removable blocking group was considered. Carbethoxy was chosen since it was known that, when attached to carbon carrying several electron-withdrawing substituents, it could be easily removed by alkaline hydrolysis.[6] Accordingly, the halogenation of some negatively substituted ethyl nitroacetates, generally *via* their sodium or potassium salts, and the hydrolytic cleavage of the halogenation products were investigated. For fluorination, both the perchloryl fluoride and aqueous fluorination methods were used.[1]



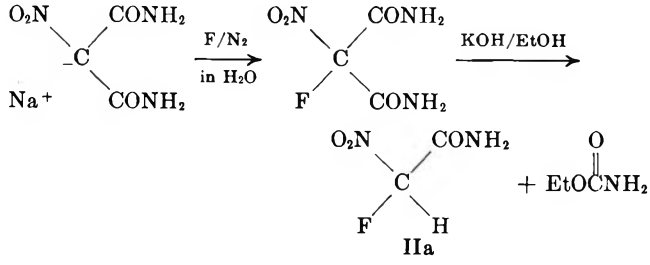
Freeman[7] reported that the reaction of sodium diethyl nitromalonate with perchloryl fluoride in N,N-dimethylformamide gave diethyl fluoronitromalonate. We have found that this reaction is more conveniently carried out in acetonitrile, where a product of excellent purity is obtained in 96% yield. Aqueous fluorination of IV, Z = COOEt, also proceeded smoothly giving V, Z = COOEt, hal = F, in 94% yield. As was expected, the latter compound was very susceptible to attack by base and with potassium hydroxide in ethanol yielded diethyl carbonate and potassium ethyl fluoronitroacetate. On treatment of the salt with cold sulfuric acid, ethyl fluoronitroacetate (Ia) was obtained in 97% yield (based on V). Ethyl chloronitroacetate (Ib) was prepared analogously, by chlorinating IV, Z = COOEt, and treating the product with base.

The fluorination of potassium ethyl nitrocyanoacetate (IV, Z = CN)[8] with perchloryl fluoride gave ethyl fluoronitrocyanoacetate (V, Z = CN, hal = F) in 25% yield. When the latter compound was treated with base, however, the nitrile group was attacked preferentially and the only product isolated was Ia, in complete contrast to the reported conversion of ethyl dinitrocyanoacetate into dinitroacetonitrile on treatment with ethoxide in ethanol.[9]



Treatment of ethyl fluoronitrocyanoacetate with concentrated sulfuric acid furnished V, Z = $CONH_2$, hal = F, as the only product. In the reaction of the latter ester amide with potassium hydroxide in ethanol the carbethoxy and carbamyl groups were attacked at about the same rate and, after acidification of the reaction mixture, Ia and fluoronitroacetamide (IIa) were obtained in about equal amounts.

A second, much shorter, route to IIa was found in the direct fluorination of sodium nitromalonamide in aqueous solution (perchloryl fluoride in acetonitrile did not react). The fluoronitromalonamide obtained thereby was converted into fluoronitroacetamide by treatment with potassium hydroxide in ethanol.



This reaction sequence was also readily adapted to the synthesis of chloronitroacetamide (IIb); see Experimental Section.

Preparation of chlorofluoronitromethane from Ia was relatively straightforward. Chlorination of the latter in aqueous solution in the presence of sodium bicarbonate gave ethyl chlorofluoronitroacetate which, upon hydrolysis with water, produced IIIa in good yield.

An attempt to remove the amide group in chlorofluoronitroacetamide (prepared by chlorination of the potassium salt of IIa in cold carbon tetrachloride suspension) was less successful; on treatment with potassium hydroxide in ethanol a complex mixture resulted which contained only traces of IIIa. Also unsuccessful were attempts, with sodium nitrite in sulfuric acid or nitrosyl tetrafluoroborate in acetonitrile,[10] to convert chlorofluoronitroacetamide into the carboxylic acid which would be expected to decarboxylate readily. In both cases the amide was recovered unchanged.

Experimental Section[11]

Diethyl Fluoronitromalonate. A. By Perchloryl Fluoride Fluorination.—Sodium diethyl nitromalonate (190 g) was placed

(4) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Amer. Chem. Soc.*, **80**, 6533 (1958)] and H. Gershon, J. A. A. Renrick, W. K. Wynn, and R. D'Ascoli [*J. Org. Chem.*, **31**, 916 (1966)] showed, however, that in the case of diethyl malonate the monofluorination product can be obtained under certain reaction conditions.

(5) H. Shechter and A. B. Roberson, Jr., *ibid.*, **25**, 175 (1960).

(6) See, for example, E. Bergman, *ibid.*, **23**, 476 (1958).

(7) J. P. Freeman, *J. Amer. Chem. Soc.*, **82**, 3869 (1960).

(8) M. Conrad and A. Schulze, *Ber.*, **42**, 737 (1909).

(9) C. O. Parker, *Tetrahedron*, **17**, 109 (1962).

(10) L. Tsai, T. Miwa, and M. S. Newman, *J. Amer. Chem. Soc.*, **79**, 2530 (1957); G. A. Olah and J. A. Olah, *J. Org. Chem.*, **30**, 2386 (1965).

(11) CAUTION—Alkali salts of nitromethanes are sensitive to impact when dry and should be handled with care. All operations connected with perchloryl fluoride and aqueous fluorinations should be carried out in a well shielded and vented area; see also ref 1, Experimental Section. In view of the high toxicity of fluoro- and difluoronitroacetic acid and many of their derivatives and in the absence of toxicologic studies the compounds reported here must be regarded as similarly dangerous poisons. Melting and boiling points are uncorrected. Elemental analyses were by Professor Mary Aldridge, Chemistry Department, American University, Washington, D. C.

in a 2-l. three-necked flask fitted with a gas inlet tube, stirrer, and a coldfinger type condenser which was cooled with Dry Ice–acetone. Acetonitrile (1500 ml) was added, and the suspension was cooled to 5°. Perchloryl fluoride diluted with nitrogen (1:1) was introduced subsurface for 6 hr while the temperature was maintained at 5–10°. The original bright yellow solution had then become very light yellow. Sodium chlorate was filtered off (CAUTION), and the filtrate was concentrated at reduced pressure below 50°. The remaining oil was washed with dilute sodium bicarbonate solution and water and dried ($MgSO_4$) to give 179 g (96%) of diethyl fluoronitromalonate of excellent purity (glpc).

B. By Aqueous Fluorination.—A solution of 269 g of diethyl nitromalonate in 2.5 l. of water containing 121 g of sodium bicarbonate was made in the above apparatus. At 0–5° fluorine diluted with nitrogen (1:1) was introduced subsurface until the solution became colorless. The organic phase was separated and combined with the methylene chloride extract of the aqueous phase. Drying ($MgSO_4$) and removal of the solvent gave 275 g (94%) of essentially pure diethyl fluoronitromalonate.

Ethyl Fluoronitroacetate.—A solution of 61.5 g of potassium hydroxide (85%) in 575 ml of ethanol was added dropwise at −10° to a solution of 200 g of diethyl fluoronitromalonate in 575 ml of ethanol. After complete addition, the mixture was stirred 30 min at the same temperature, then poured into ice-cold dilute sulfuric acid. Immediate extraction with methylene chloride prevents the product from hydrolyzing. The extract was dried ($MgSO_4$) and distilled to give 120.6 g (96.7%) of product, bp 38–41° (0.5 mm).

Anal. Calcd for $C_4H_6FNO_4$: F, 12.57; N, 9.28. Found: F, 12.3, 11.7; N, 9.5, 9.3.

Ethylfluoronitrocyanoacetate.—Potassium ethyl nitrocyanoacetate[8] (26 g) was suspended in 250 ml of acetonitrile in the fluorination apparatus described above. Perchloryl fluoride was introduced for 2–3 hr at 5–10°. Potassium chlorate was filtered off (CAUTION), and the filtrate concentrated at 40–50° under reduced pressure. When much of the solvent had been removed, the residue was poured into cold dilute sulfuric acid; this was extracted with methylene chloride; and the extract was dried ($MgSO_4$) and distilled. The yield was 5.8 g (25%), bp 53–54° (4 mm).

Anal. Calcd for $C_5H_5FN_2O_4$: F, 10.78; N, 15.90. Found: F, 10.6, 10.3; N, 15.7, 15.5.

Carbethoxyfluoronitroacetamide.—Ethyl fluoronitrocyanoacetate (6.15 g) was added to 30 ml of 5% oleum cooled in an ice bath. The mixture was stirred 8 hr below 5°, then drowned on crushed ice. The methylene chloride extract upon removal of the solvent left 5.8 g (86%) of an oil whose ir spectrum indicated the absence of starting material. The amide was distilled at 90° (0.1 mm) in a molecular still and did not crystallize.

Anal. Calcd for $C_5H_7FN_2O_5$: F, 9.79; N, 14.44. Found: F, 9.5, 9.4; N, 14.1, 14.2.

Fluoronitroacetamide from Carbethoxyfluoronitroacetamide.—A solution of 9 g of the above ester amide in 10 ml of ethanol was added at −10° to 3.5 g of potassium hydroxide in 50 ml of ethanol. The precipitate was filtered off through a jacketed sintered-glass funnel cooled to 0° with ice or ice–water (CAUTION),[12] washed with ice-cold ether, and dissolved in ice-cold dilute sulfuric acid. The aqueous phase was extracted with ether. The extract was dried ($MgSO_4$) and evaporated to leave 5 g of a mixture of ethyl fluoronitroacetate and fluoronitroacetamide. Crystallization from chloroform gave 1 g of fluoronitroacetamide, mp 74–75°.

Anal. Calcd for $C_2H_3FN_2O_3$: F, 15.57; N, 22.95; neut equiv, 122.06. Found: F, 15.2, 15.2; N, 22.6, 22.6; neut equiv, 122.

Improved Preparation of Nitromalonamide.—Nitromalonamide is obtained in better yield, and the nitration may be carried out on a considerably larger scale than reported in the literature[13] if 90% instead of "fuming" nitric acid is used as the nitrating agent. Malonamide (225 g) was added over a 30-min period to 1290 ml of 90% nitric acid. During the addition, the temperature was kept at 10–15° by cooling with an ice bath. The mixture was stirred an additional 45 min with continued cooling and filtered through a sintered-glass funnel; the product was washed by placing into and digesting with a mixture of ice and water and isolated by filtration. The air-dried malonamide weighed 267.5 g (82.8%).

Fluoronitromalonamide.—Nitromalonamide (41 g) was dissolved in 500 ml of water containing 25 g of sodium bicarbonate, and the solution was fluorinated with a fluorine–nitrogen mixture (1:1) as described above. The solution was then saturated with sodium chloride and extracted exhaustively with ether. The ether was dried ($MgSO_4$) and evaporated to give 18 g (39%) of crude fluoronitromalonamide. Recrystallized from chloroform–acetonitrile or ethanol, it melted at 143–144°.

Anal. Calcd for $C_3H_4FN_3O_4$: F, 11.52; N, 25.46. Found: F, 11.4, 11.4; N, 25.0, 24.9.

Fluoronitroacetamide from Fluoronitromalonamide.—Fluoronitromalonamide (22.5 g) was dissolved in 100 ml of ethanol. After cooling to 0° (reprecipitation), a solution of 12 g of potassium hydroxide (85%) in 75 ml of ethanol was added while the temperature was kept below 5°. The mixture was stirred 2.5 hr at the same temperature and filtered through an ice-cooled sintered-glass funnel;[12] the precipitate was washed with cold ether and dissolved in cold dilute sulfuric acid. After saturation with sodium chloride, the solution was exhaustively extracted with ether; the ether solution was dried ($MgSO_4$) and freed from solvent to give 9.2 g (55%) of crude fluoronitroacetamide, identical with the material obtained from carbethoxy fluoronitroacetamide.

Chloronitromalonamide.—Nitromalonamide (14.7 g) was converted into the sodium salt by stirring for 1 hr (ice cooling) with a solution of 6 g of sodium hydroxide in ethanol. The air-dried salt was suspended in carbon tetrachloride, and chlorine was bubbled through until the solution contained excess chlorine. The mixture was then stirred 2 hr in an ice bath and filtered. Extraction of the solid with ether gave crude chloronitromalonamide. After one recrystallization from 2:1 carbon tetrachloride–acetonitrile the yield was 10 g (55%), mp 125–130°. One additional recrystallization raised the melting point to 129–130°.

Chloronitroacetamide.—To 4 g of chloronitromalonamide in 30 ml of ethanol was added with cooling 1.8 g of potassium hydroxide in 15 ml of ethanol. The salt was filtered off, washed with ether, and dissolved in cold dilute sulfuric acid. The solution was saturated with sodium chloride and extracted with ether to give 2 g (65%) of crude chloronitroacetamide, 1.4 g after recrystallization from chloroform–acetonitrile, mp 64–67°.

Anal. Calcd for $C_2H_3ClN_2O_3$: C, 17.35; H, 2.18; Cl, 25.58; N, 20.24. Found: C, 17.6, 17.5; H, 1.9, 1.8; Cl, 25.2, 25.2; N, 19.7, 20.3.

Chlorofluoronitroacetamide.—Potassium fluoronitroacetamide, prepared freshly from 22.5 g of fluoronitromalonamide as described above, was suspended in ice-cold carbon tetrachloride and treated with chlorine at ice-bath temperature until the solvent became slightly yellow (small excess of chlorine). The solvent was removed *in vacuo*, and the residue was triturated with a small amount of water. The aqueous phase was extracted with methylene chloride; the extract was dried ($MgSO_4$) and evaporated to give 12.3 g (58%) of crude chlorofluoronitroacetamide. Recrystallized from methylene chloride–petroleum ether, it melted at 54–55°.

Anal. Calcd for $C_2H_2ClFN_2O_3$: Cl, 22.63; F, 12.13; N, 17.90. Found: Cl, 22.9, 22.6; F, 12.3, 12.6; N, 17.7, 17.9.

Ethyl Chlorofluoronitroacetate.—Ethyl fluoronitroacetate (80 g) was suspended in 900 ml of ice water; 30.5 g of sodium bicarbonate was added; and chlorine gas was introduced with continued cooling. The solution was kept neutral with sodium bicarbonate, and chlorination continued for 2 hr. The product was extracted into methylene chloride; the solution was dried; the solvent was removed; and the residue was distilled under reduced pressure to yield 77 g (78.4%), bp 54° (15 mm).

Anal. Calcd for $C_4H_5ClFNO_4$: F, 10.24; N, 7.56. Found: F, 9.8, 9.9; N, 7.8, 7.6.

Chlorofluoronitromethane.—Ethyl chlorofluoronitroacetate (65 g) was stirred vigorously with 550 ml of water for 24 hr at room temperature. The mixture was chilled, and the organic layer was separated. The aqueous phase was saturated with sodium chloride, and the organic layer was again separated and combined with the material obtained before. The aqueous phase was then extracted twice with a small amount of methylene chloride. The extract was dried and fractionated to give an additional 3.7 g of product. The total yield was 27.8 g (69.8%), bp 78–79°.

Anal. Calcd for $CHClFNO_2$: Cl, 31.25; F, 16.76; N, 12.35. Found: Cl, 30.4, 30.7; F, 15.6, 16.1; N, 11.7, 11.8.

(12) Cooling of the funnel is essential, as the precipitate may decompose violently at room temperature.

(13) T. B. Johnson and B. H. Nicolet, *J. Amer. Chem. Soc.*, **36**, 360 (1914).

The consistently low analytical values are attributed to difficulties in handling the material due to its high volatility. No impurities could be detected by glpc, ir, and nmr analysis.

Registry No.—Ia, 3620-16-4; IIa, 14011-22-4; IIb, 14011-20-2; IIIa, 2375-33-9; V, Z = CN, hal = F, 17659-21-1; V, Z = $CONH_2$, hal = F, 17659-22-2; fluoronitromalonamide, 17659-24-4; chloronitromalonamide, 5514-96-5; chlorofluoronitroacetamide, 17659-23-3; ethyl chlorofluoronitroacetate, 1683-93-8.

Isolation and Structure of Norjavanicin

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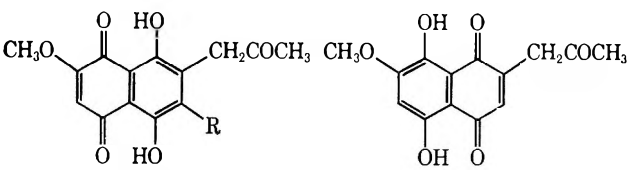
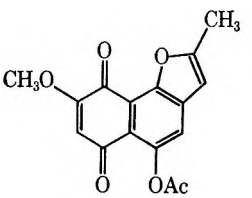
Substituted naphthazarins have been found in sea urchins,[1] microorganisms,[2] higher plants,[3] and frequently in species of *Fusaria*.[4,5] Structures **1a** and **4** proposed for javanicin[6] and fusarubin[7,8] have been verified by syntheses.[9,10] We have isolated fusarubin and a new quinone, norjavanicin, from a mold obtained as an aerial contaminant and identified as a *Fusarium* species.

An examination of the culture filtrate of the *Fusarium* species grown on a defined medium showed the presence of a colorless, optically active, aliphatic ketone, the triglyceride of oleic acid, and at least 11 pigments. A minor component was obtained from the pigment complex by preparative thin layer chromatography (tlc) followed by crystallization. It had the electronic spectrum of a 2-methoxynapthazarin,[6,7] and since its elemental analysis, $C_{14}H_{12}O_6$, differed from that of javanicin by a methyl group, it was named norjavanicin. The lack of infrared (ir) absorption in the normal hydroxyl region, 3300–3600 cm^{-1}, and the presence of a single type of quinone carbonyl (1610 cm^{-1}), strongly shifted by chelation,[11] supplied confirmatory evidence of the presence of the naphthazarin nucleus. In addition to the chelated quinone carbonyls, the presence of an aliphatic ketone or aliphatic ester was indicated by a 1725-cm^{-1} absorption band. The nmr spectrum of norjavanicin is composed of six singlet signals: a methoxyl resonance at δ 3.91, a quinone ring hydrogen at 6.15, a C-methyl resonance at 2.28, and a methylene resonance at 3.78. Since there is one phenolic and one quinone hydrogen,[12] each ring must bear one substituent. Structure **1b**, 6-desmethyljavanicin, is shown to be the correct structure by conversion of norjavanicin into its anhydromonoacetate and by comparison of the mass spectra of javanicin[10] (*m/e* 43, 205, 219, 230, 248, and 290) and norjavanicin (*m/e* 43, 191, 206, 216, 234, and 276). As required by the desmethyl structure, all of the principal mass spectral peaks of norjavanicin are also present in the mass spectrum of javanicin shifted +14 mass units with the exception of a common peak at *m/e* 43. Cracking of the acetonyl side chain appears to be the major reaction in the mass spectral decomposition of both of these compounds. One mode of cleavage is loss of the acetylium ion to produce a very strong *m/e* 43 peak in both spectra and another is the loss of ketene from the molecular ion radical to produce an intense M − 42 peak in the spectra of both compounds.

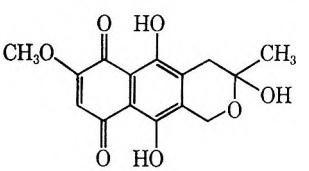


1a, R = CH_3
b, R = H

2



3



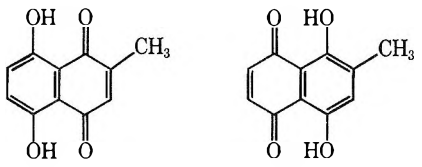
4

Acetylation of norjavanicin with acetic anhydride and sulfuric acid converts it into monoacetylanhydronorjavanicin (**3**). Javanicin itself undergoes similar dehydration on acetylation.[13] The anhydromonoacetate structure is confirmed by the loss of the 1725-cm^{-1} carbonyl band of norjavanicin following acetylation, appearance of an aryl acetate band at 1765 cm^{-1}, and shift of the quinone carbonyl band from the chelated (1610 cm^{-1}) to unchelated position (1685 cm^{-1}). In the nmr spectrum of **3** a doublet furano methyl signal (δ 2.44, J = 1 cps) has replaced the acetonyl methyl signal of norjavanicin.

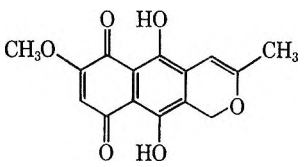
Ample evidence supports assignment of structure **1b** to norjavanicin rather than tautomer 2. Introduction of an alkyl substituent into the 2 position of naphthoquinone has been found to decrease the reduction potential by about 76 mV.[14] The tautomerism of methylnaphthazarin (**5**, **6**) can be viewed as an internal redox system. The alkyl substituent effect can be used to predict that tautomer **5**, with a substituted quinone ring, will be more stable than **6**, possessing an unsubstituted quinone ring. In the nuclear magnetic resonance spectrum of methylnaphthazarin

(1) Leading reference: R. E. Moore, H. Singh, and P. J. Scheuer, *J. Org. Chem.*, **31**, 3645 (1966).
(2) N. N. Gerber and B. Wieclawek, *ibid.*, **31**, 1496 (1966); K. Eckardt, *Ber.*, **98**, 24 (1965); S. Natori, Y. Kumeda, and N. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 633 (1965); H. Brockmann, W. Muller, and K. Van der Merve, *Naturwissenshaften*, **49**, 131 (1963); H. Brockmann and E. Hieronymus, *Ber.*, **88**, 1379 (1955).
(3) I. Morimoto, T. Kishi, S. Ikegami, and Y. Hirata, *Tetrahedron Lett.*, 4737 (1965). For review of earlier literature, see R. H. Thompson, "Naturally Occurring Quinones," Academic Press, New York, N. Y., 1957.
(4) G. Kreitman, O. K. Sebek, and F. F. Nord, *Arch. Biochem.*, **28**, 77 (1950).
(5) G. P. Arsenault, *Tetrahedron Lett.*, 4033 (1965).
(6) H. R. B. Arnstein and A. H. Cook, *J. Chem. Soc.*, 1021 (1947).
(7) H. W. Ruelius and A. Gauhe, *Ann.*, **569**, 38 (1950); **570**, 121 (1951).
(8) G. P. Arsenault, *Can. J. Chem.*, **43**, 2423 (1965).
(9) E. Hardegger, E. Widmer, K. Steiner, and A. Pfiffner, *Helv. Chim. Acta*, **47**, 2031 (1964).
(10) E. Widmer, J. W. Meyer, A. Walser, and E. Hardegger, *ibid.*, **48**, 538 (1965).
(11) H. Bloom, L. H. Briggs, and B. Cleverly, *J. Chem. Soc.*, 178 (1959).
(12) R. E. Moore and P. J. Scheuer, *J. Org. Chem.*, **31**, 3272 (1966).
(13) S. Weiss and F. F. Nord, *Arch. Biochem.*, **22**, 288 (1949).
(14) L. F. Fieser and M. Fieser, *J. Amer. Chem. Soc.*, **57**, 491 (1935).

the methyl proton resonance occurs as a doublet (δ 2.23, J = 1.4 cps) coupled to the single quinone proton (δ 6.87). The presence of a doublet methyl resonance confirms methyl-substituted quinone structure **5**. Since the methoxyl substituent effect (131 mV) on quinone stabilization is considerably larger than the alkyl substituent effect,[14] norjavanicin tautomer **1b** is perferred over 2.[15] The fact that the acetonyl methylene signal of norjavanicin is not coupled to an allylic proton indicates that the acetonyl substituent is in the phenolic ring, substantiating assignment of structure **1b** to norjavanicin and ruling out an extended quinone structure of the type proposed for the crystal structure of Cordeauxia-quinone.[16] Norjavanicin is formulated as the 2-methoxy-7-acetonylnaphthazarin rather than the 6-acetonyl isomer because of the obvious biosynthetic relationship to, and possibly even origin from, the acetogenins javanicin and fusarubin.



5 **6**



7

The major diffusible pigment was identified as fusarubin (**4**) by its elemental analysis and ultraviolet–visible, ir, nmr, and mass spectra. Both pairs of methylene protons in the ketal ring of fusarubin are in nonequivalent environments and give rise to broad signals at δ 5.17 and *ca.* 3.1. The proton resonance at δ 6.36 has a chemical shift suggestive of a proton on a quinone ring rather than a proton on a phenolic ring,[12] indicating that fusarubin has structure **4** rather than one of the other naphthazarin tautomeric structures.

Brief treatment of fusarubin with hot acetic acid effects dehydration to anhydrofusarubin **7** in which the protons of the remaining methylene group are in equivalent environments. The methylene proton signal now occurs as a sharp singlet at δ 5.27. In addition the C-methyl signal of anhydrofusarubin appears as a doublet (δ 1.92, J = 0.9 cps) coupled to the newly created allylic proton. The quinone proton signal occurs at δ 6.38. The electronic spectrum, nmr spectrum and tlc behavior of anhydrofusarubin are identical to those of the major purple quinone present in the *Fusarium* pigment complex. On standing in contact with the atmosphere, anhydrofusarubin slowly undergoes rehydration to fusarubin.

(15) Moore and Scheuer determined the structures of 34 substituted naphthazarins by nmr spectroscopy[12] and deduced from this an order for the attraction of quinonoidal properties by a substituent in the naphthazarin nucleus: OH > OCH_3 > OAc > CH_2CH_3 ≫ H ≫ $COCH_3$. This order may be compared that Fieser and Fieser's conclusion that "the groups which lower the potential of the parent quinone are those which facilitate substitution in the benzene ring; those which produce an increase in the potential have the opposite effect and retard benzene substitution."[14]

(16) M. Fehlmann and A. Niggli, *Helv. Chim. Acta*, **48**, 305 (1965).

Experimental Section

Nmr spectra were recorded on a Varian Associates A-60 instrument in chloroform with tetramethylsilane as the internal reference. Spectra of fusarubin were run in pyridine with tetramethylsilane as the internal reference. Ir spectra were determined with a Perkin-Elmer Model 37 instrument. Ultraviolet–visible spectra were determined in 95% ethanol with a Cary Model 11 instrument. Microanalyses were carried out by Dr. A. Bernhardt, Mülheim, Germany. Mass spectra were determined by Dr. K. L. Rinehart on an Atlas CH-4 mass spectrometer with an ionization energy of 70 eV.

Culture Conditions.—The *Fusarium* was grown without shaking on a medium containing 2% glucose, 1% ammonium chloride, 0.1% potassium monohydrogen phosphate, and 0.01% magnesium sulfate in tap water. Vegetative growth was maintained by transfer every 3 weeks. A complex mixture of pigments was obtained at the end of 3 weeks by extracting the culture filtrate with ether. The yield of ether-extractable solids was 50 mg/l. Ether extraction of the dried mycelia gave a 1.3% yield of an unsaturated triglyceride and virtually no pigment.

Norjavanicin (1b).—Norjavanicin and an unidentified aliphatic ketone were separated from the mixture of pigments by preparative tlc on silica gel G (Merck) developed with chloroform containing 5% methanol. The band corresponding to norjavanicin was extracted with chloroform. Removal of solvent gave a 120-mg mixture of amorphous, bright red solid and white needles. The mixture was dissolved in ether and extracted with basic aqueous magnesium acetate. Evaporation of the ether layer and two crystallizations of the residue from ethanol–chloroform gave colorless needles of an unidentified ketone, mp 244–250°.

The aqueous magnesium acetate extract was acidified and extracted with ether. Evaporation of the ether layer gave 64 mg of amorphous norjavanicin. Norjavanicin was crystallized twice from methanol–chloroform, giving red needles: mp 200–204°; ir 1725, 1610, 1580, 1440, 1360 cm^{-1} (chloroform).

Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 60.76; H, 4.48.

Monoacetylanhydronorjavanicin (3).—Norjavanicin (40 mg) was suspended in 1.5 ml of acetic anhydride. The suspended solid dissolved immediately on addition of a drop of concentrated sulfuric acid with attendant color change from red to yellow. Crystals began separating on standng. After 15 min the reaction mixture was poured into ice–water. The amorphous yellow-brown precipitate was purified by preparative tlc employing silica gel G and 2% methanol in chloroform as developing solvent. The material recovered from chromatography was recrystallized twice from ethanol to give 9 mg of yellow needles of monoacetylanhydronorjavanicin: mp 218° dec; ir 1765, 1685, 1642, 1627, 1590 cm^{-1} (chloroform).

Isolation of Fusarubin (4).—Crude pigment (1.2 g) was extracted with 10 ml of hot ethanol, followed by two 5-ml portions of hot acetone. The 270 mg of bright red residue was extracted with ethanol in a Soxhlet extractor. Red needles separated from the ethanol during the course of extraction. The crystals were collected and recrystallized in the same manner giving 202 mg of fusarubin: mp 210° dec; ultraviolet–visible (95% ethanol) λ_{max} 534 mμ (ϵ 3800), 498 (5800), 472 (5000), and 303 (6500).

Anal. Calcd for $C_{15}H_{14}O_7$: C, 58.83; H, 4.61. Found: C, 58.71; H, 4.55.

Anhydrofusarubin (7).—Fusarubin (67 mg) was dissolved in 3 ml of acetic acid and heated 10 min at 80°. After evaporation of the solvent, the residue was dissolved in benzene, and the resulting solution was filtered to remove a small quantity of insoluble fusarubin. Removal of solvent gave 50 mg of chromatographically pure anhydrofusarubin,[7] which decomposed above 200°.

Registry No.—**1b**, 17790-94-2; **3**, 17790-95-3; **4**, 17790-96-4.

Acknowledgments.—The author wishes to thank Dr. Lynn Brady, Dr. R. G. Benedict, and Dr. D. E. Stuntz for isolation and identification of the *Fusarium*. Financial assistance from a State of Washington research grant is gratefully acknowledged.

Reactions of (Hydroxymethyl)ferrocene. Esters[1a]

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Very little has been reported in the literature on the synthesis of esters of (hydroxymethyl)ferrocene. Nesmeyanov has described the preparation of ferrocenylmethyl acetate by decomposition of (ferrocenylmethyl)-trimethylammonium iodide in the presence of sodium acetate or acetic acid.[2] Good yields of the same acetate have been reported from (dimethylaminomethyl)ferrocene and acetic anhydride.[2] Ferrocenylmethyl benzoate has been prepared by the reaction of (hydroxymethyl)ferrocene and benzoyl chloride in the presence of pyridine,[3] and also by heating (dimethylaminomethyl)ferrocene with methyl benzoate.[2] The reaction of (hydroxymethyl)ferrocene with ferrocenoyl chloride has given the corresponding ester in the presence of pyridine.[4] Evidently, therefore, the only previously acceptable preparations of these compounds have involved decomposition of the quaternary ammonium salts of (dimethylaminomethyl)ferrocene and reaction of acid halides with (hydroxymethyl)ferrocene. Presumably the reason, at least in our experience, is that direct esterification using strong acid catalysis yields significant amounts of ferricenium ion as a decomposition product.

We can now report preparation of esters of (hydroxymethyl)ferrocene directly from the alcohol and the free carboxylic acid *without added catalysts*. Presumably the organic acid alone suffices as a catalyst because of the unusually facile formation of the ferrocenylmethyl carbonium ion.[5] The reaction is accomplished quite simply by heating the (hydroxymethyl)ferrocene with an excess of the carboxylic acid on the steam bath for short periods. Products are obtained in yields up to 70%. Ferrocenylmethyl esters of straight chain aliphatic carboxylic acids through heptanoic acid were prepared, and the benzoate was prepared in good yield by heating (hydroxymethyl)ferrocene with benzoic acid in the absence of solvent or added catalyst.

Nesmeyanov reported formation of ethers by heating (hydroxymethyl)ferrocene in alcohols with acetic acid.[6] We have found that ether formation is not preferred when (hydroxymethyl)ferrocene is heated with an excess of 3-hydroxybutyric acid and that the hydroxy ester can be obtained in 57% yield. When this reaction was repeated using equal parts of water and 3-hydroxybutyric acid, ferrocenylmethyl 3-hydroxybutyrate again was obtained in good yields. In order to eliminate the possibility that the secondary hydroxyl group of 3-hydroxybutyric acid might be unreactive in ether formation, isopropyl alcohol was heated in aqueous solution with (hydroxymethyl)ferrocene, using a small amount of acetic acid. The product, ferrocenylmethyl isopropyl ether, was obtained in good yield. It thus appears that at least in the instance of 3-hydroxybutyric acid, ester formation is preferred over ether formation with or without an aqueous medium. Similar competition reactions are currently being investigated and will be reported later.

(1) (a) This work was supported by the Propellant Division of the Air Force Rocket Propulsion Laboratory, Edwards Air Force Base, Calif., under Contract F-04611-67-C-0034. (b) To whom enquiries should be addressed.

(2) A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and V. D. Tyurin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1997 (1962); *Chem. Abstr.*, **58**, 9132*g* (1963).

(3) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).

(4) E. J. Kupchik and R. J. Kiesel, *ibid.*, **31**, 456 (1966).

(5) M. Cais and A. Eisenstadt, *ibid.*, **30**, 1148 (1965).

(6) A. N. Nesmeyanov, E. G. Perevalova, and Yu. A. Ustynyuk, *Dokl. Akad. Nauk SSSR*, **133**, 1105 (1960); *Chem. Abstr.*, **54**, 24616*g* (1960).

Experimental Section

Melting points were determined on a Buchi apparatus and are corrected with the excpetion of products which were liquids at room temperature. Because of a pronounced tendency toward supercooling, the latter compounds were crystallized at low temperatures, and a heating curve was used to obtain the melting point. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. Moist extracts were dried over anhydrous magnesium sulfate, and solvent was then removed at 20 mm using a rotary flash evaporator.

Ferrocenylmethyl Acetate.—A solution of (hydroxymethyl)-ferrocene (4.0 g, 0.0158 mol, from Research Organic Chemicals Co.) in glacial acetic acid (60 ml) was heated on the steam bath for 40 min, cooled, and filtered. Water (300 ml) was added to the filtrate, and the solid which precipitated was recovered and washed with sodium bicarbonate solution, then water. There resulted 3.27 g (69%) of yellow solid, mp 68–72°.

Chromatography on alumin (Alcoa F-20) with hexane afforded pure ferrocenylmethyl acetate, mp 75–77° (lit.[2] mp 74–76°), in 32% yield. The infrared spectrum was as reported.[2]

Anal. Calcd for $C_{13}H_{14}O_2Fe$: C, 60.50; H, 5.47. Found: C, 60.75; H, 5.56.

Ferrocenylmethyl Butyrate.—A solution of (hydroxymethyl)-ferrocene (2.5 g, 0.0115 mol) in butyric acid (15 ml) was heated on a steam bath for 1 hr. The reaction mixture was cooled and poured into water. The oil which separated was taken up in ether, and the ether extracts were washed with aqueous sodium carbonate and then with water. The ethereal solution was dried and evaporated, and the residue was chromatographed on F-20 alumina with hexane. The yield of ferrocenylmethyl butyrate, mp 35–36°, was 2.5 g (72%).

Anal. Calcd for $C_{15}H_{18}O_2Fe$: C, 62.96; H, 6.34. Found: C, 63.31; H, 6.43.

Other esters made in a similar manner were propionate, mp 55–57°, 35% yield; valerate, mp 7–8°, $n^{20}D$ 1.5535, 56% yield; caproate, mp −5 to −3°, $n^{20}D$ 1.5560, 48% yield; heptanoate, mp 12–14°, $n^{20}D$ 1.5522, 53% yield.

Ferrocenylmethyl Benzoate.—Benzoic acid (1.0 g, 0.0082 mol) was heated with (hydroxylmethyl)ferrocene (1.0 g, 0.0046 mol) on a steam bath for 45 min. The cooled reaction mixture was dissolved in ether. The ethereal solution was washed with aqueous sodium carbonate and water, dried, and evaporated affording 1.2 g (82%) of ferrocenylmethyl benzoate, mp 130–131° (lit.[3] mp 130–132°). The infrared spectrum agreed with the structural assignment.

Ferrocenylmethyl 3-hydroxybutyrate was made in essentially the same manner; the yield from (hydroxymethyl)ferrocene (2.5 g, 0.0115 mol) and 3-hydroxybutyric acid (15 ml) was 2.0 g (57%) of ferrocenylmethyl 3-hydroxybutyrate as viscous oil.

Anal. Calcd for $C_{15}H_{18}O_3Fe$; C, 59.63; H, 6.00. Found: C, 59.94; H, 6.40.

The infrared spectrum confirmed the structural assignment.

Similar reaction of (hydroxymethyl)ferrocene and 3-hydroxybutyric acid using a 1:1 (molar) mixture of the hydroxy acid and water at reflux for 3.5 hr gave ferrocenylmethyl 3-hydroxybutyrate in 67% yield.

Ferrocenylmethyl Isopropyl Ether.—A solution of (hydroxymethyl)ferrocene (5.0 g, 0.023 mol) in isopropyl alcohol (45 ml), acetic acid (0.2 ml), and water (35 ml) was heated at the reflux temperature for 24 hr. The product obtained by ether extraction was chromatographed on F-20 alumina using hexane to yield ferrocenylmethyl isopropyl ether, 4.0 g (67%), mp 33–34°.

Anal. Calcd for $C_{14}H_{18}OFe$: C, 65.14; H, 7.03. Found: C, 64.93; H, 6.88.

Registry No.—Ferrocenylmethyl acetate 12300-24-2; ferrocenylmethyl butyrate, 12300-27-5; ferrocenylmethyl propionate, 12300-25-3; ferrocenylmethyl valerate, 12300-29-7; ferrocenylmethyl caproate, 12300-30-0; ferrocenylmethyl heptanoate, 12300-32-2; ferrocenyl methyl benzoate, 12300-31-1; ferrocenylmethyl 3-hydroxybutyrate, 12300-28-6; ferrocenylmethyl isopropyl ether, 12300-26-4.

Acknowledgment.—The authors wish to acknowledge the assistance of Mr. R. D. Giles and Mr. J. W. Blanks in this effort.

Conformational Analysis. XI.[1,2] 2-Carbomethoxy-7-oxabicyclo[2.2.1]heptane and 2-Carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene

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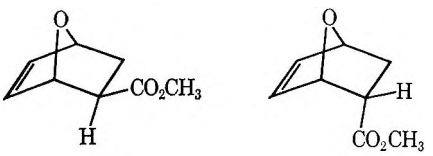
In recent years, the question of the effective size of lone-pair electrons relative to the bonded hydrogen atom has been of interest.[3] While there is some evidence that lone-pair electrons have larger spatial requirements than the bonded hydrogen atom,[4] there is considerable evidence to the contrary.[5] Recently Eliel[6] reported some important observations on the conformational preferences of alkyl groups in the 1,3-dioxane ring system. However, there is little data available with which to extrapolate to systems containing polar groups attached to a heterocycle such as 1,3-dioxane.[7]

The concept of effective steric size of lone-pair electrons is at best a nebulous one. Solvents may solvate one heterocyclic conformation more effectively than an alternate conformation. The problem then develops into one of separating differential steric requirements and solvent stabilization of conformations. A second problem resides in the variation of the nonbonded electron density of a heteroatom as a function of the hybridization of attached bonds. Incorporation of a heteroatom into rings of varying size should change the spatial requirements of the lone-pair electrons. Therefore, conclusions derived from a particular ring system may not be applicable to other heterocycles.

In order to study the possible effects of solvents and hybridization on the conformations of substituents attached to heterocycles, we have chosen the 7-oxabicyclo[2.2.1]heptene and 7-oxabicyclo[2.2.1]heptane ring systems. These rings eliminate the possibility of nonidealized conformations such as might exist in monocyclic compounds. Only the change in position of a substituent as a result of direct equilibration need be considered. The ring system also provides an oxygen atom in a strained configuration which could lead to lone-pair spatial requirements differing from those determined in other studies.

The equilibration of the isomeric 2-carbomethoxy-7-oxabicyclo[2.2.1]heptenes was accomplished by taking advantage of the relative instabilities of Diels–Alder adducts from furan with dienophiles.[8] Equal volumes of furan and methyl acrylate were sealed in nmr tubes and maintained at 75°. The τ 6 region of the nmr spectrum of the mixture was monitored. The three-proton methyl singlet at τ 5.90 gradually decreased with time relative to two high-field singlets which began to develop. A resonance at τ 5.99 appeared first and increased in intensity while a second resonance at τ 5.92 appeared at a slower rate. After 2 days the τ 5.99 resonance maximized and started to decrease, whereas the τ 5.92 resonance continued to increase. After approximately 5 days the relative intensities of the τ 5.92 and 5.99 resonances remained constant. The τ 5.92 and 5.99 resonances were assigned to the methyl singlets of the *exo* and *endo* adducts I and II, respectively. This assignment was based on the known thermal behavior of the Diels–Alder adducts of furan and established by chemical conversion into known derivatives. Mixtures of nonequilibrium composition were reduced by hydrogen over palladium on charcoal, and the isomeric saturated esters were separated from a 12-ft, 25% DEGS on Chromosorb W column. The individual esters were reduced by lithium aluminum hydride to the known saturated primary alcohols.[9]



I II

The equilibrium constant (*exo/endo*) was calculated to be 0.98 ± 0.06 at 75° from the integrated areas of the τ 5.92 and 5.99 resonances. The total yield of adduct was approximately 10% at the temperature examined. The reversibility of the equilibrium and the cleanness of the reaction were demonstrated by allowing equilibration to occur at 63° and then reequilibrating these samples at 75° and *vice versa*. At 63° a 14% yield of adduct results after 20 days. The equilibrium constant at 63° is 0.98 ± 0.06. Thus, while no apparent change in the value of the equilibrium constant is observed, the mole fraction of both adducts increases with decreasing temperature and *vice versa*.

A 10% solution by volume of the mixture of reacting diene and dienophile in dimethyl sulfoxide was studied

(1) Conformational Analysis. X: R. J. Ouellette, K. Liptak, and G. E. Booth, *J. Org. Chem.*, **32**, 2394 (1967).

(2) The authors acknowledge a grant from the Petroleum Research Fund of the American Chemical Society in support of this research.

(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 245.

(4) J. B. Lambert and R. G. Keske, *J. Amer. Chem. Soc.*, **88**, 620 (1966).

(5) R. J. Bishop, L. E. Sutton, D. Dineen, A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 257 (1964); K. Brown, A. R. Katritzky, and A. J. Waring, *ibid.*, 257 (1964); N. L. Allinger and J. C. Tai, *J. Amer. Chem. Soc.*, **87**, 1227 (1965); N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *ibid.*, **87**, 1232 (1965); M. J. T. Robinson, *Tetrahedron Lett.*, 1153 (1968); R. W. Baldock and A. R. Katritzky, *ibid.*, 1159 (1968).

(6) E. L. Eliel and Sr. M. C. Knoeber, *J. Amer. Chem. Soc.*, **88**, 5347 (1966); **90**, 3444 (1968).

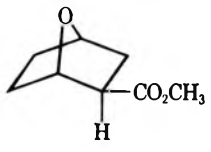
(7) F. G. Riddell, *Quart. Rev.* (London), **21**, 364 (1967).

(8) R. B. Woodward and H. Baer, *J. Amer. Chem. Soc.*, **70**, 1161 (1948); J. A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953).

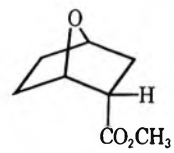
(9) M. P. Kunstmann, D. S. Torbell, and R. L. Autrey, *ibid.*, **84**, 4115 (1962).

using the same technique as for the neat liquids. The lower concentrations decreased slightly the sensitivity of the analytical method. The equilibrium constant (*exo/endo*) is 1.01 ± 0.08. The equilibrium was examined in methanol as solvent, and the equilibrium constant is 1.3 ± 0.1. The slightly higher error limit is a reflection of a partial overlap of the resonances of methyl acrylate and the *exo* Diels–Alder adduct in methanol as solvent.

The saturated esters III and IV were equilibrated by sodium methoxide in methanol as previously reported for 2-carbomethoxybicyclo[2.2.1]heptane.[10] The equi-



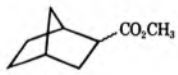
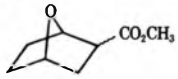
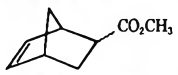
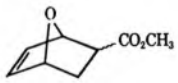
III



IV

librium constant (*exo/endo*) was determined to be 3.05 ± 0.10 at 75°. In Table I the equilibrium values de-

TABLE I

Compound	*K* (*exo/endo*)	Solvent
	2.35 ± 0.10	Methanol[a]
	3.05 ± 0.10	Methanol
	1.05 ± 0.02	Methanol[b]
	0.98 ± 0.06	Neat
	1.01 ± 0.08	Dimethyl sulfoxide
	1.3 ± 0.1	Methanol

[a] A value of 2.30 at 90° has been reported by other workers: A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Amer. Chem. Soc.*, **81**, 2799 (1959). [b] See ref 10.

termined for the oxabicyclic compounds at 75° are listed along with the previously determined values for the carbocyclic compounds.[10]

There are small, but experimentally significant, differences between the equilibrium constants of the carbobicyclic compound and their 7-oxa analogs. Oxygen could be considered to be of smaller effective steric size than a methylene group. However, there are several other structural contributions that could give rise to the observed differences in the equilibrium constant. The smaller C–O bond distance (1.43 Å) compared with the normal C–C bond distance (1.54 Å) requires that the bicyclic ring systems be modified when oxygen replaces methylene. The distance separating the carbomethoxy group and the π electrons in the unsaturated compound and the *endo*-6 proton in the saturated compound should be smaller in the oxa derivative. This should lead to a destabilization of the *endo* isomer in the oxa compounds compared with the *endo* isomer of the carbobicyclic compounds. Some and perhaps all of the increased amount of the *exo*-oxa compound at equilibrium could be due to this difference.

Dipole–dipole repulsion should destabilize the *exo*-oxa compounds relative to the *endo* isomers. However, such contributions cannot be properly evaluated with a single ring system. The determination of the equilibrium constants for a polar group such as carbomethoxy in a ring system such as 1,3-dioxane will be needed in order to determine the magnitude of dipole–dipole repulsion between an ether oxygen and a carbomethoxy group. The near equivalence of methylene and oxygen and the difference between this conclusion and those of Eliel may involve hybridization changes. In a strained system the decreased ether bridge angle should increase the s character of the lone-pair electrons. While the hybridization of the methylene carbon–hydrogen bond also should be of increased s character, the shorter carbon–oxygen bond requires a larger hydridization change for oxygen. The change in the directional character of the lone-pair electrons of the oxygen bridge with increasing s character should decrease the distance to the carbomethoxy substituent. Therefore, the effective steric size of the lone pairs of oxygen in our compounds may be larger than in 1,3-dioxane. However, many additional substituents in both the oxabicyclic and 1,3-dioxane ring systems will have to be examined before an established model can be presented.

(10) R. J. Ouellette and G. E. Booth, *J. Org. Chem.*, **30**, 423 (1965).

Experimental Section

2-Carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene.—Furan (25 g) and methyl acrylate (32 g), both stabilized with hydroquinone, were mixed and maintained at 40° for 1 month. Evaporation of unreacted material under reduced pressure at 0° yielded 10 g of a colorless oil. Attempted analysis of the product by vapor phase chromatography was unsuccessful as complete cracking occurred. Reduction of the reaction mixture as detailed in the following section followed by vpc analysis indicated that equimolar amounts of the *exo* and *endo* isomers were present.

2-Carbomethoxy-7-oxabicyclo[2.2.1]heptane.—A mixture of the isomeric unsaturated esters (2 g) was hydrogenated in 95% ethanol using palladium on charcoal (5%, 100 mg) as the catalyst. Cessation of hydrogen uptake occurred after 2 hr. The ethanol was removed by distillation, and the product was obtained as a colorless oil (65° at 8 mm). The isomers were separated on a 10 ft × 1/4 in., 20% DEGS on Chromosorb W column. The *exo* isomer had the longer retention time. The assignment of configuration was based initially on the composition of hydrogenated mixtures derived from unsaturated esters which were obtained by shorter reaction times as the *endo* isomer should be formed initially. With increasing lengths of time for the Diels–Alder reaction, the percentage of the *exo* isomer increased until at equilibrium, and *exo* and *endo* isomers were in a 1:1 ratio. Assignment of configuration was confirmed by nmr. The resonance of the 2 proton of the saturated *exo* isomer appears as a quartet at τ 7.45, while the corresponding resonance of the *endo* isomer appears as a pentuplet at 7.08.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found for *exo:* C, 61.33; H, 7.65. Found for *endo*: C, 61.70; H, 7.70.

Equilibration of *endo*- and *exo*-2-Carbomethoxy-7-oxabicyclo[2.2.1]hept-5-enes.—Equimolar amounts of furan and methyl acrylate were sealed in nmr tubes. The tubes were placed in water baths maintained at 63 and 75°. At various times, the nmr spectra were determined at the same temperature as that employed for equilibration. The methyl protons in methyl acrylate, *endo*-2-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene, and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene appear at τ 5.90, 5.99, and 5.92, respectively. The initial ratio of *endo* to *exo* product was approximately 5:2 but gradually changed to 1:1 with time. The times necessary for equilibration at 63 and 75° were approximately 15 and 4 days, respectively.

Equilibration of *endo*- and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]heptanes.—Equilibrations were carried out according to procedures previously described.[10] A 10 ft × 1/4 in., 20% DEGS on Chromosorb W column was employed for analysis.

Registry No.—I, 17791-32-1; II, 17791-33-2; III, 17791-34-3; IV, 17791-35-4.

Preparation of an α-Unsubstituted 1-Indenone and Its Dimer[1]

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Contribution No. 1609 from the Chemistry Laboratories of Indiana University, Bloomington, Indiana 47401

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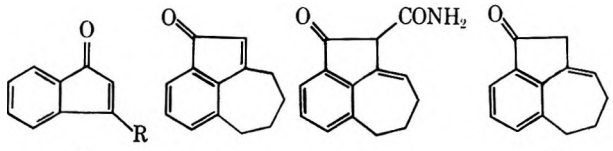
Attempts to prepare 1-indenones in which the C-2 is unsubstituted have been discouraging owing to the rapid polymerization of these compounds.[2] There are instances[3,4] when **1** (R = Ph) has been prepared in a



1 **2** **3** **4**

transient state and isolated as a ketone derivative. Feeman and Amstutz report[5] the preparation of 6-chloro-3-(*p*-chlorophenyl)-1-indenone. In one case[6] the author claims to have obtained **1** (R = Ph) in the monomeric state, but without supporting data. On the other hand the preparation of 1-indenones where R = alkyl have been sketchily described,[7,8] with little convincing documentation. This Note describes the preparation of an alkylated analog of **1** where R = a tetramethylene bridge (**2**).

Treatment of **3**[9] with refluxing hydrochloric acid yielded, along with the expected polymer, a low melting, light yellow product which lacked, as evidenced by infrared (ir) data, an amide or carboxylic acid group, and was a monomeric α,β-unsaturated ketone. The ultraviolet (uv) spectrum (see Table I) indicated that this

TABLE I

ULTRAVIOLET ABSORPTION DATA FOR **2**, **5a**, AND **5b**[a]

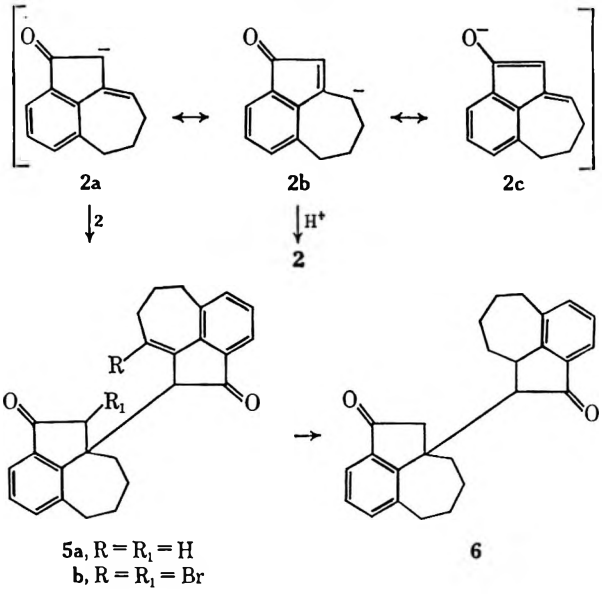
λ_{max}, mμ (log ε)		
2	**5**	**5b**
216 (4.18)	213 (4.34)	218 (4.29)
242 (4.49)	244 (4.38)	248 (4.03)
251 (4.34)		
266 (4.34)	268[b] (3.97)	
275[b] (4.20)	277[b] (3.91)	297 (3.30)
335 (3.60)	336 (3.25)	

[a] Spectra determined in 95% ethanol on a Bausch and Lomb Model 505 spectrophotometer. [b] Shoulder.

substance possessed the indenone structure **2**.[10] Structure **2** was confirmed by the nuclear magnetic resonance (nmr) spectrum which indicated a vinylic proton, an allylic and benzylic multiplet, as well as methylene and aromatic absorption. Failure of **2** to polymerize readily, as expected, may be due to the large amount of steric crowding that would exist in placing these 5,6,7-fused-ring systems in a tight array.

Hydrolysis of **3** in sodium hydroxide solution resulted in **2** and a second material, assigned structure **5a**. This compound was a high-melting white dimer of **2** possessing a nonconjugated ketone band and an uv spectrum characteristic of indanones[10] (see Table I). The nmr spectrum showed a methine singlet, a broad vinylic triplet, and aromatic and broad methylene multiplets in the ratio of 1:1:6:16. Even though a 1,2 cycloaddition dimer has been reported for 3-phenylindenone,[6] this possibility, along with a quasi Diels–Alder product was rejected, after considering the spectral data and chemical properties of **5a**. A Michael addition of anion **2a** to **2**, as illustrated in Scheme I, offers a reasonable explanation of formation of **5a** in alkaline solution.

SCHEME I



2a **2b** **2c** **2** **5a**, R = R₁ = H; **b**, R = R₁ = Br **6**

Compound **5a** absorbed 1 mol of hydrogen to produce **6**, but treatment with bromine produced a dibromide with evolution of hydrogen bromide. The brominated derivative retained its double bond but showed no vinylic hydrogens in its nmr spectrum. Addition of bromine to the double bond of **5a** followed by loss of hydrogen bromide would give the vinylic bromide, while substitution could produce the α-bromo ketone. Structure **5b** has been assigned on the basis of the two single protons characteristic of two different α hydrogens, one of which is similar to that of α-bromopropiophenone.[11]

Attempts to prepare **1** (R = CH_3, C_2H_5, i-C_3H_7) from the corresponding 2-carboxamide analog[10] under analogous conditions consistently led to yellow polymers while acid hydrolysis of 2-carboxamido-3-phenyl-1-indenone[10] produced a yellow dimer consistent in all aspects with that reported[6] for 3-phenylindenone (**1**, R = Ph).

(1) Taken from the thesis of S. W. S., submitted to Indiana University in partial fulfillment of the requirements for the degree Doctor of Philosophy, June 1968.

(2) J. Deschamps, *C. R. Acad. Sci., Paris*, **246**, 3065 (1958).

(3) A. T. Blomquist and E. J. Mariconi, *J. Org. Chem.*, **26**, 3761 (1961).

(4) B. W. Rockett and C. R. Hauser, *ibid.*, **29**, 1394 (1964).

(5) J. F. Feeman and E. D. Amstutz, *J. Amer. Chem. Soc.*, **72**, 1522 (1950).

(6) R. de Fazi, *Gazz. Chim. Ital.*, **49**, 253 (1919).

(7) R. Stoermer and E. Laage, *Ber.*, **50**, 981 (1917).

(8) P. Besinet, R. Fraisse, R. Jacquier, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 1377 (1960).

(9) E. Campaigne, R. Subramanya, and D. R. Maulding, *J. Org. Chem.*, **28**, 623 (1963).

(10) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, and D. R. Maulding, *ibid.*, **27**, 4428 (1962).

(11) The nmr spectrum of 2-bromopropiophenone (Sadtler No. 496) shows an α proton centered at δ 5.19 (CCl_4).

Experimental Section

All melting points, from a Mel-Temp capillary melting point apparatus, were corrected. Microanalyses were performed by Midwest Microlaboratories, Inc., Indianapolis, Ind. Infrared spectra were recorded with a Perkin-Elmer Model 137 Infracord. The nmr spectra were recorded on a Varian Model A-60 spectrometer, employing tetramethylsilane as an internal standard. Molecular weights were determined in chloroform on a Mechrolab vapor pressure osmometer, Model 301A.

Preparation of 6,7,8,9-Tetrahydro-2H-benz[cd]azulen-2-one (2).—A stirred, heterogeneous mixture of 22.7 g (0.1 mol) of **3**[9] and 150 ml of 15% hydrochloric acid solution was refluxed for 26 hr. After 4 hr a brown oil began to form on the acidic solution surface and, at the completion of the reflux period, this oil was separated and extracted with acetone. The orange insoluble material was filtered and recrystallized from dimethylformamide as dark yellow prisms (52%, based on weight recovery), mp >320°. This product was assumed to be a polymeric material of simplest empirical formula $C_{95}H_{80}N_5O_6$ (on basis of analysis).

Upon addition of water to the acetone extract, a second product was obtained which was filtered and recrystallized from benzene–hexane as light yellow plates. This material was identical with that substance which sublimed in the reflux condenser during the hydrolysis. Upon sublimation of this material *in vacuo* [82° (0.25 mm)], light yellow plates (20%, based on weight recovery), mp 88–90°, were obtained: λ_{max}^{KBr} 3.44 (CH), 5.92 (C=O), 6.28 μ (C=C); nmr ($CDCl_3$) δ 1.72–2.55 (4 H, m), 2.83–3.17 (4 H, m), 5.92 (1 H, s), 7.03–7.62 (3 H, m).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.78; H, 6.52; O, 8.88; mol wt, 184. Found: C, 84.61; H, 6.86; O, 8.84; mol wt, 186.

Compound **2** was also obtained by subjecting the initial brown oil to sublimation *in vacuo* at 82° (0.25 mm).

Preparation of Dimer 5a.—A yellow, homogeneous solution of 2.27 g (0.01 mol) of **3** in 50 ml of 15% sodium hydroxide solution was refluxed for 5 days with stirring (NH_3 evolution). After about 6 hr, a yellow material began to precipitate. At the conclusion of the reflux period the product was collected and recrystallized from ethyl acetate (42%), mp 252°, as white plates which could also be sublimed *in vacuo* [212° (0.3 mm)]: λ_{max}^{KBr} 3.41 (CH), 3.49 (CH), 5.82 (C=O), 6.19 μ (C=C); nmr ($CDCl_3$ δ 1.25–3.19 (16 H, m), 3.90 (1 H, s), 4.14 (1 H, t), 7.08–7.58 (6 H, m).

Anal. Calcd for $C_{26}H_{24}O_2$: C, 84.78; H, 6.52; O, 8.88; mol wt, 368. Found: C, 85.05; H, 6.38; O, 8.71; mol wt, 358.

The reddish ethyl acetate mother liquor was evaporated and yielded a product which was sublimed *in vacuo* [82° (0.25 mm)], mp 88–90°, as light yellow needles (8%). This lower melting product was found to be identical with **2** by comparison with an authentic sample using thin layer chromatography employing ether–cyclohexane in a 1:1 ratio, and by comparison of ir spectra.

Catalytic Reduction of 5a.—A solution of 1.0 g (3.0 mmol) of **5a** in 100 ml of absolute ethanol was shaken with 0.8 g of platinum oxide in an atmosphere of hydrogen for 4 hr, after which the catalyst was removed and washed with warm ethanol. The ethanol mother liquors were combined and evaporated under a stream of air, leaving a white crystalline residue of **6** recrystallized from methanol as cream prisms (70%): mp 187–189°; λ_{max}^{KBr} 3.40 (CH), 3.49 (CH), 5.87 μ (C=O). Quantitative hydrogenation indicated an uptake of 1 mol of hydrogen.

Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.32; H, 7.03; O, 8.64; mol wt, 370. Found: C, 84.22; H, 7.05; O, 8.92; mol wt, 367.

Bromination of 5a.—A solution of 1.84 g (5.0 mmol) of **5a** in 320 ml of glacial acetic acid was stirred briefly at 0° before the dropwise addition of 1.60 g (0.01 mol) of Br_2 in 10 ml of glacial acetic acid. The addition to the stirred, cold acetic acid solution required 15 min. After stirring at room temperature for 1 hr, the red solution was poured over ice and the resulting aqueous solution was allowed to stand overnight, yielding a yellow product (67%). The product was collected by filtration, washed with water, and recrystallized from tetrahydrofuran–water as white needles: mp 182–182.5°; λ_{max}^{KBr} 3.41 (CH), 3.51 (CH), 5.87 (C=O), 6.22 μ (C=C); nmr (CF_3COOH) δ 1.70–2.38 (14 H, m), 4.00 (1 H, s), 5.15 (1 H, s),[11] 7.12–7.78 (6 H, m).

Anal. Calcd for $C_{26}H_{22}O_2Br_2$: C, 59.32; H, 4.18; Br, 30.39; mol wt, 526. Found: C, 59.33; H, 4.50; Br, 29.89; mol wt, 522.

Extraction of the aqueous mother liquor with three 50-ml portions of chloroform followed by drying of the extracts with anhydrous calcium chloride, filtration, and evaporation yielded no additional products.

Registry No.—2, 17791-29-6; **5a**, 17791-30-9; **5b**, 17791-31-0; **6**, 17818-08-5.

Acknowledgment.—We gratefully acknowledge the support of this research by Public Health Service Fellowship No. GM-31959 and by Grant GM-10366 to Indiana University.

An Unusual Coupling of Cyclohexenone Cyclic Ketals

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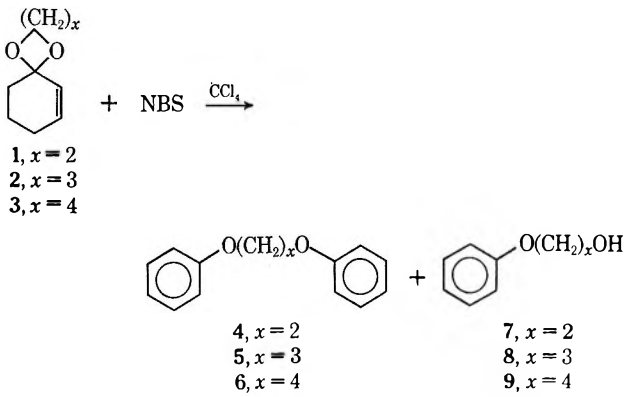
In a recent Note,[1] the preparation of 4-bromo-2-cyclohexenone ethylene ketal was reported as arising from the reaction of 2-cyclohexenone ethylene ketal and N-bromosuccinimide (NBS), using azobisisobutyronitrile and ultraviolet (uv) light as catalysts. When the reaction between 2-cyclohexenone ethylene ketal and NBS which had been recrystallized from water was carried out, a dramatically different result was obtained.



When cyclic ketal **1** was treated with 1 equiv of NBS in refluxing carbon tetrachloride, a vigorous exothermic reaction occurred after only several minutes. Removal of the succinimide and evaporation of the solvent left a material whose ir spectrum showed strong absorption at 8.05, 13.36 and 14.45 μ. Elution chromatography of the crude reaction mixture yielded a white,[2] crystalline compound (**4**) and a much smaller amount of a colorless oil (**7**), bp 68–70° (3 mm). Compound **4** displayed the following: a mass spectrum with the parent peak at *m/e* 214 and intense fragments at *m/e* 121 and 107; uv absorption maximum at 220 mμ with weak absorption at 270 and 277 mμ; and pertinent ir bands at 6.26, 6.71, 8.05, 11.31, 12.54, 13.36 and 14.45 μ. The nmr spectrum of **4** displayed signals at δ 4.25 (2 H, s), 6.84 (3 H, m), and 7.25 (2 H, m). The melting

(1) M. Graff and W. H. Gilligan, *J. Org. Chem.*, **32**, 3203 (1967).

(2) This material darkened slowly upon standing, probably indicating the presence of a small quantity of a presently unidentified bromine-containing material.

point of the material was 93–94° (lit.[3] mp 95°) after two crystallizations from ethanol.

The identification of **4** as 1,2-diphenoxyethane and **7** as 2-phenxoyethanol were made by comparison of their spectral and physical properties with those of authentic samples.

The formation of symmetrical bisphenoxylakanes was shown to be general in that cyclic ketals **2** and **3** reacted under the same conditions to yield 1,3-diphenoxypropane (**5**) and 1,4-diphenoxybutane (**6**), respectively, spectral properties of which are given in Table I.

TABLE I

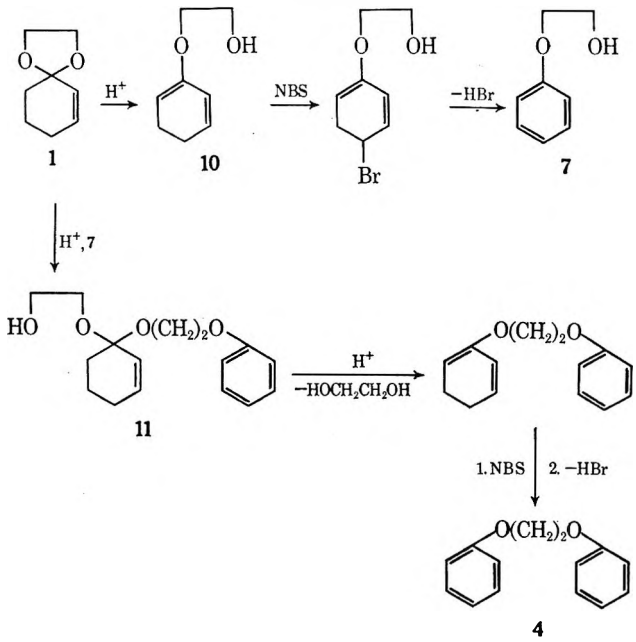
SPECTRAL PROPERTIES OF 1,3-DIPHENOXYPROPANE (**5**) AND 1,4-DIPHENOXYBUTANE (**6**)

Compd	Mass spectra, m/e	Uv, mμ	Ir, μ	Nmr, δ
5	228	221[a]	6.27, 11.45	2.21 (1, H, t)
	135	272	6.71, 12.30	4.10 (2 H, t)
	107	279	8.05, 13.30	6.79 (3 H, m)
			8.47, 14.49	7.24 (2 H, m)
6	242	220[a]	6.28, 11.42	1.93 (2 H, m)
	149	270	6.71, 12.00	3.94 (2 H, m)
	107	227	8.03, 13.39	6.77 (3 H, m)
			8.54, 14.52	7.19 (2 H, m)

[a] Maximum.

A possible coupling mechanism (Scheme I) involves opening of the cyclic acetal[4] to yield diene **10**, followed by bromination, and dehydrobomination to give 2-phenoxyethanol (**7**). This alcohol (**7**) reacts with **1** to form a new acetal (**11**) which upon protonation, elimination of ethylene glycol, bromination, and dehydrobromination yields 1,2-diphenoxyethane (**4**).

SCHEME I



The necessity of rigorously excluding moisture from allylic brominations of ethylene ketals has been previously noted[5] when an anomolous result was obtained with 2-cyclopentenone ethylene ketal and NBS.

(3) G. Gilta, *Bull. Soc. Chim. Belges*, **31**, 245 (1922).

(4) A. Marquet, H. B. Kagan, M. Dvolaitzky, C. Mamlok, C. Weidmann, and J. Jacques, *C. R. Acad. Sci., Paris*, **248**, 984 (1959).

Experimental Section

The ketals used in this work were prepared by the method of Salmi[6] from 2-cyclohexenone and the appropriate diol.

The NBS used was purchased from Matheson Coleman and Bell. It was recrystallized from water and dried in the air on a porous plate.

Reaction of 1 with NBS.—2-Cyclohexenone ethylene ketal (**1**, 1.4 g, 0.01 mol) and 1.8 g (0.01 mol) of NBS were placed in 12.5 ml of carbon tetrachloride. The reaction mixture was heated to reflux, and after only 5 min a vigorous exotherm occurred. Heating was continued for an additional 10 min before the solution was cooled and the succinimide was removed by filtration. Removal of the solvent left 1.2 g of a white solid. Elution chromatography of this material with 90% petroleum ether–10% benzene from 20 g of Woelm aluminum oxide (activity grade III) yielded 0.85 g of 1,2-diphenoxyethane (**4**) and 0.30 g of 2-phenoxyethanol (**7**).

Registry No.—**4**, 104-66-5; **5**, 726-44-3; **6**, 3459-88-9; **7**, 122-99-6.

(5) C. H. DePuy, B. W. Ponder, and J. D. Fitzpatrick, *J. Org. Chem.*, **29**, 3508 (1964).

(6) E. J. Salmi, *Ber.*, **71**, 1803 (1938).

Reaction of Phosphoranes with Mannich Bases. Synthesis of α-Substituted β-Arylacrylic Acids *via* the Wittig Reaction

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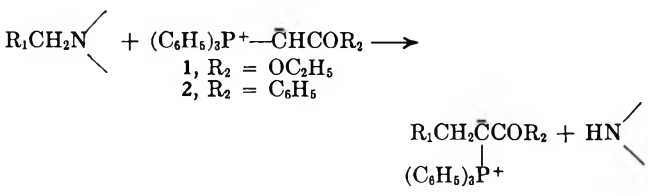
The alkylation of phosphonium ylides[1-3] is an important route to more complex ylides which are often unavailable by other methods.[4] Our continuing interest in carbon–carbon bond formation by amine replacement[5,6] led us to investigate the alkylation of phosphoranes with Mannich bases, and the synthetic utility of the products of this reaction.

Carbethoxymethylenetriphenylphosphorane (**1**) and benzoylmethylenetriphenylphosphorane (**2**) were found to react readily with Mannich bases according to Scheme I.

SCHEME I



(1) G. Wittig and M. Rieber, *Ann.*, **562**, 177 (1949).

(2) H. J. Bestmann and H. Schultz, *Tetrahedron Lett.*, No. 4, 5 (1960).

(3) H. J. Bestmann and H. Schultz, *Ber.*, **95**, 2921 (1962).

(4) For a recent review of reactions of phosphonium ylides, see A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966.

(5) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 3240 (1965).

(6) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *Tetrahedron Lett.*, 3103 (1965).

TABLE I

COMPOUNDS PREPARED BY REACTION OF PHOSPHONIUM YLIDES WITH MANNICH BASES

Compound	Type	R_1	R_2	R_3	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % P	Found, % C	Found, % H	Found, % N	Found, % P
3	A	OC_2H_5	H	H	187–189	92	77.97	5.91	2.92	6.49	78.27	5.90	2.86	6.44
4	A	C_6H_5	H	H	268–272	80	82.50	5.54	2.75	6.08	82.58	5.56	2.94	5.96
5	A	OC_2H_5	CH_3	OCH_3	190–193	87	75.99	6.18	2.69	5.94	76.05	6.09	2.50	5.99
6	A	OC_2H_5	CH_3	H	181.5–183	80	78.19	6.15	2.85	6.30	78.23	6.09	2.74	6.00
7	B	OC_2H_5			203–206	89	76.64	5.99		6.81	76.54	5.92		6.60
8[a]	B	C_6H_5			259–260.5	72				6.37				6.30
9					189–192	42	76.29	5.82	2.70	5.96	76.03	5.81	2.85	5.73
10					208–211	55	75.63	4.44		6.50	75.78	4.55		6.21
11					190–192.5	5	80.43	5.25	2.61	5.76	80.37	5.42	2.81	5.74
12[b]					177–183	20	88.34	5.46			88.68	5.24		
13					167–169.5	20	83.37	5.05	5.40		83.26	5.15	5.15	

[a] Correct carbon analysis could not be obtained. The purity of the sample was confirmed by tlc; the identity was established by hydrolysis to the known[15] 3-(*p*-hydroxyphenyl)propiophenone.

[b] Reference 13.

Application of this reaction to the most common types of Mannich bases derived from ketones, phenols, and indoles gave compounds listed in Table I. The products generally crystallized from the reaction mixture in high yields and in a high degree of purity. The identities of phosphoranes **3** and **8** were confirmed by hydrolysis to indole-3-propionic acid and 3-(*p*-hydroxyphenyl)propiophenone, respectively.

Some *o*-phenolic Mannich bases yield products different from the "normal" ylide such as **11**. Owing to the participation of the phenolic hydroxyl, the alkylation may be accompanied by lactonization (**10**), or by a "hemiketalization–dephosphoranylation" sequence, which can be viewed as an "internal Wittig" (Scheme II and **12** and **13**, Table I).

SCHEME II

It was of interest to explore the synthetic usefulness of the alkylated phosphoranes. In particular, the Wittig reaction should lead to β-arylacrylic acids having an α substituent with a reactive nucleus, such as indole or oxygenated benzene. Compounds of this type are not easily available by other methods. The obvious alternate syntheses, the Perkin reaction and the Oglialoro modification,[7] are known to give poor yields with β-arylpropionic acids.

When the alkylated ylides of Table I were allowed to react with aromatic aldehydes, the Wittig reaction occurred readily to give the compounds listed in Table II. Since isolation of the products was simplified by alkaline hydrolysis of the Wittig reaction mixture, most of the compounds were obtained as acids rather than esters. Exceptions were the esters **14**, **17**, and **18**, and the lactone **25** derived from the lactone ylide **10**.

The Wittig reaction with an *o*-hydroxyaldehyde, 2-hydroxy-1-naphthaldehyde, was accompanied by spontaneous lactonization resulting in compounds **23** and **24** (Table II).

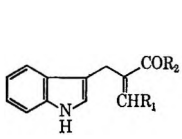
Most the the reactions of stabilized ylides with aldehydes reported to date have led to the formation of the *trans* olefin as the major product.[8] Consideration of Dreiding models of the α-substituted β-arylacrylic acids and esters of Table II suggests that in all cases the preferred form is that in which the carboxyl and aryl groups are *trans*. These observations suggest that the

(7) J. R. Johnson, *Org. Reactions*, **I**, 225 (1942).

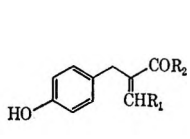
(8) (a) See ref 4, p 181; (b) M. O. House and G. R. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961); (c) D. H. Wadsworth, O. E. Schupp, E. J. Seuss, and J. A. Ford, *ibid.*, **30**, 680 (1965); (d) D. E. Bissing, *ibid.*, **30**, 1296 (1965).

TABLE II

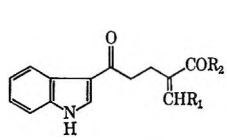
COMPOUNDS PREPARED FROM PHOSPHORANES OF TABLE I AND ALDEHYDES



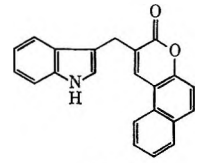
A



B



22



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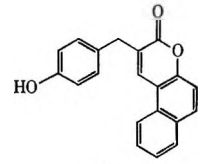
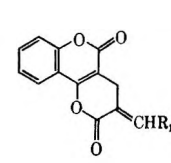
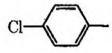
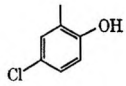
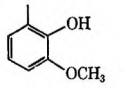
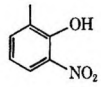
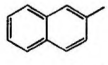
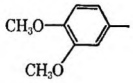
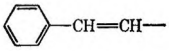
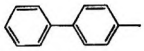
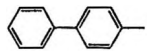


24



25

Compound	Type	R_1	R_2	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	C_2H_5, ν_{max} mμ (ε)
14	A		OC_2H_5	127–128	54	74.49	5.92	9.15	74.60	5.90	9.23	220 (40,000), 258 (19,000)
15	A		OH	189–196	52	69.35	4.53	4.49	69.37	4.71	4.35	222 (45,800), 271 (26,000)
16	A		OH	202–205	58	65.96	4.31	4.27	65.84	4.32	4.12	222 (50,100), 266 (14,500), 318 (5900)
17	A		OC_2H_5	120–131	43	71.78	6.02	3.99	72.06	5.78	4.06	221 (52,000), 276 (18,700)
18	A		OC_2H_5	123–126	24	65.56	4.95	7.65	65.63	4.90	7.42	220 (46,500), 255 (19,200), 272 (18,600)
19	B		OH	209–212.5	50	78.93	5.30		78.93	5.23		223 (23,200), 259 (36,300), 301 (16,250)
20	B		OH	180–185	36	68.78	5.77		68.92	5.85		222 (21,600), 287 (17,000), 309 (16,100)
21	B		OH	236–239.5	53	77.12	5.75		77.40	5.89		226 (14,000), 241 (7900), 316 (39,800)
22			OH	226.5–228	6.5	78.96	5.35	3.54	79.19	5.43	3.35	241 (18,800), 298 (40,500)
23				211–213.5	40	81.21	4.65	4.30	81.18	4.65	4.20	221 (69,800), 232 (55,000), 249 (15,200)
24				242–244	60	79.45	4.67		79.60	4.69		229 (50,600), 233 (54,500), 246–250 (12,000) plat, 317 (11,100), 347 (12,900)
25				229.5–231	52	78.93	4.24		78.86	4.23		254 (51,200), 347 (39,400)

acids and esters of Table II are the *trans* isomers (*trans,trans* for compound **21**[9]). This tentative assignment is supported by the intensities of the ultraviolet absorption maxima of compounds such as **14** and **15** which are of the same order of magnitude as those of *trans* cinnamic acid (ϵ_{max} 21,000).[10]

The alkylated ylids of Table I were found to be inert toward ketones, such as cyclohexanone and N-methylpiperidone, with or without benzoic acid catalysis.[11] The ylides, **4** and **8**, derived from benzoylmethylenetriphenylphosphorane are highly insoluble in most organic solvents. Under our standard conditions, **8** and 2-naphthaldehyde in dimethyl sulfoxide or N,N-dimethylformamide failed to react.

(9) The ease with which allo-5-phenyl-2,4-pentadienoic acid rearranges to the *trans,trans* form [J. C. Ghosh and S. Gupto, *Quart. J. Indian Chem. Soc.*, **2**, 241 (1925); J. C. Ghosh and M. N. Mitra, *ibid.*, **3**, 273 (1926)] suggests that the basic hydrolysis used to prepare the acids would afford only the *trans,trans* isomer.

(10) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," 2nd ed, Arnold Ltd., London, 1960, p 269.

(11) C. Ruechardt, S. Eichler, and P. Pause, *Angew. Chem. Intern. Ed. Engl.* **2**, 619 (1963).

Experimental Section[12]

Phosphoranes of Table I.—A solution of 0.1 mol of a Mannich base and 0.1 mol of a phosphorane in 500 ml of toluene was refluxed for 6–7 hr with a gentle sweep of dry nitrogen through the solution. The mixture was chilled; the crystalline precipitate was filtered off and consecutively washed with cold toluene and petroleum ether (bp 37–47°). The analytical samples were prepared by recrystallization from ethyl acetate (**3**, **7**), acetonitrile (**4**, **5**, **6**, **11**) and N,N-dimethylformamide (**8**).

In the case of **9** and **10**, the solutions were decanted from some tar and concentrated under reduced pressure. The residual gums were crystallized from acetonitrile (**9**) and toluene (**10**).

3-Phenyl-1H-naphtho[2,1-*b*]pyran (12).[13]—A solution of 2.01 g (0.01 mol) of 1-dimethylaminomethyl-2-naphthol and 3.8 g (0.01 mol) of benzoylmethylenetriphenylphosphorane in 50 ml

(12) Melting points were determined with the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The thin layer chromatography was performed using silica gel G according to Stahl (Merck, Darmstadt) as the absorbent and ethanol as the eluent. Chromatograms were developed by spraying with aqueous $KMnO_4$. The authors are indebted to the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular we wish to thank Dr. C. Greenough for the spectral data and Mrs. U. Zeek for analytical determinations.

(13) Compound has been previously described by H. Hellmann and J. Pohlmann, *Ann.*, **642**, 40 (1961): mp 180–184°.

of toluene was refluxed for 6 hr with a gentle sweep of nitrogen through the solution. The toluene was removed under reduced pressure leaving a semicrystalline solid which was recrystallized three times from acetonitrile.

3-Phenyl-1H-pyrano[3,2-*f*]quinoline (13).—This compound was obtained from 5-[(dimethylamino)methyl]-6-quinolinol in analogy to **12** after 2 hr of refluxing and crystallization from ethanol or ethyl acetate.

Hydrolysis of 3.—A solution of 10 ml of 10% NaOH and 2 g of **3** in 40 ml of 95% ethanol was refluxed for 2 hr and concentrated under reduced pressure. The aqueous residue was diluted with 50 ml of water and washed several times with chloroform in order to remove triphenylphosphine oxide. The aqueous portion was chilled and acidified with 5 *N* HCl. The precipitated solid was recrystallized from benzene. The physical and analytical properties of the product were identical with those of indole-3-propionic acid: mp 132–133° (lit.[14] mp 132–133°); ν_{max}^{Nujol} 1697 cm^{-1} (–COOH).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.83; H, 5.89; N, 7.34.

Hydrolysis of 8.—A mixture of 1 g of **8** and 1 g of KOH was refluxed in 100 ml of 75% ethanol for 6 hr. The clear solution was concentrated under reduced pressure, and the aqueous residue was diluted with 75 ml of water. The resulting oily precipitate which solidified on standing was identified as triphenylphosphine oxide.[15] The aqueous filtrate was acidified with concentrated HCl, and the crystalline precipitate was filtered off and recrystallized from ethanol. The physical and analytical properties of the product were identical with those of 3-(*p*-hydroxyphenyl)-propiophenone: mp 118.5–120.5° (lit.[16] mp 116–117°); ν_{max}^{Nujol} 3400 (–OH), 1675 cm^{-1} (>CO).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.69; H, 6.24. Found: C, 79.66; H, 6.27.

The Wittig Reaction (Compounds of Table II).—The following procedures are illustrative of the methods employed for the preparation of the acids, esters, and lactones of Table II.

Ethyl α-(4-Pyridylmethylene)indole-3-propionate (14).—A solution of 30.5 g of **3** and 6.9 g of 4-pyridinecarboxaldehyde in 250 ml of dioxane was refluxed for 21 hr and evaporated under reduced pressure. The residual gum was dissolved in 200 ml of ether, and the solution was extracted with three 50-ml portions of 4 *N* HCl. The acid solution was made basic with 5% NaOH solution and extracted with chloroform to afford 22 g of crude product upon evaporation. Crystallization from 100 ml of ether followed by recrystallization from 50% aqueous ethanol gave analytical material: ν_{max}^{Nujol} 740 (ms), 1070 (m), 1202 (ms), 1257 (ms), 1600 (w), 1710 (s), 3150 (m) cm^{-1}.

Ethyl α-(2-Hydroxy-3-methoxybenzylidene)indole-3-propionate (17).—A solution of 1.52 g of 2-hydroxy-3-methoxybenzaldehyde and 4.77 g of **3** in 75 ml of dioxane was refluxed for 18 hr. The dioxane was removed under reduced pressure, and the residual gum was extracted with five 25-ml portions of Skellysolve B. The remaining gum was dissolved in ethyl acetate and chromatographed on a column of 300 g of Florisil. Concentration of the first few fractions gave crystalline material. The crystals were combined, and recrystallized from ethanol: ν_{max}^{Nujol} 730 (m), 750 (m), 960 (m), 1020 (m), 1185 (ms), 1225 (ms), 1250 (s), 1575 (mw), 1610 (mw), 1690 (ms), 3375 (m), 3395 (ms) cm^{-1}.

2-(*p*-Hydroxybenzyl)-5-phenyl-2,4-pentadienoic Acid (21).—A solution of 5.28 g of cinnamaldehyde and 18 g of **7** in 300 ml of dioxane was refluxed for 24 hr. The dioxane was removed under reduced pressure, and the residue was taken up in 100 ml of 50% ethanol. The solution was treated with 8 g of KOH and refluxed for 4 hr. The ethanol was removed under reduced pressure, and the concentrate was diluted to *ca.* 100 ml with H_2O. The aqueous mixture was extracted with four 50-ml portions of ether. The aqueous phase was made strongly acidic with concentrated HCl, and the precipitated product was filtered, washed with cold H_2O, and recrystallized from absolute ethanol: ν_{max}^{Nujol} 730 (m), 785 (mw), 985 (m), 1100 (mw), 1165 (m), 1215 (ms), 1275 (ms), 1280 (ms), 1515 (ms), 1590 (s), 1610 (ms), 1665 (ms), 3400 (m) cm^{-1}.

α-(4-Biphenylmethylene)-α-oxoindole-3-valeric Acid (22).—A solution of 10.38 g of **9** and 3.64 g of 4-biphenylcarboxaldehyde in 150 ml of dioxane was refluxed for 24 hr. The dioxane was removed under reduced pressure, and the residue was taken up in 50 ml of 50% ethanol. After addition of 4 g of KOH and refluxing for 4 hr, the ethanol was removed under reduced pressure, and the aqueous concentrate was diluted to *ca.* 50 ml with H_2O. The mixture was washed with four 50-ml portions of ether, followed by four extractions, each with 25 ml of ethyl acetate. The combined ethyl acetate extracts were dried over Na_2SO_4 and concentrated to a gum under reduced pressure. The gum was crystallized from ethanol: ν_{max}^{Nujol} 690 (m), 750 (m), 970 (mw), 1150 (mw), 1230 (m), 1520 (m), 1580 (m), 1610 (ms), 1675 (ms), 3150 (ms) cm^{-1}.

2-(Hydroxy)-α-(*p*-hydroxybenzyl)-1-naphthalene Acrylic Acid δ-Lactone-(24).—A solution of 1.72 g of 2-hydroxy-1-naphthaldehyde and 4.54 g of **7** in 75 ml of dioxane was refluxed for 18 hr and evaporated under reduced pressure. The partially crystalline residue was extracted with three 25-ml portions of boiling Skellysolve B and recrystallized from ethanol: ν_{max}^{Nujol} 740 (m), 820 (ms), 1070 (m), 1170 (mw), 1230 (m), 1515 (m), 1580 (m), 1680 (s), 3300 (ms), cm^{-1}.

3-(4-Biphenylylmethylene)-3,4-dihydro-2H,5H-pyrano[3,2-c][1]-benzopyran-2,5-dione (25).—A solution of 4.7 g of **10** and 1.82 g of 4-biphenylcarboxaldehyde in 25 ml of dioxane was refluxed for 24 hr. The dioxane was removed under reduced pressure, leaving a semicrystalline residue. This was triturated with five 50-ml portions of boiling ether. The residue was recrystallized from CH_3CN: ν_{max}^{Nujol} 760 (m), 960 (mw), 1040 (mw), 1110 (mw), 1575 (mw), 1645 (m), 1725 (s), 1745 (m), cm^{-1}.

Mannich bases used as starting materials are either commercially available[17] or were prepared by standard methods.[18] The previously undescribed **5**-[(dimethylamino)methyl]-6-quinolinol was obtained from a solution of 6-hydroxyquinoline (7.25 g), dimethylamine (2.7 g), and 37% formaldehyde (4.25 ml) in ethanol (150 ml). The solution was brought to reflux, allowed to stand for 2 days at room temperature, and concentrated under reduced pressure. The oily residue crystallized on standing. The analytical sample was prepared by recrystallizations from ethyl acetate and ethanol with the aid of charcoal: mp 106–107.5°; yield 55%; λ_{max} 239 mμ (ε 33,800), 285 (2900), 336 (3800).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.23; H, 7.07; N, 13.55.

Registry No.—**3**, 17791-03-6; **4**, 17791-04-7; **5**, 17791-05-8; **6**, 17791-06-9; **7**, 17791-07-0; **8**, 17818-06-3; **9**, 17791-08-1; **10**, 17791-09-2; **11**, 17791-10-5; **12**, 14271-36-4; **13**, 17791-12-7; **14**, 17791-13-8; **15**, 17791-14-9; **16**, 17791-15-0; **17**, 17791-16-1; **18**, 17791-17-2; **19**, 17791-18-3; **20**, 17791-19-4; **21**, 17791-20-7; **22**, 17791-21-8; **23**, 17791-22-9; **24**, 17791-23-0; **25**, 5807-40-9; 3-(*p*-hydroxyphenyl)propiophenone, 17791-25-2; 5-[(dimethylamino)methyl]-6-quinolinol, 17791-26-3.

(14) M. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Amer. Chem. Soc.*, **66**, 200 (1944).

(15) A. Michaelis, *Ann.*, **229**, 306 (1885).

(16) V. A. Zasosov, E. I. Metel'kova, and S. N. Milovanova, *Zh. Obshch. Khim.*, **26**, 2499 (1956); *Chem. Abstr.*, **51**, 4994*d* (1956).

(17) Aldrich Chemical Co., Inc.

(18) H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, Weinheim, 1960.

The Geometrical Isomers of 1,5-Diphenylpentadien-3-ol

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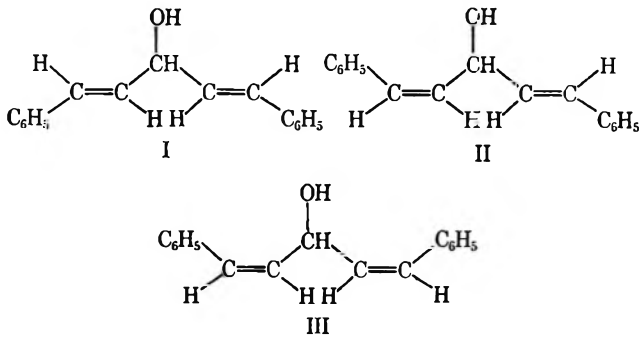
In a previous report[1] we described the preparation of the geometrical isomers of dibenzalacetone (1,5-diphenyl-1,4-pentadien-3-one). This paper describes

(1) J. G. Dinwiddie, Jr., H. M. White, and W. J. Day, *J. Org. Chem.*, **27**, 327 (1962).

the preparation of the geometrical isomers of 1,5-diphenyl-1,4-pentadien-3-ol and attempts to resolve the *cis,trans* isomer. At the time this work was started there were no known examples of optical isomerism where the asymmetry of the molecule was due to differences in the geometrical isomerism of otherwise identical groups. The resolution of compounds exhibiting such *cis,trans* asymmetry has recently been reported by Riemschneider.[2]

The preparation of 1,5-diphenyl-*trans*-1-*trans*-4-pentadien-3-ol (I) by the sodium borohydride reduction of the *trans,trans* isomer of dibenzalacetone has been reported by Huls and Simon,[3] and this method was used in this work. The *cis,trans* (II) and *cis,cis* (III) isomers were prepared by hydrogenation over Lindlar catalyst of 1,5-diphenylpent-1-yn-*trans*-4-en-3-ol (IV) and 1,5-diphenyl-1,4-pentadiyn-3-ol (V), respectively. IV was prepared by the reaction of phenylacetylenemagnesium bromide with cinnamaldehyde in 62% yield. This preparation was subsequently reported by Iwai and coworkers[4] in somewhat poorer yield. Compound V was prepared by the method of Liang.[5] An attempted preparation of II by sodium borohydride reduction of 1,5-diphenyl-*cis*-1-*trans*-4-pentadien-3-one gave only polymeric material with a molecular weight about twice that of the desired product.



I II III

The infrared spectrum of each isomer showed the characteristic absorption of *cis*- and/or *trans*-substituted double bonds.[6] The melting points and ultraviolet absorption data are included in Table I. The uv absorption of I is in agreement with the values reported in the literature.[2g,7,8]

TABLE I

PROPERTIES OF THE ISOMERS OF 1,5-DIPHENYL-1,4-PENTADIEN-3-OL

Isomer	Mp, °C	λ_{max}, mμ	ϵ_{max}
trans,trans (I)	64	263	33,100
cis,trans (II)	57	258	20,600
cis,cis (III)	71	236	18,350

(2) (a) R. Riemschneider and K. Brendel, *Angew. Chem.*, **73**, 655 (1961). (b) R. Riemschneider and A. Rook, *Naturwisschaften*, **48**, 500 (1961). (c) R. Riemschneider and A. Rook, *Monatsch. Chem.*, **92**, 1197, 1227 (1961). (d) R. Riemschneider and H. Kampfer, *Z. Naturforsch.*, **16b**, 704 (1961). (e) R. Riemschneider and D. Kirstein, *ibid.*, **17b**, 522 (1962). (f) R. Riemschneider and H. Kampfer, *Ann.*, **665**, 35 (1963). (g) R. Riemschneider, K. Brendel, and J. Takei, *ibid.*, **665**, 43 (1963).

(3) R. Huls and Y. Simon, *Bull. Soc. Roy. Sci. Liege*, **25**, 89 (1956).

(4) I. Iwai, Y. Yura, T. Konotsune, and K. Tomita, *Yakugaku Zasshi*, **80**, 156 (1960).

(5) C. K. Liang, *Bull. Soc. Chim. Fr.*, **53**, 33 (1933).

(6) N. Sheppard and D. M. Simpson, *Quart. Rev.* (London), **6**, 1 (1952).

(7) F. Bohlman, *Chem. Ber.*, **85**, 1144 (1952).

(8) G. Hesse and P. Thieme, *Ann.*, **686**, 64 (1965).

The *trans,trans* isomer was found to be sensitive to light. Molecular weight determinations indicated that a dimer was formed initially on exposure to light, followed by more extensive polymerization. The *cis,trans* alcohol was also sensitive, polymerizing very rapidly in the presence of light and over a period of 2–3 days in the absence of light.

Each of the isomeric alcohols yielded the *trans,trans*-dibenzalacetone when oxidized by stirring over manganese dioxide in an organic solvent. The oxidation proceeded most rapidly with the all-*trans* isomer, being quantitative in 6 hr, whereas the all-*cis* isomer was not completely oxidized after 72 hr. The indications are that the steric requirements for proper contact with the surface of the heterogeneous oxidizing agent require the isomerization of the *cis* double bonds.

The chemical instability of II precluded the possibility of effecting a practical resolution. It was decided to resolve the starting material, IV and then produce the enantiomeric *cis,trans* alcohols by catalytic reduction of the triple bond. The biphthalate of IV was prepared in the usual manner, converted into the strychnine salt and crystallized from benzene. Successive fractions of the salt gave no change in optical rotation and this method was abandoned.

The Δ^5-3-β-acetoxyetiocholenate ester of IV (VI) was prepared and resolved by recrystallization from hexane.[9,10] The Δ^5-3-β-acetoxyetiocholenyl chloride was prepared from pregnenolone acetate by a modification of the procedure of Djerassi and Staunton.[9] Thirty per cent formalin solution was used to destroy the excess sodium hypobromite used in the oxidation to the acid, and oxalyl chloride was used to convert the acid into the acid chloride. When thionyl chloride was used, following the published procedure, good yields of the acid anhydride were obtained rather than the acid chloride.

After three recrystallizations, the specific rotation of the ester in chloroform at 25° decreased and reached a value of −10.46°. Further recrystallizations produced no additional change.

Alkaline hydrolysis of VI to yield optically active IV was attempted, but the only product was an intractable tar. During the original purification of VI by chromatography on acid-washed alumina, one column had been allowed to stand overnight before being eluted. The major fraction obtained from this column was an alcohol with an ir spectrum almost identical with that of IV. This method was investigated as a practical method of obtaining the alcohol from the ester.

A sample of optically active ester (VI) was placed on a column of acid-washed alumina and allowed to stand for 52 hr before elution. The alcohol (VII) obtained from this column was optically active and was hydrogenated over Lindlar catalyst to the corresponding *cis,trans* alcohol (VIII) which was also optically active. Examination of the ir spectrum of VIII showed that it was not identical with that of the racemic *cis,trans* alcohol (II). Apparently rearrangement had occurred on the alumina column. While moisture was not scrupulously avoided, the alumina used was Merck acid washed, and the solvents used were believed to be

(9) C. Djerassi and J. Staunton, *J. Amer. Chem. Soc.*, **83**, 736 (1961).

(10) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

dry. This rearrangement certainly does not require the conditions reported by Herz and Caple, who found that it was necessary to saturate the eluting solvent with water to effect the rearrangement of an unsaturated ester.[11]

The acetylenic alcohol (VII) was oxidized to the corresponding ketone (IX) with the Kiliani reagent.[12] The same ketone was prepared by the base-catalyzed condensation of acetophenone with phenylpropargylaldehyde. The ir spectrum, analytical data, and method of preparation indicated that IX was 1,5-diphenylpent-1-yn-3-en-5-one. The acetylenic alcohol, VII, was therefore 1,5-diphenylpent-1-yn-3-en-5-ol, and the hydrogenated alcohol, VIII, was 1,5-diphenyl-*cis*-1-*trans*-3-pentadien-5-ol.

Iwai[13] has reported the preparation of IX by the Meyer–Schuster rearrangement of V. The compound reported by Iwai melts at 124° and has carbonyl absorption at 1692 cm^{-1}. The ketone to which we have assigned the same structure melts at 97° and shows carbonyl absorption at 1650 cm^{-1}. Our method of synthesis and the physical properties of the product agree well with the work of Stetter and Reischl.[14] On the basis of the evidence cited we believe that our structural assignment is correct. One attempt to duplicate Iwai's results yielded only starting material.

A sample of partially resolved VI with a specific rotation in chloroform of −17.1° was hydrogenated over Lindlar catalyst to yield 1,5-diphenyl-*cis*-1-*trans*-4-pentadien-3-(Δ^5-3-β-acetoxyetiocholenate) (X). X was allowed to stand on a column of acid-washed alumina as before. The alcohol eluted from the column was optically active, and was shown to be 1,5-diphenyl-*trans*-1-*trans*-3-pentadien-5-ol (XI) by comparison with an authentic sample prepared by the method of Bohlman.[7] The occurrence of optical activity in the rearranged alcohol demands that the parent alcohol (II) must have been asymmetric and requires a stereospecific pathway for the rearrangement.

Experimental Section[15]

cis,trans-1,5-Diphenylpentadien-3-ol (II).—A solution of 2 g of 1,5-diphenylpent-1-yn-4-en-3-ol in 50 ml of methanol was stirred over 1 g of Lindlar catalyst in an atmosphere of hydrogen until 1 mol of hydrogen had been absorbed. The solution was filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from petroleum ether (bp 30–60°) yielding 1.8 g (90%) of white needles: mp 58°; ir 3330, 1005, and 970 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.28; H, 6.66.

cis,cis-1,5-Diphenylpentadien-3-ol (III).—This compound was prepared by the hydrogenation of 1,5-diphenylpentadiyn-3-ol over Lindlar catalyst in methanol. After the absorption of 2 mol of hydrogen, the catalyst was filtered off, and the solvent was removed under reduced pressure. The residue was recrystallized from petroleum ether (bp 30–60°) to give a quantitative yield of white needles: mp 70.5–71.5°; ir 3390, 1030, and 1005 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.28; H, 6.64.

Oxidation of the Isomeric 1,5-Diphenylpentadien-3-ols.—A solution of 2.0 g of *trans,trans*-1,5-diphenylpentadien-3-ol in 25 ml of acetone and 30 ml of petroleum ether (bp 30–60°) was stirred over 10 g of manganese dioxide for 6 hr. The manganese dioxide was removed by filtration; the solvent was removed on a steam bath; and the residue was recrystallized from methanol to give 1.8 g of *trans,trans*-1,5-diphenylpentadien-3-one, which was identified by comparison with an authentic sample.

When a solution of 0.5 g of *cis,trans*-1,5-diphenylpentadien-3-ol in 10 ml of acetone and 25 ml of petroleum ether (bp 30–60°) was stirred over 5 g of manganese dioxide for 12 hr the product was shown to be *trans,trans*-1,5-diphenylpentadien-3-one.

Similar treatment of 0.5 g of *cis,cis*-1,5-diphenylpentadien-3-ol yielded after 12 hr a residue that showed both hydroxyl and carbonyl ir bands. Additional oxidation for 60 hr did not completely remove the alcohol. Recrystallization from methanol gave 0.2 g of the *trans,trans* ketone.

1,5-Diphenylpent-1-yn-4-en-3-(Δ^5-3-β-acetoxyetiocholenate) (VI).—A solution of 5 g of Δ^5-3-β-acetoxyetiocholenic acid in 15 ml of oxalyl chloride was allowed to stand for 8 hr at room temperature. The excess oxalyl chloride was removed under reduced pressure (oil pump) leaving a yellow crystalline residue of the acid chloride. The acid chloride was dissolved in 25 ml of pyridine (freshly distilled from barium oxide), and a solution of 3.2 g of 1,5-diphenylpent-1-yn-4-en-3-ol in 25 ml of pyridine was added. The flask was tightly stoppered and allowed to stand for 8 hr. The reaction mixture was poured into excess ice-cold dilute hydrochloric acid, filtered, and air dried, yielding 5.5 g of crude ester. The crude ester was chromatographed on acid-washed alumina. The benzene eluent yielded 2 g of material which crystallized from petroleum ether as white needles, mp 145–149°. Three additional crystallizations from *n*-hexane afforded 1.03 g of ester: mp 162°; $[\alpha]^{25}D$ −10.46° ($CHCl_3$). The rotation and melting point were unchanged by further crystallizations.

Anal. Calcd for $C_{39}H_{44}O_4$: C, 81.21; H, 7.69. Found: C, 81.32; H, 7.56.

Hydrolysis and Rearrangement of 1,5-Diphenylpent-1-yn-4-en-3-(Δ^5-3-β-acetoxyetiocholenate).—A solution of 1.25 g of VI in 25 ml of benzene was placed on a column (2.5 × 30 cm) of acid-washed alumina. The column was washed with two 5-ml portions of benzene, closed, and allowed to stand for 52 hr. The column was eluted with 500 ml of benzene followed by 400 ml of 10% ether–benzene. The solvent was removed from the ether–benzene fraction, leaving 0.4162 g of 1,5-diphenylpent-1-yn-3-en-5-ol. Recrystallization from petroleum ether (bp 30–60°) gave white needles: mp 57°; $[\alpha]^{25}D$ −6.45° ($CHCl_3$); ir 3390, 2240, and 950 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.31; H, 5.93.

1,5-Diphenyl-*cis*-1-*trans*-3-pentadien-5-ol (VIII).—A solution of 0.1586 g of optically active 1,5-diphenylpent-1-yn-3-en-5-ol in 25 ml of methanol was stirred over 0.5 g of Lindlar catalyst in an atmosphere of hydrogen until uptake of hydrogen ceased. The catalyst was filtered off, and the solvent was removed under reduced pressure, leaving 0.1362 g of 1,5-diphenyl-*cis*-1-*trans*-3-pentadien-5-ol: $[\alpha]^{25}D$ −14.05° (CH_3OH); ir 3636, 3390, 1060, and 985 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.47; H, 7.00.

Reduction, Hydrolysis, and Rearrangement of 1,5-Diphenylpent-1-yn-4-en-3-(Δ^5-3-β-acetoxyetiocholenate).—A solution of 1.215 g of partially resolved VI, $[\alpha]^{25}D$ −17.1°, in 30 ml of methanol was stirred over 0.5 g of Lindlar catalyst in an atmosphere of hydrogen until 66 ml (1 mol) of hydrogen had been taken up. The solvent was removed under reduced pressure, the residue dissolved in 10 ml of benzene and placed on a column of acid-washed alumina. The column was closed and allowed to stand for 70 hr. The column was developed with benzene followed by 10% benzene–ether.

The solvent was removed from the ether–benzene fraction leaving 0.1017 g of *trans,trans*-1,5-diphenylpentadien-5-ol, $[\alpha]^{25}D$ −5.00° ($CHCl_3$). The identity of the alcohol was established by comparison of its ir spectrum with that of an authentic sample.

Oxidation of 1,5-Diphenylpent-1-yn-3-en-5-ol (VII).—Kiliani reagent[12] was added dropwise to a stirred solution of 0.5 g of 1,5-diphenylpent-1-yn-3-en-5-ol in 25 ml of acetone until the orange

(11) W. Herz and G. Caple, *J. Amer. Chem. Soc.*, **84**, 3518 (1962).

(12) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **24**, 1367 (1959).

(13) I. Iwai and Y. Okahima, *Yakugaku Zasshi*, **79**, 1284 (1959).

(14) H. Stetter and A. Reischl, *Chem. Ber.*, **93**, 1253 (1960).

(15) All analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on Perkin-Elmer Model 137 Infracord either as liquid films or potassium bromide disks. All melting points are uncorrected and were taken on a Scientific Glass Melt meter. Optical rotations were taken on a Rudolph Model 70 polarimeter. Ultraviolet spectra were taken in chloroform solution on a Perkin-Elmer Model 4000A spectrophotometer.

color of the reagent persisted. The reaction mixture was extracted with ether. The ether extract was washed with water and dried over sodium sulfate, and the ether was removed on a steam bath. The residue was recrystallized from methanol to give 0.3 g (60%) of 1,5-diphenylpent-1-yn-3-en-5-one as yellow needles, mp 97°. The ir spectrum was identical with that of a sample prepared by an unambiguous route.

Preparation of 1,5-Diphenylpent-1-yn-3-en-5-one (IX).—A mixture of 1.3 g of phenylpropargylaldehyde and 1.2 g of acetophenone was added dropwise to a stirred solution of 2.5 g of sodium hydroxide in 20 ml of water and 16 ml of methanol. The temperature of the reaction was maintained below 20° by an ice bath. The mixture was stirred for 0.5 hr after addition was completed and filtered, yielding 0.6 g of light yellow solid. Recrystallization from methanol gave 0.5 g of lemon yellow needles, mp 97° (lit.[14] mp 101.5°).

Anal. Calcd for $C_{17}H_{12}O$: C, 87.90; H, 5.21. Found: C, 88.04; H, 5.23.

Registry No.—I, 17791-55-8; II, 17791-56-9; III, 17791-57-0; VI, 17791-58-1; VIII, 17791-59-2; 1,5-diphenylpent-1-yn-3-en-5-ol, 17791-60-5.

The Reductive Cyclization of 4-Tosyloxybicyclo[5.2.1]decan-10-one[1]

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Received June 5, 1968

The photolysis of bicyclo[5.2.1]decan-10-one (**7**) yields octamethyleneketene[3] rather than the tricyclic alcohol **8**, a product which might have been anticipated on the basis of the reported photoisomerization of monocyclic ketones to bicyclic alcohols.[4] This compound has now been synthesized by the sequence of reactions depicted in Scheme I. Employing a bis-homologation ring-expansion procedure,[5] 4-hydroxycyclohexanone (**1**) was converted in 54% yield into a mixture comprised of approximately equal parts of the epimers **2** and **3**, one of which was stable in the keto alcohol form (*i.e.*, **2**) and one of which was stable in the hemiketal form (*i.e.*, **10**). Unfortunately, the hemiketal proved to be so resistant to ring opening that carbonyl derivatives could not be prepared; its utility as a synthesis intermediate being thereby limited, attention was directed to the keto alcohol **2**. This compound, isolated *via* its tosylate **4**, was shown to be epimerically related to **3** (and **10**) by acetolysis to a mixture of the olefin **5** and the actate **6** followed by methanolysis of **6** to the hemiketal **10**. Reductive cyclization of **4** with lithium in ammonia–dimethoxyethane yielded a complex mixture of products, the volatile portion of which was shown by vpc to contain two major components. One of these possesses an analysis compatible with a $C_{10}H_{16}O$ formula and has an nmr and mass spectrum interpretable in terms of the tricyclic alcohol **8**. The other material possesses an analysis compatible with a $C_{10}H_{16}O_2$ formula, has an nmr spectrum which indicates that the two oxygens are present as tertiary hydroxyl groups, and gives a periodate test which indicates the hydroxyl groups to be vicinal. The most reasonable structure commensurate with these data is the diol **9**.

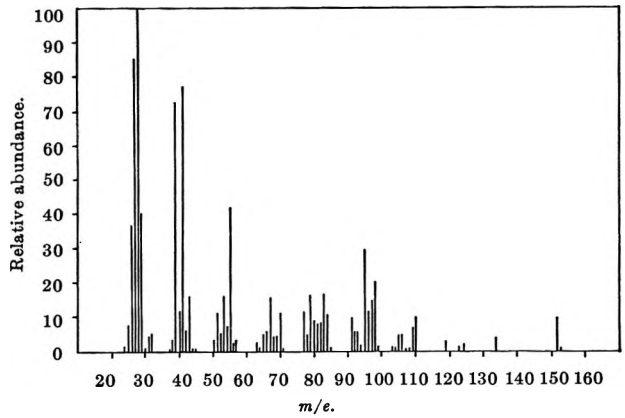


Figure 1.—Mass spectrum of tricyclo[5.2.1.$0^{4,10}$]decan-10-ol (**8**).

No attempt to unravel the details of the mechanism of the reductive cyclization was undertaken. The formation of the alcohol **8** is reasonably explained as an addition of one (or two) electrons to the carbonyl group to yield a radical anion (or a dianion) which then effects a transannular displacement of the tosyl group, a reaction having some resemblance to the reductive cyclization of keto esters which has been investigated in this laboratory.[6]

Experimental Section[7]

10-Oxatricyclo[5.2.1.$1^{4,11}$]undecan-11-ol (10).—A 34.2-g (0.300 mol) sample of 4-hydroxycyclohexanone[8] in 120 ml of methanol, cooled in an ice–salt bath, was mixed with 1.0 g of powdered, anhydrous potassium carbonate. To the stirred suspension 87.0 g (0.300 mol) of N,N′-dinitroso-N,N′-dicarbethoxybutanediamine[5] in 120 ml of methylene chloride was added dropwise over a period of 70 min at a rate such that the temperature was maintained at 5–10°. After an additional 30 min 99% of the theoretical amount of nitrogen had been evolved, and the reaction mixture was processed. The combined crude product from two reactions was distilled through a 20-cm Vigreux column to give (A) 8.1 g, bp 25–96° (0.3 mm); (B) 27.5 g, bp 96–111° (0.1 mm), mainly at 109–111° (0.1 mm); (C) 34.2 g, bp 111–130° (0.15 mm); and (D) 6.1 g bp 130–145° (0.15 mm). Vpc analysis on column 1[7] of fractions A and B indicated that they contained mainly a single component, and by preparative-scale vpc separation on column 3[7] a pure sample of 10-oxatricyclo-[5.2.1.$1^{4,11}$]undecan-11-ol (**10**) was obtained as a colorless solid: mp 109–111° (after three melting–solidifying cycles the melting point rose to 111–113°); ν^{KBr}, in cm^{-1}, 3006 (hydroxyl), no absorption in carbonyl region; nmr (CCl_4), in ppm, 14-proton multiplet at 1.17–2.50, one-proton multiplet at 4.06–4.50 (O–CH at C-4), one-proton singlet at 4.35 (OH).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.03; H, 9.53.

Attempts to make hydroxyl derivatives (benzoate and *p*-toluenesulfonate) and carbonyl derivatives (semicarbazone and

(1) This work was supported, in part, by Grant No. DA ARO(D)-31-124-G533 from the U. S. Army Research Office.

(2) National Institutes of Health Predoctoral Fellow, 1963–1966.

(3) C. D. Gutsche and J. W. Baum, *J. Amer. Chem. Soc.*, **90**, 5862 (1968).

(4) M. Barnard and N. C. Yang, *Proc. Chem. Soc.*, 302 (1958).

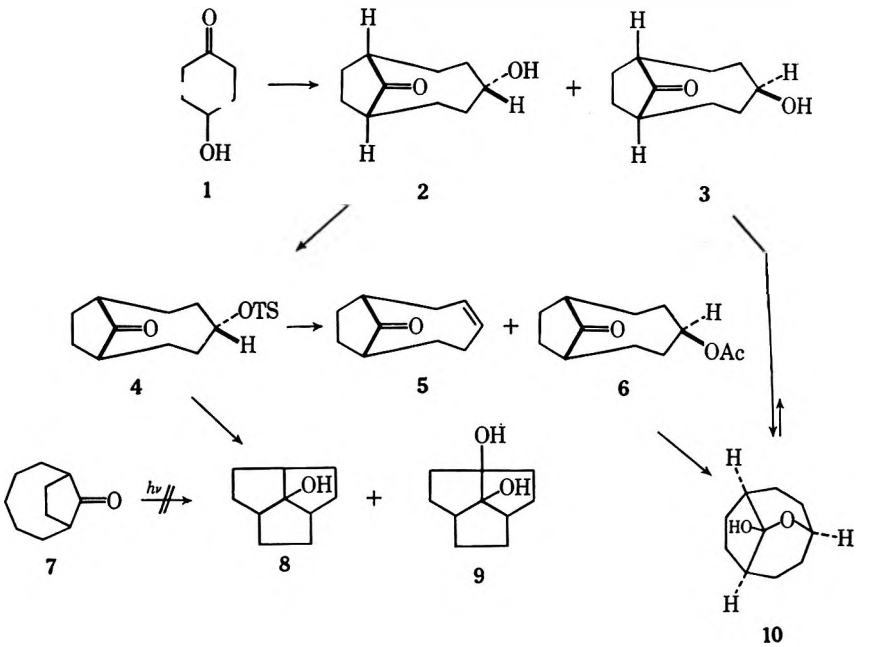
(5) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, **82**, 4067 (1960).

(6) C. D. Gutsche, I. Y. C. Tao, and J. Kozma, *J. Org. Chem.*, **32**, 1782 (1967).

(7) All melting points and boiling points are uncorrected. The infrared (ir) spectra were measured on a Perkin-Elmer Infracord instrument. The nmr spectra were measured on Varian HA-60 and A-60A spectrometers; the resonances are expressed in parts per million downfield shift from tetramethylsilane, present as an internal reference. Microanalyses were performed by Dr. Josef Zak, Mikroanalytisches Laboratorium, Vienna, Austria. Vpc analyses were performed on units containing thermistor detectors and using the following columns: (1) a 1/4 in. × 16 ft column packed with 15% w/w neopentylglycol sebacate polymer on 40-50 mesh type ABS Anakrom (a product of Analytical Engineering Laboratory, Inc., Hamden, Conn.); (2) a 1/4 in. × 6 ft column packed with 5% w/w Dow No. 710 silicone oil on 40-50 mesh type ABS Anakrom; (3) a 1/2 in. × 9 ft column packed with 15% w/w Dow No. 710 silicone oil on 40-50 mesh type ABS Anakrom.

(8) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

SCHEME I
CONVERSION OF 4-HYDROXYCYCLOHEXANONE INTO TRICYCLO[5.2.1.0^{4,10}]DECAN-10-OL



2,4-dinitrophenylhydrazone) of **10** were without success. Vpc analysis on column 1[7] of fraction C indicated that it contained *ca.* 65% *exo*-4-hydroxybicyclo[5.2.1]decan-10-one (**2**) and that fraction D contained *ca.* 33% **2** along with two higher boiling components presumed to be the epimers of 2-(γ-methoxypropyl)-5-hydroxycycloheptanone. On the basis of the weights of the distillation fractions and the composition as indicated by vpc analysis, the yield of the hemiketal **10** is *ca.* 30% and the yield of the hydroxy ketone **2** is *ca.* 24%.

4-*exo*-*p*-Toluenesulfonyloxybicyclo[5.2.1]decan-10-one (4).—A 22.6-g sample of fraction C described above was dissolved in 150 ml of pyridine, cooled to −5°, and treated with 26.6 g of *p*-toluenesulfonyl chloride in 100 ml of pyridine. The mixture was stirred at −5° for 4 hr and then allowed to stand at −20° for 18 hr. The crude product obtained after removal of the solvent was washed with three 50-ml portions of petroleum ether (bp 63–69°) (which removed 12.5 g of oily material) to leave 29.0 g of a semisolid. Recrystallization from acetone yielded 13.6 g (48.5%) of **4**, mp 126–128°, in the first crop and 2.7 g (10%), mp 125–127°, in the second crop. Further recrystallization from acetone yielded colorless plates: mp 127–127.5°; ν^{KBr}, in cm^{-1}, 1734 (cyclopentanone carbonyl); nmr ($CDCl_3$), in ppm, 14-proton multiplet at 1.50–2.58 (CH and CH_2 of bicyclic ring), three-proton singlet at 2.45 (CH_3Ar), one-proton broad singlet at 4.00–4.23 (O–CH at C-4), two-proton doublet at 7.34 (J = 8.5 Hz) (Ar–H), two-proton doublet at 7.74 (J = 8.2 Hz) (Ar–H).

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.88; S, 9.94. Found: C, 63.10; H, 6.86; S, 9.76.

Acetolysis of 4-*exo*-*p*-Toluenesulfonyloxybicyclo[5.2.1]decan-10-one (4).—Following a published procedure,[9] a 0.645-g sample of **4** was refluxed for 7 hr with a mixture containing 0.500 g of sodium acetate, 2.5 ml of glacial acetic acid, and 0.5 ml of acetic anhydride. The reaction mixture was worked up to give 0.298 g of a colorless liquid, the vpc of which on column 1[7] indicated it to be a mixture of two materials. This product was dissolved in a solution containing 1.0 g of sodium methoxide in 15 ml of methanol, and the reaction mixture was refluxed overnight. The resulting product was separated by vpc on column 1[7] to yield a compound (36%), mp 113°, shown to be identical, by means of ir spectral comparison, with the hemiketal **10**, and 64% bicyclo[5.2.1]dec-3-en-10-one (**5**): ν^{KBr}, in cm^{-1}, 1732 (cyclopentanone carbonyl); nmr (CCl_4), in ppm, 12-proton multiplet at 1.00–2.55 (CH and CH_2 of ring), two-proton multiplet at 5.33–5.91 (=CH). A 2,4-dinitrophenylhydrazone of **5** was obtained, after chromatography on alumina and recrystallization from ethanol, as red-orange plates, mp 185–187° (softening at 172° followed by resolidification).

(9) F. Fleck and H. Schinz, *Helv. Chim. Acta*, **33**, 140 (1950).

Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.19; H, 5.64; N, 16.73.

Reduction of 4-*p*-toluenesulfonyloxybicyclo[5.2.1]decan-10-one (4).—To 650 ml of liquid ammonia (distilled from lithium) *ca.* 0.024 g of lithium and 1.6 g of the tosylate **4** were added. After addition of another 1.6 g of **4** dissolved in 10 ml of dry 1,2-dimethoxyethane, the blue color of the solution was rapidly discharged. Thereafter, small pieces of lithium and a solution of **4** in 1,2-dimethoxyethane were alternately added over a 1.5-hr period so that the blue color was just maintained. A total of 16.12 g (0.050 mol) of **4**, 2.67 g (0.385 g-atom) of lithium, and 100 ml of 1,2-dimethoxyethane was used. The mixture was cooled to −70° and treated with 20.6 g of solid ammonium chloride, whereupon the blue color was discharged and a white precipitate appeared. The ammonia was evaporated, and the residue was worked up to give a crude product which was twice distilled through a short-path apparatus, the distillate boiling up to 150° (30 mm) being collected. By means of vpc on column 2[7] the two major components of this product were isolated. One of these, mp 122–124°, was assigned the structure of tricyclo-[5.2.1.0^{4,10}]decan-10-ol (**8**): ν^{KBr}, in cm^{-1}, 3350 (s), 3000 (s), 1470 (m), 1400 (w), 1320 (s), 1240 (w), 1195 (m), 1100 (w), 1040 (s), 1010 (w), 980 (vw), 955 (vw), 895 (m), 870 (w), 805 (vw), 765 (vw); nmr (CCl_4), in ppm, 15-proton multiplet at 1.00–2.50 (CH and CH_2 of ring), one-proton singlet at 3.75 (hydroxyl; band disappears after treatment of sample with D_2O). The mass spectrum of **2**, as illustrated in Figure 1, shows a parent peak at m/e 152 which is unusually strong for a tertiary alcohol.[10]

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.43; H, 10.24.

The other component, mp 133–136° after recrystallization from acetone, was assigned the structure of tricyclo[5.2.1.0^{4,10}]-decane-4,10-diol (**9**) on the basis of a positive periodate test and its spectral characteristics: ν^{KBr}, in cm^{-1}, 3400 (vs), 3000 (s), 1460 (m), 1420 (m), 1360 (w), 1315 (m), 1230 (m), 1180 (m), 1160 (m), 1105 (m), 1070 (s), 1040 (m), 1020 (w), 1000 (w), 982 (s), 952 (w), 920 (w), 895 (m), 790 (w); nmr (CCl_4), in ppm, 14-proton multiplet at 1.0–2.5 (CH and CH_2 of ring), two-proton singlet at 4.04 (hydroxyl; disappears after treatment of sample with D_2O) (note the absence of any D_2O-insensitive band in 3.50–4.50 region characteristic of a O–CH moiety).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.50.

Registry No.—**4**, 17790-98-6; **5**, 17790-99-7; **5** 2,4-dinitrophenylhydrazone, 17791-00-3; **8**, 17791-01-4; **9**, 17791-02-5; **10**, 17818-05-2.

(10) We are indebted to Dr. O. P. Tanner and Mr. M. T. Jackson of the Monsanto Co. for their assistance in obtaining the mass spectrum using a CEC 21-104 instrument.

Additions and Corrections

Vol. 27, 1962

C. C. Price and W. H. Snyder: The Base-Catalyzed Isomerization of Allyl to Propenyl Sulfides.

Page 4641. Column 1, paragraph 5. 60–65% *trans* should be 60–65% *cis*.

Vol. 28, 1963

Neil Baggett and Roger W. Jeanloz: 2,4-Di-*O*-methyl and 3-*O*-Methyl Ethers of 1,6-Anhydro-β-L-idopyranose.

Page 1846. In column 1, paragraph 2, line 10, $[\alpha]_D$ values should read $[\alpha]^{20}D$ −35° (in water, *c* 0.9); $[\alpha]^{20}D$ −35° (in acetone, c 1.0).

Page 1846. In column 1, paragraph 5, line 10, $[\alpha]_D$ value should read $[\alpha]^{15}D$ −15°.

Page 1846. In column 1, paragraph 9, line 25, $[\alpha]_D$ value should read $[\alpha]^{22}D$ −26°.

Page 1847. In column 1, paragraph 1, line 2, $[\alpha]_D$ value should read $[\alpha]^{15}D$ −52°.

Vol. 30, 1965

H. J. Shine and E. E. Mach: Ion Radicals. V. Phenothiazine, Phenothiazine 5-Oxide, and Phenothiazone-3 in Acid Solutions.

Page 2132. Column 2, Table I. The values of $10^4\epsilon$ for solutions of phenothiazone-3 (compound III) were calculated incorrectly and should read 2.5 (237 mμ), 1.8 (270–287 mμ), 1.2 (369 mμ), and 0.9 (500 mμ).

William P. Schneider, E. Louis Caron, and Jack W. Hinman: Occurrence of Tomentosic Acid in Extracts of *Bixa orellana*.

Page 2856. Our identification of tomentosic acid from *Bixa orellana* was mainly by direct comparison with samples labeled "tomentosic acid," "tomentosic bromolactone," and "methyl tomentosate" obtained from Dr. L. Ramachandra Row. Since our publication, we have obtained a mass spectrum of the "methyl tomentosate" of Dr. Row and find that the molecular ion (502 mass units) corresponds to that of methyl arjunolate rather than to "methyl tomentosate" (518 mass units). Also, Dr. K. H. Pegel of the University of Natal, Durban, South Africa, has compared the infrared spectrum of Row's "tomentosic acid" with that of arjunolic acid and found them to be identical (private communication). We must thus withdraw our claim for the occurrence of "tomentosic acid" in *Bixa orellana*.

Attempts to clarify the origin of the samples of "tomentosic acid," "methyl tomentosate," and "tomentosic bromolactone" sent to us by Dr. Row have remained fruitless. Further, the similarity of many of the physical and chemical properties reported by Row, *et al.*, for "tomentosic acid" and its derivatives with those of arjunolic acid makes it unclear at this time whether "tomentosic acid" is in fact a distinct triterpene acid.

Vol. 32, 1967

J. F. Bunnett and E. Baciocchi: Comparison of Mercaptide and Alkoxide Ions as Reagents for Olefin-Forming β Elimination.

Page 11. The proper spelling of the last name of the second author is "Baciocchi."

Anil C. Ghosh, Kazuko Mori, A. C. Rieke, Sunil K. Roy, and D. M. S. Wheeler: Synthesis of Diterpenoid Acids. V. Insertion of Two Quaternary Methyl Groups.

Page 723. The symbols A and B should be interchanged on line 20 and between lines 40 and 41.

Karlheinz K. Brandes, R. Suhrmann, and R. J. Gerdes: The Reaction of Solid Phenylmethanes with Potassium.

Page 742. The molar conductances given in the second paragraph must be multiplied by 10^3.

Pages 743 and 744. The value 3.00 has to be added to log Λ_0 in Figures 4 and 5. The molar enthalpies of dissociation are not affected by these corrections.

Yoshiro Yasuda, Nariyoshi Kawabata, and Teiji Tsuruta: Reaction of Butylmagnesium Bromide with Ketones.

Page 1720. Abstract, line 3. Delete the following: "Addition of methanol or acetic acid to the Grignard reagent also caused the formation of *n*-octane."

Page 1721. Column 2, line 31. Delete the following: "Addition of methanol or acetic acid to an ether solution of *n*-butylmagnesium bromide also caused the formation of *n*-octane in 57 and 45% yields, respectively."

The principal part of the paper is not influenced by these retractions.

D. C. Humber, A. R. Pinder, and R. A. Williams: Synthetic Experiments in the Eudalene Group of Bicyclic Sesquiterpenes. III. Total Synthesis of (+)-α- and (+)-β-Eudesmols.

Page 2336. In **4**, the methyl group shown at C-4 should be H. In **12** and **14**, the H at C-7 is *cis* to the OH at C-5. In **16** and **22**, the methyl group shown at the carbon holding the isopropenyl group should be H.

Page 2336. Column 1, line 7 from bottom. "4-diethylaminobutan-3-one" should read "1-diethylaminobutan-3-one."

Page 2339. Column 1, line 11 from the bottom. "$[\phi]_{269}$ −3900°" should read "$[\phi]_{269}$ +5900°" and "$[\phi]_{216}$ −31000°" should read "$[\phi]_{216}$ +31000°." The ORD data given for compound **23** apply to compound **9** and the data for compound **23** should be "ORD in methanol (*c* 0.12): $[\phi]_{500}$ −110°, $[\phi]_{400}$ −150°, $[\phi]_{304}$ +1140°, $[\phi]_{261}$ −3520°, $[\phi]_{250}$ −3330° sh, $[\phi]_{213}$ −7040°." The ORD values listed under compound **9** should be deleted.

Page 2440. Column 1, line 4 from bottom. The nmr data for (−)-*trans*-dihydrocarissone should read $\delta_{TMS}^{CCl_4}$ 0.91 and 1.02 (doublet, J = 6.5 cps, 3 H, C-4 CH_3), 1.10 (singlet, 3 H, angular CH_3), 1.18 [singlet, 6 H, $(CH_3)_2C$], and 2.42 ppm (singlet, 1 H, OH).

Richard M. Kellogg, M. B. Groen, and Hans Wynberg: Photochemically Induced Cyclization of Some Furyl- and Thienylethenes.

Page 3094. Reference 19 should read as follows.

(19) D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.* (India), **B16**, 65 (1957); *Chem. Abstr.*, **51**, 13841*i* (1967). O. Dann and M. Kokorvdz [*Chem. Ber.* **91**, 181 (1958)] report a compound which they identify as benzo[1,2-*b*;4,5-*b*']dithiophene but which has a melting point and an ultraviolet spectrum identical with those of Rao and Tilak's compound and our **4a**. The mistaken structure assignment of Dann and Kokorvdz arose from an erroneous assumption of the direction of ring-closure reaction.

Ralph J. De Pasquale and Christ Tamborski: The Reactions of Sodium Pentafluorophenolate with Substituted Pentafluorobenzenes.

Page 3164. Table I, column R, lines 9 and 10. "C_6H_5" should read "C_6F_5."

Page 3164. Table I, column L:M, line 9. "1:3[b]" should read "1:3."

Page 3165. Column 1, line 34. "$[A]_1$" should read "$[A]_0$."

Page 3165. Column 2, line 40. "...F < Cl..." should read "...F > Cl..."

Donald D. Roberts and James G. Traynham: A Solvolytic Investigation of Cyclooctyl and *trans*-2-Hydroxycyclooctyl Bromides and *p*-Toluenesulfonates.

Page 3181. Column 2, Table V. The first three lines are for **1B**; the last two lines are for **1T**.

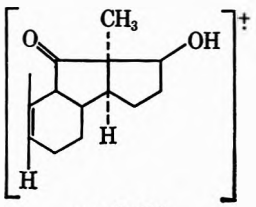
Irving J. Borowitz and Howard Parnes: Kinetics of the Reaction of Triphenylphosphine with α-Haloacetophenones.

Page 3562. Column 1, paragraph 5. The reaction of chloroacetophenone with triphenylphosphine was found to be 4.4 times as fast as that with pyridine at 34.90 ± 0.01° and not 44 times as stated. The rate constants are correct as given and only the ratio was incorrectly stated. The corrected ratio therefore negates the discussion in paragraph 5 on page 3562 which attempted to explain the 44:1 ratio.

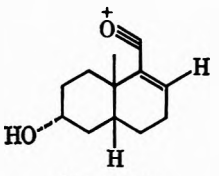
Paul Kurath: Structure and Stereochemistry of the Benzilic Acid Rearrangement Product of 3α,17β-Diacetoxy-11-hydroxy-5β-androst-9(11)-en-12-one.

Page 3628. Structure 8 in Scheme I should have the same stereochemistry for the methyl groups as shown for 6 and 7.

Page 3632. Structures q and t in Scheme III should be as follows.



q, *m/e* 220



t, *m/e* 193

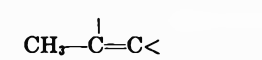
A. H. Weinstein: Sulfonation–Debutylation of 2,6-Di-*t*-butyl-*p*-cresol.

Page 3669. Column 2, Scheme I. Formula II should be the 2-chlorosulfonylphenol listed as compound II in the text and not a 2-chlorosulfonyl aromatic sulfonic acid.

Stanley R. Sandler: Reactions of *gem*-Dihalocyclopropanes with Electrophilic Reagents. Formation of Allyl Derivatives and/or Dienes.

Page 3878. Column 2. In Scheme II, the ion B is missing the bromine atom at C-3.

Page 3880. In Table IV, for XI the structural assignment opposite δ = 1.85 should be as follows.



Ronald A. LeMahieu: The Reaction of Di-*n*-butylcadmium with Derivatives of Ketal Acids.

Page 4150. Column 1. The legend for formula I should read R = Cl or $OCOC_2H_5$. The legend for formula Vb should read R = $CO_2C_2H_5$. The legend for formula IXb should read R = $CO_2C_2H_5$.

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C. A. Bunton, S. J. Farber, and Eleanor J. Fendler: The Hydrolysis of *p*-Nitrophenyl Diphenyl Phosphate.

Page 31. Table V, line 9. 10^4k_ψ = 172 sec^{-1}. The corresponding value of k_2 is correct.

G. Grethe, H. L. Lee, M. Uskoković, and A. Brossi: Syntheses in the Isoquinoline Series. Synthesis and Chemical Transformation of 2,3-Dihydro-4(1H)-isoquinolones.

Page 496. The title of Figure 1 should read as follows.

Figure 1.—Infrared absorption in the region of 1400–2000 cm^{-1} for the salts of the keto esters **30** (A), **32** (B), and **34** (C) taken in KBr pellets.

G. Grethe, V. Toome, H. L. Lee, M. Uskoković, and A. Brossi: Syntheses in the Isoquinoline Series. Selective Demethylation of 6,7- and 7,8-Dimethoxy-2,3-dihydro-4(1H)-isoquinolones.

Page 505. The title of Figure 1 should read as follows.

Figure 1.—Ultraviolet spectra of 2-benzyl-2,3-dihydro-6-hydroxy-7-methoxy-4(1H)-isoquinolone hydrobromide (**9b**) in ethanol (—), in ethanol saturated with sodium acetate (---), and in 0.002 *M* ethanolic sodium ethoxide (···).

Page 505. The title of Figure 2 should read as follows.

Figure 2.—Ultraviolet spectra of 2-benzyl-2,3-dihydro-7-hydroxy-6-methoxy-4(1H)-isoquinolone hydrochloride (**10**) in ethanol (—), in ethanol saturated with sodium acetate (---), and in 0.002 *M* ethanolic sodium ethoxide (···).

Page 506. The title of Figure 3 should read as follows.

Figure 3.—Ultraviolet spectra of 2,3-dihydro-7-hydroxy-6-methoxy-1(4H)-naphthalenone (**15**) in ethanol (---) and ethanol saturated with sodium acetate (—).

Page 506. The title of Figure 4 should read as follows.

Figure 4.—Ultraviolet spectra of 2,3-dihydro-6-hydroxy-7-methoxy-1(4H)-naphthalenone (**16**) in ethanol (---) and ethanol saturated with sodium acetate (—).

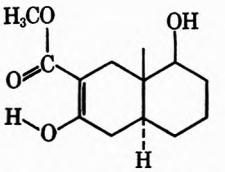
James W. Wilt, Charles F. Parsons, Charles A. Schneider, David G. Schultenover, S. J., and William J. Wagner: The Preparation and Study of Some 1-Norbornenyl and Norbornenyl-1-carbinyl Derivatives.

Page 694. The name of the second author should be Charles F. Parsons.

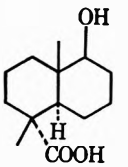
Page 699. Column 1. The ΔS^* values in Table I are in error. The value for tosylate **42** is -17.0 ± 0.1 eu. The value for tosylate **38** is -12.0 ± 0.1 eu. The discussion presented in the paper is affected by this correction to the extent that the inductive retardation by the double bond in **38** is reflected not only in enthalpic differences but also in entropic ones. We view this as an indication of less charge development in the activated complex from **38** compared with that from **42**. This is in line with our view that the transition state is reached later from **38** than from **42**, as we stated in the paper.

Thomas A. Spencer, Thomas D. Weaver, Rodolfo M. Villarica, Richard J. Friary, Jeanette Posler, and Martin A. Schwartz: Syntheses of Methyl Deisopropyldehydroabietate. Diterpenoid Synthesis by the AB → ABC Approach.

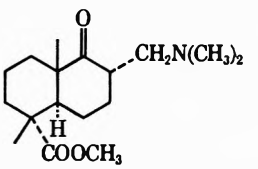
Page 713. Column 2. Structural formula **11** should be as shown.



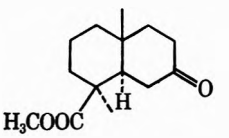
Page 714. Column 1. Structural formula **19** should be as shown.



Page 714. Column 2. Structural formula **25** should be as shown.



Page 714. Column 2. Structural formula **39** should be as shown.



T. Uematsu and R. J. Suhadolnik: 7-Deazaadenine Ribonucleosides. The Use of Periodate Oxidation in Degradation Studies.

Page 726. The first paragraph of this paper, which should have been published as a Note, was inadvertently published as an abstract.

M. S. Chang and J. U. Lowe, Jr.: Di(cyclopropanecarbonyl)-furoxan.

Page 866. Paragraph 3, line 3. After colorless, insert, "solid and a yellow solid reminiscent of the formation of a colorless." In formula II, change exocylic N—O bond to dative N→O. In formula IV, insert double bond in positions 4–5 of isoxazole ring.

John Jacobus, Morton Raban, and Kurt Mislow: The Preparation of (+)-N-Methyl-1-(1-naphthyl)ethylamine and the Determination of Its Optical Purity by Nuclear Magnetic Resonance.

Page 1142. Footnote 8. "Toluenesulfonates" should read "methanesulfonates."

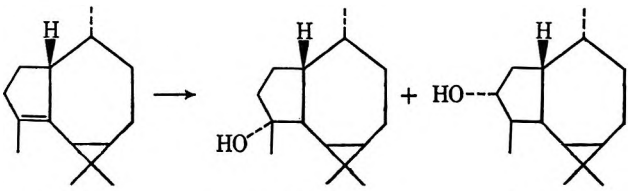
Page 1144. The rotation of (+)-N-methyl-1-(1-naphthyl)-ethylamine in ethanol is strongly dependent on the water content of the ethanol. In rigorously dried ethanol (stored over Linde 4A Molecular Sieves), the rotation is $[\alpha]^{24}D$ +89° (*c* 3.51). The value originally reported, $[\alpha]^{25}D$ +74° (c 3.885), refers to *ca.* 90% ethanol.

B. Franzus, W. C. Baird, Jr., and J. H. Surridge: Synthesis of *exo,exo*-5,6-Dideuterio-*syn*-7-acetoxynorbornene and *exo,exo*-5,6-Dideuterio-2-norbornene.

Page 1289. Column 2. The nmr data published for *exo,exo*-5,6-dideuterio-*syn*-7-acetoxynorbornene in our paper are incorrect. The chemical-shift data should be corrected to read as follows: vinyl hydrogens, δ 5.95; bridge hydrogen, δ 4.45; bridgehead hydrogens, δ 2.90; CH_3COO hydrogens, δ 1.94; *exo* hydrogens, δ 1.75; *endo* hydrogens, δ 0.96.

Alan M. Krubiner, Norman Gottfried, and Eugene P. Oliveto: Studies in the 21-Methyl Steroid Series. Organoborane Rearrangements and a Novel Synthesis of 21-Methyl-19-nor Steroids.

Page 1716. Column 2. Structures VII, VIII, and IX should be as shown.



VII VIII IX

Donald J. Burton and Frank E. Herkes: Fluoro Olefins. II. Isomerization of β-Substituted Perfluoro Olefins. Kinetic *vs.* Equilibrium Control.

Page 1855. Table I. Footnote *c* should read "Lithium chlorodifluoroacetate employed at 80° in DMF."

Page 1857. Table IV. Line 3 of body of table should read as follows.

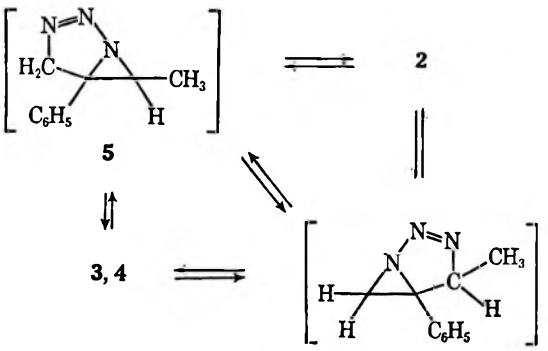
RbF	79	12.1	87.9	7.3

R. A. Silverman and D. M. Burness: Reactions of Thiols with 2,5-Dihydro-2,5-dimethoxyfuran. A New Synthesis of 2-Furyl Thioethers.

Page 1870. Table I. In the "Formula" column the next to the last entry should read $C_{12}H_{12}N_4O_2S$, and not $C_{11}H_9N_4OS$.

Vasudewan Nair: The Reaction of Azirines with Diazomethane to Produce Allylic Azides.

Page 2122. Formulas 5 and 5a should have been included, as shown below.



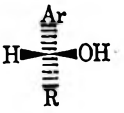
5a

S. P. Pappas and Norman A. Portnoy: Substituent Effects on the Photoaddition of Diphenylacetylene to 1,4-Naphthoquinones.

Page 2202. Column 2. Compound VIb, listed last in the Experimental Section, has mp 225–226°, rather than the indicated mp 225–256°.

Gloria G. Lyle and Matt J. Piazza: Rotatory Dispersion Studies. VI. Phenylosotriazole Derivatives of the Aldo Sugar Family.

Page 2478. Column 1. The diagram should be as shown below.



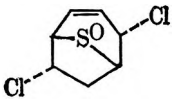
Ar = benzene or aromatic heterocycle

E. Le Goff and R. B. LaCount: Dibenzopentalenoquinone and a Radical-Anionic Salt of its Tetracyanodimethan Derivative.

Page 2530. Column 1. The second sentence should read "Polarographic reduction of **8** in acetonitrile showed three half-wave potentials at +0.099, −0.3, and −0.9 V corresponding to two one-electron reductions and a two-electron reduction, respectively."

F. Lautenschlaeger: The Reaction of Sulfur Dichloride with Cyclic Polyolefins.

Page 2629. Column 2. Structure **10** should be as shown below.



10

Page 2633. Column 1, paragraph 6. Line 2 should read "2.95 protons for the group CH_2=CH, and 0.9 protons for CHCl."

William C. Bailey, Jr., Ajay K. Bose, Robert M. Ikeda, Richard H. Newman, Henry V. Secor, and Charles Varsel: The Isolation from Tobacco of 2-Hydroxy-2,6,6-trimethylcyclohexylideneacetic Acid γ-Lactone and Its Synthesis.

Page 2820. Column 1, paragraph 1. The first line should read as follows: "The lactone I is readily prepared starting with the."

Page 2821. Column 1, paragraph 2, line 2. (1) should be (I).

Page 2821. Column 2, next to last paragraph. Formula should be $C_{13}H_{23}N_3OS$.